SMOKING and HEALTH

a report of the Surgeon General

- ☐ The Health Consequences of Smoking
- ☐ The Behavioral Aspects of Smoking
- ☐ Education and Prevention

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THE SECRETARY'S FOREWORD

On January 11, 1964, the first Surgeon General's Report on Smoking and Health was published. It created an instant—and justified—worldwide reaction. For the report, a document of impeccable scientific authority, established a frightening link between cigarette smoking and several disabling or fatal diseases.

- The report established that cigarette smoking is causally related to lung cancer in men.
- It revealed that cigarette smoking is directly related to illness and death from heart disease and other ailments; that cigarette smoking is the leading contributory cause of death from chronic bronchitis and other lung disorders.
- The report, in short, pronounced cigarette smoking a health hazard of sufficient importance in the United States to warrant remedial action.

Today, 15 years after the original report, we publish a new Surgeon General's Report on Smoking and Health. This book is more than a compendium of new data confirming the conclusions of the original report. For this document reveals, with dramatic clarity, that cigarette smoking is even more dangerous—indeed, far more dangerous—than was supposed in 1964.

- The new report, for example, presents sobering information about a subject not extensively treated in the 1964 report: women and smoking. Among other things, the evidence suggests that mothers who smoke during pregnancy face the possibility of creating long-term, irreversible effects on their babies. And as smoking levels among women go up, disease and death rates go up also: lung cancer has increased fivefold among women since 1955. Women who smoke like men die like men who smoke.
- The report sheds new light on dramatically increased risks to smokers exposed to certain occupational hazards. Workers in the asbestos, rubber, coal, textile, uranium, and chemical industries, among others, face these risks.
- And the new report, unlike its predecessor, takes up the subject of smoking among children. The percentage of girls aged 12 to 14 who smoke, for example, has increased eightfold since 1968. Among the age group 13 to 19, there are now 6 million regular smokers. One hundred thousand children under 13 are regular smokers.

This document is significant for another reason. It demolishes the claims made by cigarette manufacturers and a few others fifteen years ago and today: that the scientific evidence was sketchy; that no link between smoking and cancer was "proven." Those claims, empty then, are utterly vacuous now. Fifteen years of additional research overwhelmingly ratify the original scientific indictment of smoking as a contributor to disease and premature death. Indeed, even the cigarette industry's own research from January 1964 through December 1973, at a cost of approximately $15 million, confirmed the lethal dangers of cigarette smoking. Today there can be no doubt that smoking is truly slow-motion suicide.

In truth, the attack upon the scientific and medical evidence about smoking is little more than an attack upon science itself: an attack upon the epidemiological, clinical, and experimental research disciplines upon which these conclusions are based. Like every attack upon science by vested interests, from Aristotle's day to Galileo's to our own, these attacks collapse of their own weight.

But why, the reader may nevertheless ask, should government involve itself in an effort to broadcast these facts and to discourage cigarette smoking?

Why, indeed? For one reason, because the consequences of smoking are not simply personal and private. Those consequences, economic and medical, affect not only the smoker, but every taxpayer.

When we consider two major national problems of health policy, we find that cigarette smoking intensifies and complicates each one.

First among these problems is the spiraling cost of health care. Health care costs nationwide now amount to $205 billion a year—of which the Federal Government pays $59 billion. Smoking accounts for an estimated $5 to $8 billion in health care expenses, not to mention the cost of lost productivity, wages, and absenteeism caused by smoking-related illness; an annual cost estimated at $12 to $18 billion.

No person, given these staggering costs, can reasonably conclude that smoking is simply a private concern; it is demonstrably a public health problem also.

A second major problem is that our health care system overemphasizes expensive medical technology and institutional care, while it largely neglects preventive medicine and health promotion.

Certainly, if the government is to shift its health strategy toward preventive rather than merely curative medicine, it cannot ignore smoking. *For smoking is the largest preventable cause of death in America.* When demographers look at death rates for diseases related to cigarette smoking, they identify 80,000 deaths each year from lung cancer, 22,000 deaths from other cancers, up to 225,000 deaths from cardiovascular disease, and more than 19,000 deaths from chronic pulmonary disease—every single one of them related to smoking. That is why smoking is Public Health Enemy Number One in America.

Having established the clear danger of smoking and the legitimacy of smoking as a public health issue, however, a final question remains: How much can government usefully do to publicize the hazards of cigarette smoking; to encourage citizens to stop smoking—or not to start?

Cigarette smoking, after all, is not like most other environmental hazards. It cannot be curbed simply through massive public and private expenditures, as in the case of water pollution abatement, on which $265 billion will be spent in the next 10 years. Cigarette smoking is not subject to the same kinds of government regulation and control that are now used, for example, to check the emission of toxic substances into the environment. These hazards can be dealt with through straightforward programs of abatement and strict regulation. When it comes to smoking, there is, of course, a role to be played by regulation and by economic and other incentives. But in a free society, research and education must be the major tools of any public-health program to deal with smoking.

So the stepped-up smoking-and-health program launched by the Department of Health, Education, and Welfare a year ago is primarily one of research, education, and persuasion. I described it last year, in testimony before the House Subcommittee on Health and the Environment, in these words:

> 'Make no mistake, our efforts are to reduce smoking. But they are efforts grounded in persuasion and information that appeal to the common sense of our citizens. They are not efforts based on coercion and scare tactics. I have the greatest empathy for the millions of Americans who want to stop smoking, but who find it very, very difficult to do so...
> '...If our citizens...are given all the facts from government, or other sources, and still do not wish to give up a personal habit, however hazardous, then, except for protecting the rights of non-smokers, I think government can properly do no more.'

How successful can such efforts be? Quite successful, to judge from the record:

Today, more than 30 million Americans are ex-smokers. This does not include the number of people who, after considering the risks, chose never to take up the habit; they must also number in the millions.

The number of cigarettes consumed per person in the United States has declined from 4,345 in 1963 to 3,965 in 1978. In fact, per capita cigarette consumption this past year is at its lowest level in 20 years.

These facts, without a doubt, are in large part due to efforts by public health agencies and voluntary groups to inform the public about the risks of smoking.

These efforts are not mere publicity; the record suggests that every time government and voluntary agencies have intensified their efforts to spotlight the risks of smoking, more smokers have given up the habit and more have decided not to take it up.

Moreover, we know from surveys of public opinion and attitudes that the great majority of smokers—90 percent—have either tried to quit smoking or would probably quit, if only they could find an effective way to do so.

These people need help.

So, too, do millions of children and young people who must have the facts if they are to make a truly informed choice whether to smoke. Indeed, it is children who are the main focus of our efforts to inform and persuade. It is nothing short of a national tragedy that so much death and disease are wrought by a powerful habit often taken up by unsuspecting children, lured by seductive multimillion dollar cigarette-advertising campaigns.

This new Report of the Surgeon General typifies the Department's approach to the issue of smoking and health. It is based on scientific research. Its purpose is to provide facts. Its persuasive power is in the weight of the scientific evidence.

We set out to publish it for three reasons: First, we wished to bring together new information on smoking and health which has accumulated in the 15 years since Surgeon General Luther Terry released the epochal report of 1964.

Second, we wished to extend the area of inquiry into smoking and health beyond medicine into the fields of education and behavioral science. For many of the remaining unanswered questions about smoking and health are in these latter fields. We have some evidence, for example, that women smokers have more trouble giving up smoking than men—but why? Some observers believe that women are more concerned than men about gaining weight when they stop smoking. But in fact we do not know; the answers to that and other questions about smoking must be pursued through future behavioral research.

Third and finally, we wished to provide a firm base of knowledge on which health agencies throughout this nation—and the world—can build their efforts to reduce cigarette-related death and disability. For the problem of cigarette smoking is not just domestic; it is worldwide. Smokers in the United States consume 615 billion cigarettes a year; worldwide, the consumption of cigarettes approaches three trillion each year.

This, then, is the report: a compendium of 22 scientific papers on smoking and health, commissioned by the Surgeon General of the Public Health Service, compiled by 12 agencies of the Department of Health, Education, and Welfare, and reviewed by scientists who are recognized experts in their fields of inquiry. Thirteen of the papers

comprise a report on the health consequences of smoking, which the Secretary of Health, Education, and Welfare is required by law to submit to Congress each year. The remaining chapters deal with behavioral aspects of smoking and with education and prevention.

This report is, in my judgment, a major contribution to knowledge about smoking and health—and a major resource for physicians, public health officials, educators, and others who are concerned with advancing the nation's health through a sound strategy of prevention.

Joseph A. Califano, Jr.
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January 11, 1979

PREFACE

On January 11, 1964, the Surgeon General's Advisory Committee on Smoking and Health concluded: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

Today, this report reinforces that major conclusion. It is backed up by the weight of thousands of additional studies performed throughout the world. Fifteen years later, the scientific evidence on the health hazards of cigarette smoking is overwhelming.

The information in the health consequences and behavioral parts of this report has been brought together by 10 agencies of the United States Public Health Service. As will be seen, these agencies have different research or regulatory missions but a common concern with cigarette smoking as a contributor to illness, disability, and death.

Since 1964, an estimated 30 million men and women have quit the cigarette smoking habit. The prevalence of regular cigarette smoking in the adult population has declined from approximately 42 percent to 33 percent (Appendix). Yet, in 1978, an estimated 54 million men and women smoked 615 billion cigarettes. Each year, the health damage resulting from cigarette smoking costs this nation an estimated 27 billion dollars in medical care, absenteeism, decreased work productivity, and accidents. A great fraction of these costs are borne by the entire public—smokers and nonsmokers—through health insurance, disability payments, and other private and taxpayer-supported programs. In 1979, cigarette smoking is the single most important preventable environmental factor contributing to illness, disability, and death in the United States (Chapters 2 and 3).

This 1979 report describes our current knowledge of the health consequences of smoking, the behavioral aspects of smoking, and efforts in education and prevention. It presents strong conclusions where they are warranted by the accumulated evidence. It provides alternative working hypotheses when the available facts are not sufficient to warrant conclusions. It suggests future lines of inquiry where there are gaps in existing knowledge.

Adhering to this spirit of inquiry and recognizing the magnitude of the public health problem, we must ask: What is our current knowledge about "appropriate remedial action?" What scientific, economic, and behavioral facts are important for the design of public policy toward cigarette smoking? What have we learned so far, and where do we go from here? To answer these questions, we must confront three central facts: Individuals vary in their health risks associated with cigarette smoking. Individuals vary in their cigarette-smoking behavior. The cigarette product itself is changing.

High Risk Populations

The adverse health effects of smoking vary considerably in their nature and severity among individuals. They depend, for example, on the duration and frequency of smoking, on the presence or absence of concurrent illness or other environmental exposures, and on the individual's age and sex. Some health effects are immediate, while others may be delayed for years.

Most importantly, certain individuals may be particularly prone to these adverse health effects.

Women, youth, minorities, and workers exposed to occupational hazards in no way constitute an exhaustive list of especially high risk individuals. Every chapter in this report attempts to focus on particular types of individuals of highest susceptibility. Cigarette smoking acts synergistically with hypertension and elevated cholesterol to enhance the risk of developing coronary heart disease (Chapter 4). Cigarette smoking may be a promoter or co-carcinogen among those individuals exposed to other cancer-causing agents (Chapter 5). It has been suggested that there may be groups of smokers highly susceptible to lung damage from cigarette smoke whose characteristics might be detected by pulmonary function tests and histological studies or by the presence of alpha-1-antitrypsin deficiency (Chapter 6). Those other risk factors which may make maternal smoking more dangerous to the fetus need to be isolated, such as anemia, poor cardiac function, unfavorable age, and other socioeconomic factors (Chapter 8). Individuals with rhinitis or asthma may in fact be more sensitive to the nonspecific noxious effects of smoke (Chapter 10). Cigarette smoking increases the risk of peripheral vascular disease in diabetics (Chapter 4).

Women and Smoking

The findings in the report have grave public health implications for women of all ages. Although the prevalence of cigarette smoking among adult males has declined from approximately 53 percent in 1964 to 38 percent in 1978 (Appendix), the overall percentage of adult female smokers remains virtually unchanged at about 30 percent (Appendix). Cigarette smoking among younger women has increased, particularly among teenage girls. The mortality rate from lung cancer for women in 1978 was almost three times as high as in 1964, and the ratio of male to female mortality from lung cancer has decreased by almost one-half (Chapter 5). Women who have smoking characteristics similar to men experience overall mortality rates similar to men (Chapter 2).

Cigarette smoking is a major independent risk factor for fatal and nonfatal heart attacks and sudden death in both men and women (Chapter 4). The risk of heart attack is increased about tenfold in those

women smokers who use estrogen-containing oral contraceptives (Chapters 4 and 12).

The weight of evidence demonstrates that smoking during pregnancy has a significant adverse effect upon the well-being of the fetus and the health of the newborn baby (Chapter 8).

There is abundant evidence that maternal smoking directly retards the rate of fetal growth (Chapter 8) and increases the risk of spontaneous abortion, of fetal death, and of neonatal death in otherwise normal infants. More important, there is growing evidence that children of smoking mothers may have measurable deficiencies in physical growth, intellectual development, and emotional development that are independent of other known risk factors (Chapter 8). Children of mothers who smoke during pregnancy do not catch up with children of nonsmoking mothers in various stages of development (Chapter 8).

Children and Teenagers

Smoking among teenage boys has remained virtually constant, and among teenage girls it is actually increasing (Chapters 17, 18, and Appendix). The average age of experimentation with cigarettes and initiation of regular cigarette smoking has been decreasing (Chapter 17 and Appendix). Survey data suggest that teenage and early-youth smoking habits are major determinants of lifelong cigarette consumption. The mortality rates from all causes are significantly higher among those who initiate smoking earlier in life (Chapter 2).

Evidence is accumulating that the health effects of smoking evolve over a lifetime (Chapters 2, 3, 4, 5 and 6). Even when a morbid or fatal consequence of smoking occurs in later life, its antecedents may be present even in childhood. For example, autopsy studies show that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries (Chapter 4). Several scientific questions have been raised about effects of smoking on the severity of atherosclerosis in childhood and adolescence and the premature development of adult forms of these lesions (Chapter 4).

Clinical, experimental, pathological, and epidemiological studies in humans and animals demonstrate that cigarette smoking produces measurable lung damage, even in very young age groups (Chapter 6). Young cigarette smokers, even those without respiratory symptoms, have evidence of small airway dysfunction more frequently than nonsmokers (Chapter 6). A number of recent studies have established a higher prevalence of regular cough, phlegm production, wheezing, and other respiratory symptoms in teenage and young adult smokers as compared to nonsmokers (Chapter 6). The connection between pediatric respiratory illness and adult chronic respiratory disease has been supported in prospective studies (Chapter 6).

Children and teenagers are susceptible in many ways to the effects of others' smoking. Numerous research studies have found a signifi-

cant relation between childrens' respiratory illness and parental smoking (Chapter 11). Childrens' cigarette smoking habits are strongly influenced by the smoking habits of family members and peers (Chapters 17 and 18).

Minorities

The health consequences of cigarette smoking in minorities may be particularly severe, yet little is known about these health consequences at present. Survey data indicate that the prevalence of cigarette smoking among blacks exceeds that of whites (Appendix). Lung cancer death rates among blacks exceed those of whites (Chapter 5). The effects of maternal smoking on fetal development and infant health may be especially significant among minority mothers with other risk factors for complication of pregnancy (Chapter 8). Nonwhite workers in industrial settings may be particularly susceptible to the combined effects of cigarette smoking and occupational exposure to toxic agents (Chapters 5 and 7).

Smoking and Occupational Exposure

In every race, sex, and age group, blue-collar workers are especially susceptible to the combined effects of cigarette smoking and exposure to toxic industrial agents (Chapter 7). Fumes from fluorocarbon polymers are decomposed by the heat of burning cigarettes (Chapter 7). These and other chemicals contaminate cigarettes, which are then smoked (Chapter 7). Cigarette smoke contains many of the same chemicals found to be workplace toxins, such as hydrogen cyanide and carbon monoxide (Chapter 7). Exposure to coal dust, cotton dust, chlorine, and radiation combine additively with cigarette smoke to produce lung damage (Chapters 6 and 7). Cigarette smoking acts synergistically with exposure to asbestos to produce lung cancer (Chapters 5 and 7). Other documented examples of synergistic action include rubber fumes, dust, and radiation from uranium mining (Chapter 7). Studies have shown that cigarette smoking contributes to accidents in the workplace (Chapter 7).

Cigarette Smoking Behavior

The design of policy depends not only on our ability to identify high-risk groups but also on our understanding of differences in the cigarette-smoking behavior of these individuals. As numerous references in Chapters 15–21 and the Appendix emphasize, there are serious gaps in our understanding of the initiation of the smoking habit, the nature of cigarette dependence and withdrawal, and the cessation of smoking. Yet to design and implement effective policies, we must know how various target groups differ in each of these dimensions.

Evidence is cited in this report that women may differ from men in the initiation, maintenance, and cessation of smoking. It has been suggested that the abstinence syndrome is more severe in women (Chapter 15). Women are apparently more likely to fail in organized cessation programs (Chapter 19). Survey data suggest an increase in the prevalence of heavier smoking among younger females entering the smoking population (Appendix).

In this respect, we need to study the effects of introducing filter cigarettes in the 1950's and 1960's and the effects of the newer lower "tar" cigarettes in the 1970's upon the initiation of smoking, especially among young women (Appendix). We need to know whether advice is effective in influencing cigarette smoking, particularly among pregnant women during prenatal care.

Among children and teenagers, the experimental phase of cigarette smoking (Chapter 17) may in fact be the critical point of intervention. It is possible, and some investigators have suggested (Chapter 17), that younger and older adolescents respond differently to different types of antismoking intervention (Chapter 17). It also remains unclear whether teenagers respond more to contemporary peer pressure to smoke or to adult smoking images (Chapter 17). If adult family members in fact have the most critical influence on teenage smoking initiation, then the critical target population may be the adults and not their children (Chapter 17). Although the literature on the responsiveness of cigarette consumption to price is conflicting, some studies suggest that the demand for cigarettes among teenagers may be more price sensitive (Chapter 18).

Survey data suggest that individuals who attempt to quit cigarette smoking have had considerably more success in rapid and complete cessation than in gradual reduction in the amount smoked (Chapter 15). Some studies in fact suggest that withdrawal symptoms are more severe during gradual reduction (Chapter 15). Other studies suggest that very few smokers can satisfy their addiction on less than 10 to 12 cigarettes daily (Chapter 16). On the other hand, there is some evidence that lighter smokers are more successful at cessation (Chapter 18 and Appendix). There is also inconclusive evidence that lower "tar" and nicotine cigarettes can be a vehicle for cessation. These results need to be reviewed in light of the emergence of new personalized programs of smoking cessation which have reported recent success (Chapter 16).

Finally, the available survey data indicate that the prevalence of smoking is higher among minorities and blue-collar workers (Appendix). Yet very little is known about motivations for initiation and cessation of smoking among these individuals.

The Changing Cigarette Product

The cigarette product itself has changed considerably in the past 25 years. In 1954, when reports linking cigarettes to lung cancer first appeared, less than 1 percent of cigarettes produced were filter-tipped (Appendix). The average "tar" delivery of cigarettes was approximately 36 mg. The average nicotine delivery was over 2 mg (Chapter 14 and Appendix). In the years following this antismoking publicity, the consumption of filter cigarettes rose rapidly, and the average "tar" and nicotine deliveries of cigarettes decreased. By 1964, at the time of the Surgeon General's first report, the market share of filter cigarettes had reached 60 percent (Appendix). The average "tar" delivery of a cigarette was about 23 mg. The average nicotine delivery was approximately 1.3 mg (Chapter 14 and Appendix).

Since then, the average "tar" and nicotine deliveries have continued to decline. This was encouraged by a series of Government actions beginning in 1966. In that year, the Public Health Service issued its finding that "the preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of a cigarette, the less harmful [will] be the effect." This was followed by the decision of the Federal Trade Commission to begin measuring the "tar" and nicotine yields of cigarettes and to permit manufacturers to begin using this information in their advertising.

By 1977, the sales-weighted average "tar" per cigarette approached 17 mg; the sales-weighted average nicotine per cigarette approached 1.1 mg (Chapter 14 and Appendix). This decline in "tar" and nicotine resulted from important changes in cigarette production technology—the development of tobacco sheet reconstitution, improvements in cigarette filtration and cigarette paper, the genetic manipulation of tobacco strains, and increased use of plant stems and other tobacco portions formerly regarded as waste. In the past 5 years, the market share of cigarettes with "tar" delivery of 15 mg or less has increased dramatically and is now expected to exceed 30 percent. In 1977, nearly one-half of the cigarette industry's $0.8 billion advertising and promotional budget was devoted to these cigarettes.

How should we interpret these changes? What do these "tar" and nicotine measurements represent?

In one year, a typical one-pack-per-day smoker takes in 50,000 to 70,000 puffs through the burning column of a unique chemical factory which contains over 2,000 known compounds (Chapter 14). Many of these compounds are established carcinogens (Chapter 14) and appear in the particulate phase or "tar" of the smoke. A nonspecific decrease in "tar," however, does not necessarily imply a specific decrease in any single dangerous substance. Moreover, there is as yet no unequivocal evidence for the existence of "safe" levels of these carcinogenic chemicals. Even if we could identify and selectively eliminate certain known carcinogenic chemicals from cigarette smoke, there may be

numerous, as yet unidentified, dangerous substances remaining (Chapter 14).

In addition to "tar" and nicotine, cigarette smoke contains a gaseous phase with numerous components such as hydrogen cyanide, volatile aromatic hydrocarbons, and carbon monoxide. Carbon monoxide, in particular, has been identified throughout this report as a possible critical factor in coronary heart disease, atherosclerosis and sudden death, occupationally related illness, chronic respiratory disease, fetal growth retardation, and the noxious effects of passive smoking (Chapters 4, 6, 7, 8, and 11). At present, we do not have standard, reproducible measurements of the delivery of carbon monoxide in all U.S. cigarettes. Yet, some published studies suggest that some allegedly less harmful cigarettes may have higher concentrations of carbon monoxide. In Great Britain, the carbon monoxide delivery of certain filter cigarettes exceeded that of other nonfilter cigarettes (Chapter 14).

There is substantial experimental evidence, and some supporting data from retrospective studies, that cigarettes with reduced "tar" and nicotine delivery should in principle have reduced risks of health hazard (Chapters 2, 4 and 5). However, there is only one single controlled prospective study, quoted numerous times throughout this report, of the effect of "tar" and nicotine content on mortality rates. Such a study has not been repeated. The risks of overall mortality and specific mortality from lung cancer and coronary heart disease were lower in those smoking lower "tar" and nicotine cigarettes than in those smoking higher "tar" and nicotine cigarettes. But the risks for low "tar" and nicotine cigarette smokers were still significantly higher than in nonsmokers. This study did not evaluate the risk of mortality from other causes, such as chronic obstructive lung disease. It does not establish that low "tar" and nicotine cigarettes diminish the effect of smoking on the unborn fetus or the developing child. Moreover, the period of observation in this study was 1960 to 1972. Cigarettes regarded as low in "tar" and nicotine during this time do not represent current products. This study does not establish that currently available low "tar" and nicotine cigarettes are necessarily less hazardous.

The "tar" and nicotine content of cigarettes is measured by machines which smoke cigarettes according to a predetermined puff rate, butt length, duration of puff, and volume of puff. An individual smoker does not necessarily consume cigarettes in this standardized manner. It is possible for a low "tar" and nicotine smoker to inhale in one day much more of these constituents than a smoker of cigarettes with higher "tar" and nicotine content. Some studies suggest that individuals who smoke low "tar" and nicotine cigarettes may inhale more deeply or smoke the cigarette further down to the butt to compensate for the lower concentration of nicotine (Appendix). In other experiments, individuals given low "tar" and nicotine cigarettes

increase the number of cigarettes they smoke. In this respect, there is little epidemiological information concerning the trade-off between smoking a few higher "tar" cigarettes and smoking many lower "tar" cigarettes. A few long-term follow-up studies suggest that many smokers who voluntarily switch to low "tar" cigarettes may not increase their frequency of cigarette consumption. The interpretation of these studies is complicated, however, by our lack of understanding of the motives and circumstances of an individual's decision to switch to a lower "tar" cigarette.

The effect of a decrease in "tar" and nicotine content applies not only to changes in the habits of current smokers, but also to the cigarette consumption of potential new smokers (Appendix). Although there is no conclusive evidence on this point, we need to know whether the lowering of "tar" and nicotine in cigarettes over the past 20 years has made it easier for our youth to experiment with and later become habituated to cigarettes (Appendix).

Finally, the successful marketing of these low "tar" and nicotine cigarettes has required the addition of numerous flavor additives. The nature and composition of these additives is to some extent a proprietary matter. Nevertheless, we do not know whether these undisclosed additives are themselves harmless.

Until these scientific and behavioral issues are resolved, there can be no final assessment of the public health benefits of our present search for less hazardous cigarettes. The preponderance of scientific evidence continues, as in 1966, to suggest that cigarettes with lower "tar" and nicotine are less hazardous. It has become clear in the years since, however, that in presenting this information to the public three caveats are in order: Consumers should be advised to consider not only levels of "tar" and nicotine but also (when the information becomes available) levels of other tobacco smoke constituents, including carbon monoxide. They should be warned that, in shifting to a less hazardous cigarette, they may in fact increase their hazard if they begin smoking more cigarettes or inhaling more deeply. And most of all, they should be cautioned that even the lowest yield of cigarettes presents health hazards very much higher than would be encountered if they smoked no cigarettes at all, and that the single most effective way to reduce the hazards associated with smoking is to quit.

Public Policy

The decision to smoke is a personal decision, but once this is said, it remains unquestionably the responsibility of health officials to insure that smokers and potential smokers are adequately informed of the hazards. This is especially true in a society where hundreds of millions of dollars are spent each year promoting cigarettes and where these

and many other influences are encouraging young people to take up smoking.

The consideration of what is meant by "adequately informed" is a scientific and public health policy problem.

As this report shows, our knowledge of the relevant facts regarding the health hazards of cigarette smoking has increased manyfold since 1964. And efforts at adequately informing the public have had some success. According to survey data (Chapter 16), a majority of smokers, both adults and teenagers, respond affirmatively to questions about the health hazards of smoking and the desirability of quitting. Yet, perhaps because nicotine is a powerful addictive drug, millions of smokers seem unable to translate this information into personal action. Further, we know so little about how to prevent smoking among children and teenagers that the numbers of new smokers have remained virtually constant.

Earlier in this preface we noted changes that have taken place in the composition of the smoking population, in smoking behavior, in the character of the cigarette itself, and in smoking risks. We must take these changes into account in our efforts to inform. If we can now identify groups of people who are at high risk, what interventions can we design to reach them? Have previous educational efforts been too broadly based? Do the changes in the nature of the cigarette argue for a shift in emphasis, from less hazardous cigarettes to less hazardous smoking? Are there specific instances where the weight of the scientific evidence and the magnitude of the health problem require action by society, other than merely imparting information?

In addressing these questions, we must be sure we are active rather than reactive in our approach. The hazards of cigarette smoking have been established and the question has turned to what society's response to these hazards should be. If this report is successful, it will encourage the medical and public health communities to continue their search for what the Advisory Committee 15 years ago defined as "appropriate remedial action."

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Office on Smoking and Health

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Introduction

In the 15 years which have elapsed since the Report of the Advisory Committee on Smoking and Health to the Surgeon General of the U.S. Public Health Service (*15*), there has been an increasing number of scientific studies on the relationship between tobacco consumption and health. Where the 1964 Committee had access to some 6,000 articles in the world literature on smoking and health, there are now more than 30,000 such articles. In fact, no sound epidemiologic study of chronic disease today would omit from its design a history of tobacco use as a significant factor. It is on this greatly expanded source of data that this current review and re-evaluation of the evidence on the hazard of smoking to human health is based.

For historical perspective, it should be remembered that concern over the effect of tobacco on health did not begin with the Report to the Surgeon General, although that evaluation was the first American review and judgmental analysis of the tobacco hazard for all aspects of human mortality, morbidity, and specific diseases other than lung cancer. Indeed, almost from the moment of its introduction into Europe in 1558, the *Nicotiana tabacum* prompted serious concern over the effects which uses of this leaf had on human health. In less than 60 years, tobacco had become a staple agricultural commodity in Virginia and its principal currency. The "tobacco culture" expanded rapidly both societally and agronomically in America; in Europe, in the 17th Century, Simonis Paulli published his treatise "On the Abuse of Tobacco" (*6*).

Although the growth of tobacco use has been extensively documented, reliable data on its use within the total U.S. population did not become available until 1880 (*8*). Since then, per capita tobacco consumption has increased almost three-fold, with dramatic changes in its forms of use. Prior to World War I, tobacco chewing was the principal use in the United States, but the 1920's saw cigarette consumption, particularly of prefabricated cigarettes, increase astronomically as use of chewing and other smoking tobacco declined. A cigarette consumption plateau in the 1930's was followed by a sharp increase during World War II, when widespread adoption of the cigarette habit by women was added to large-scale consumption by American troops. These changes in overall consumption and forms of tobacco use had marked influences on mortality and disease patterns.

Concern over the effects of tobacco use on health increased over the years, but it was not until the 20th century that systematic scientific studies of the problem were launched. Clinical impressions and suspicions had been recorded and some had persisted for decades and centuries before appropriate tools for scientific investigation were developed. For example, the relationship between cancer of the lip and tobacco use was noted by Holland early in the 18th century (*5*) and Soemmerring made the same observation in 1795 (*13*). Not until 1920,

however, was the first systematic approach to that association made (*1*). In 1900, statisticians began to note increases in lung cancer. In 1928, Lombard and Doering presented initial suspicions of a relationship between tobacco and disease when they noted that heavy smoking was more common among cancer patients than among control groups (*7*).

In the 1930's, trends in diseases such as lung cancer became evident, promoting the start of intensive inquiries and animal experiments into disease relationships and into the chemical composition and pathogenetic effects of tobacco and tobacco smoke. In 1938, Pearl found that heavy smokers had a shorter life expectancy than nonsmokers (*9*), and 1939 saw the beginnings of large-scale epidemiologic studies of the relationship between tobacco use and lung cancer. A large number of clinical and pathological observations on effects of tobacco smoke on man had accumulated by this time.

The end of the 1930's marked the beginning of almost 40 years of retrospective (case-control) studies on selected diseases suspected of association with tobacco use (primarily lung cancer, chronic bronchitis, emphysema, and coronary artery disease) and prospective studies of diseases and mortality among cohorts of smokers and nonsmokers. By the early 1950's, there had been reports of many significant epidemiologic studies, and four of the seven prospective (cohort) mortality studies had been launched. Tobacco was increasingly being identified as a health hazard. In 1954, a group of tobacco manufacturers, growers, and warehousemen established the Tobacco Industry Research Committee to launch a research program on tobacco use and health.

The accumulation of consistent results from a growing number of studies on lung cancer led the then Surgeon General, Dr. Leroy E. Burney, to instigate the establishment by the National Cancer Institute, the National Heart Institute, the American Cancer Society and the American Heart Association of a scientific study group to assess the problem. The group agreed that a causal relationship between cigarette smoking and lung cancer existed (*11*); and on July 12, 1957 the Surgeon General placed the Service on record as saying that the weight of evidence indicated a causative relationship between excessive smoking and lung cancer. A brilliant analysis and defense by Cornfield, et al. of the evidence supporting this causal relationship by appeared in 1959 (*3*). In that year, the U.S. Public Health Service reiterated its position and took one step further when Burney stated that the principal factor in the increased incidence of lung cancer was smoking, particularly smoking of cigarettes (*2*).

In the early 1960's, a trend toward policies of intervention was hastened and encouraged by a number of events. On June 1, 1961, the presidents of the American Cancer Society, the American Public Health Association, the American Heart Association, and the National

Tuberculosis Association urged President Kennedy to establish a commission to study the tobacco problem. On January 4, 1962, representatives of these organizations met with Surgeon General Luther L. Terry once more to urge action. A proposal from Terry to the Secretary of Health, Education, and Welfare called for an expert advisory committee to assess existing knowledge and make appropriate recommendations. In March, a resolution introduced by Senator Maurine Neuberger (SJR174) called for the establishment of a Presidential commission on tobacco and health, but it was never brought to a vote.

On April 16, the Surgeon General presented a detailed proposal for an advisory group to re-evaluate the 1959 position of the Service. He cited new studies on major adverse health effects, evidence that medical opinion was now very strong against smoking, a request from the Federal Trade Commission for guidance on labeling and advertising of tobacco products, and a recent report of the Royal College of Physicians of London which concluded that "cigarette smoking is a cause of lung cancer and bronchitis and probably contributes to the development of coronary heart disease..." (*10*).

Consultations between the White House and Public Health Service officials led to Surgeon General Terry's announcement on June 7, 1962, of the planned formation of an expert committee to review all data on smoking and health. Representatives of the American Cancer Society, the American College of Chest Physicians, the American Heart Association, the American Medical Association, the Tobacco Institute, Inc., the Food and Drug Administration, the National Tuberculosis Association, the Federal Trade Commission, and the President's Office of Science and Technology met with the Surgeon General on July 27 to establish the work of the expert committee and to agree on a list of some 150 scientists and physicians qualified to evaluate data on the relationship between tobacco use and health. Terry selected 10 from the list and, thus, the Surgeon General's Advisory Committee on Smoking and Health was launched at its first meeting on November 9, 1962.

The members of the Committee were: Stanhope Bayne-Jones, M.D., L.L.D., Former Dean, Yale School of Medicine; Walter J. Burdette, M.D., Ph.D., University of Utah; William G. Cochrane, M.A., Harvard University; Emmanuel Farber, M.D., Ph.D., University of Pittsburgh; Louis F. Fieser, Ph.D., Harvard University; Jacob Furth, M.D., Columbia University; John B. Hickam, M.D., University of Indiana; Charles LeMaistre, M.D., University of Texas; Leonard M. Schuman, M.D., University of Minnesota; and Maurice H. Seevers, M.D., Ph.D., University of Michigan.

The judgments of the Advisory Committee led to a series of significant conclusions, released in 1964 in the now historic Report of

the Advisory Committee to the Surgeon General of the Public Health Service on Smoking and Health (*15*):

1. Cigarette-smoking males were found to have a 70 percent excess risk of mortality over nonsmokers. Female smokers were found to have an elevated risk of mortality, but less than that of males.

2. Cigarette smoking was judged to be causally related to lung cancer in men, the magnitude of the effect of cigarette smoking far outweighing all other factors. A similar trend was noted in females, but studies then available presented insufficient grounds for a firm judgment on causality (*4*). Included as evidence in the judgment of causality were the several findings of a dose-response relationship: The risk of death from lung cancer increased directly with duration of smoking, number of cigarettes smoked per day, inhalation, and, indirectly, with age when smoking began; discontinuance of smoking lowered the risk. For the combined group of pipe, cigar and pipe, and cigar smokers, the risk of lung cancer was greater than for nonsmokers, but was much less than for cigarette smokers.

3. Cigarette smoking was judged to be the most important of the causes of chronic bronchitis in both men and women in the United States and was found to increase the risk of dying from chronic bronchitis and emphysema.

4. Male cigarette smokers were found to have significantly higher death rates from coronary artery disease than nonsmoking males. The data then available were borderline for a judgment of causality by the rigid criteria employed for all disease entities.

5. A causal relationship was not established at the time for a number of other cardiovascular diseases.

6. Significant associations between several other cancer sites and tobacco use were judged to be causal, including pipe smoking and lip cancer, and cigarette smoking and laryngeal cancer.

7. Although the evidence revealed associations between cancer of the oral cavity and the several forms of tobacco use, between such tobacco use and esophageal cancer, and between cigarette smoking and urinary bladder cancer, the data subjected to the judgment criteria did not at that time support a judgment of causality.

A number of other diseases or conditions suggested to be associated with smoking by clinical impressions or by showing excess mortalities in the prospective studies were also scrutinized. They included: peptic ulcer, tobacco amblyopia, cirrhosis of the liver, accidents, influenza and pneumonia, and low infant birth weight.

In the instance of peptic ulcer, epidemiologic studies indicated a consistent excess risk of mortality from peptic ulcer, particularly gastric ulcer, among cigarette smokers, but in 1964 a judgment of causality could not be made.

Tobacco amblyopia had been clinically associated with pipe and cigar smoking, but the Committee could find no substantiation of this

clinical impression, since there had been no epidemiologic studies of this now rare entity and experimental studies had not been adequately controlled.

Cirrhosis of the liver had been found to contribute to excess mortality among cigarette smokers in the seven prospective studies. However, because of the relationship of alcohol consumption (and nutritional deficiencies) to cirrhosis, the correlation of heavy drinking with heavy smoking, and lack of definitive studies on the compartmentalization of these two factors at the time, there was inadequate support of a causal association.

As for accidents, an obvious relationship between smoking and fires in the home was noted in 1964.

A moderate excess risk of mortality from influenza and pneumonia was noted in six of the seven prospective studies but this association had not been evaluated by further studies. Other acute respiratory illnesses had been studied in families and in college graduates and no differences had been found between cigarette smokers and nonsmokers.

There had been some interest in the relationship between maternal smoking during pregnancy and pregnancy outcome. By 1964, five retrospective and two prospective studies revealed an association of cigarette smoking during pregnancy with lower birth weight and premature deliveries. A relationship with fetal and/or neonatal death was deemed equivocal at the time.

Finally, although smokers were found to differ from nonsmokers in a number of ways, none of the studies appraised by the Advisory Committee revealed any single variable discriminating significantly between the two groups. The report emphasized that "the overwhelming evidence points to the conclusion that smoking—its beginning, habituation and occasional discontinuance—is to a large extent psychologically and socially determined."

The Committee concluded: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

The release of the Advisory Committee's Report to the Surgeon General stimulated many studies and reports, the data from which augmented the earlier studies, strengthened the conclusions of the Committee, provided information in areas for which data had not existed, and shed light on the pathogenetic mechanisms of the thousands of compounds in tobacco and tobacco smoke. These studies were epidemiologic, clinical, experimental, and, in the area of smoking control, psychologic and sociologic as well.

The Federal Cigarette Labeling and Advertising Act of 1965 (P.L. 89-92) required the Secretary of Health, Education, and Welfare to submit regular reports to Congress on the health consequences of smoking, together with legislative recommendations. The purpose was

to monitor the scientific literature on smoking and health. This surveillance of world literature was performed by the National Clearinghouse for Smoking and Health (now succeeded by the Office on Smoking and Health). The updated reports were issued in 1967, 1968, 1969, 1971, 1972, 1973, 1974, 1975, 1976, and 1978.

This current 15th anniversary volume on smoking and health is offered as a detailed review and reappraisal of smoking and health relationships. Its contents are the work of numerous scientists both within and outside the Department of Health, Education, and Welfare. All are acknowledged elsewhere.

On the following pages, this introductory chapter seeks to summarize the principal findings and extensions of knowledge contributed by the scientific community over these 15 years. An attempt has been made to highlight particularly the earlier gaps in knowledge that have been closed or shortened in the intervening period.

Summary

Health Consequences of Smoking

Mortality

This 1979 appraisal strengthens earlier conclusions as to the relationship between smoking and mortality. Materials reviewed include the seven original prospective studies and new data derived from long-term follow-up of three of these investigations: the British doctors' study (20 years), the Hammond study (12 years) and that initiated by Dorn (16 years). Also reviewed are data from Japanese and Swedish prospective studies. The overall findings yield quantitative results over time which are substantially identical with earlier conclusions. These findings include:

1. The overall mortality ratio for all male current cigarette smokers, irrespective of quantity, is about 1.7 (70 percent excess) compared to nonsmokers.
2. Mortality ratios increase with amount smoked. The two-pack-a-day male smoker has a mortality ratio of 2.0 compared to nonsmokers.
3. Overall mortality ratios are directly proportional to the duration of cigarette smoking. The longer one smokes, the greater the risk of dying.
4. Overall mortality ratios are higher for those who initiated their cigarette smoking at younger ages compared to those who began smoking later.
5. Overall mortality ratios are higher among cigarette smokers who inhale than among those who do not.
6. Although mortality ratios for smokers are highest at the younger ages and decline with increasing age, the actual number of excess deaths attributable to cigarette smoking increases with age.

7. Former cigarette smokers experience declining overall mortality ratios as the years of discontinuance increase. After 15 years of cessation, mortality ratios for former cigarette smokers are similar to those who never smoked. Although mortality ratios for any given age for former smokers are directly proportional to the amount smoked before cessation and inversely related to the age of smoking initiation, cessation of smoking does diminish such individuals' risk regardless of these former factors, provided they are not ill at time of cessation. (Actually, the mortality ratios among those who had discontinued smoking less than 1 year before enrollment in several of the prospective studies were higher than for current cigarette smokers. This was also manifest in the total mortality rates for former cigar and pipe smokers. Further analyses separating those who stopped smoking because of illness from those ex-smokers who stopped for other reasons revealed higher mortality rates among the former.)

8. Cigar smoking is not without risk of increased mortality. The overall mortality ratios for cigar smokers are somewhat higher than for nonsmokers and are directly proportional to the number of cigars smoked per day.

9. Pipe smoking seems to have a slight effect in increasing overall mortality, but individuals who combine their pipe smoking (or cigar smoking) with cigarette smoking experience a level of risk of mortality intermediate between those who smoke only pipes or cigars and those who smoke only cigarettes.

A number of new findings in the relationship between smoking and overall mortality were found over the 15-year interval:

1. Calculations from prospective study data have indicated that life expectancy at any given age is significantly shortened by cigarette smoking. For example, a 30- to 35-year-old, two-pack-a-day smoker has a life expectancy 8 to 9 years shorter than a nonsmoker of the same age.

2. Overall mortality ratios increase with the "tar" and nicotine content of the cigarette. For smokers of low "tar" and nicotine cigarettes (less than 1.2 mg nicotine and less than 17.6 mg "tar"), overall mortality ratios are 50 percent greater than for nonsmokers, and 15 to 20 percent less than for all smokers of cigarettes.

3. For the 1964 report, data were inadequate for firm judgments on the mortality status of female cigarette smokers. Adequate follow-up in the prospective studies during these past 15 years has revealed mortality ratios for female cigarette smokers somewhat less than those for male smokers. This difference is deemed to be due to differences in exposure (later age of initiation, fewer cigarettes per day, and use of cigarettes with lower "tar" and nicotine content). Female dose-responses (quantity, age at initiation, duration of smoking, inhalation, "tar" and nicotine content) are the same as for male cigarette smokers.

Subsets of females with smoking characteristics similar to those of men experience mortality rates similar to those of male smokers.

4. From the detailed data of two prospective studies (Hammond and Dorn) the excess in mortality is noted to be greatest for the 45- to 54-year age groups among men and women. Thus, smoking mortality is premature mortality.

Cause-Specific Mortality

1. Although mortality ratios are particularly high among cigarette smokers for such diseases as lung cancer, chronic obstructive lung disease, and cancer of the larynx, coronary heart disease is the chief contributor to the excess mortality among cigarette smokers.

2. Lung cancer and chronic obstructive lung disease, in that order, follow after coronary heart disease in accounting for the excess mortality.

3. Pipe and cigar smoking are associated with elevated mortality ratios for cancers of the upper respiratory tract, including cancer of the oral cavity, the larynx, and the esophagus.

Morbidity

Following the 1964 Report to the Surgeon General, the National Center for Health Statistics began collecting information on smoking as part of the National Health Interview Survey. On the basis of probability samples of the population, estimates can be made for the general population. These data have proven valuable in assessing the relationships between tobacco use and illnesses, disability, and other health indicators. The findings include:

1. In general, male and female current cigarette smokers tend to report more chronic conditions, such as chronic bronchitis and/or emphysema, chronic sinusitis, peptic ulcer disease, and arteriosclerotic heart disease, than persons who never smoked.

2. A dose-response gradient was noted with the amount of cigarettes smoked per day for most of the chronic conditions. Particularly impressive is the gradient for chronic bronchitis and/or emphysema, with an increase in prevalence among male smokers of two packs or more a day to four times that of those who have never smoked, and among female smokers of two packs or more, to 10 times that of those who never smoked.

3. The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes.

4. Indicators of morbidity which are not dependent upon physicians' diagnoses include measures of disability such as work-days lost, days in bed, and days of limitation of activity resulting from chronic diseases.

(a) Male current smokers of cigarettes reported a 33 percent excess, and female current smokers a 45 percent excess, of work days lost in comparison to persons who never smoked. Male former smokers had an excess of 41 percent, and female former smokers an excess of 43 percent, of work days lost. From the 1974 survey data, this calculates to more than 81 million excess days of work lost for the U.S. population in 1 year.

(b) Male current smokers had a 14 percent excess, and female current smokers a 17 percent excess, of days of bed disability over those who never smoked. Smokers in all age and sex groups, except for women over age 65, reported more days in bed due to illnesses than did persons who never smoked. From 1974 data, this calculates to more than 145 million excess days of bed disability for the U.S. population in 1 year.

(c) The excesses of disability measures are dose-related.

(d) For most age and sex groups, a higher proportion of current and former smokers report longer limitation of activity due to chronic diseases than do persons who never smoked.

5. A tendency was noted for higher proportions of former smokers and those who never smoked, as compared to present smokers, to assess their own health status as excellent.

6. Current smokers and former smokers reported more hospitalizations than nonsmokers in the year prior to interview. Data on the reasons for these hospitalizations have not been analyzed.

While most studies show a reduction in the risk of mortality among former smokers, data on disability and illness often show continued high risk among former smokers. This finding should be interpreted more as an indication of the need for both additional data and further analysis of existing data, rather than as an indication of the lack of a beneficial impact on health status from smoking cessation.

These findings on morbidity are consistent with the vast amount of evidence on the relationship between cigarette smoking and mortality.

Cardiovascular Diseases

The tremendous amount of research on the relationship between cardiovascular disease and smoking, undoubtedly stimulated by a lack of adequate information in the areas of the nature of atherosclerosis, the mechanisms of atherogenesis, and the pathogenetic pathways for smoking components, has provided a basis for firmer judgments on the relationship than could be made in 1964. The present report on cardiovascular disease and smoking draws heavily on the 1976 reference report on smoking and health (*14*) and adds more recent data.

Systematic observations on the association between smoking and cardiovascular diseases have been made on considerably more than a

million individuals in the United States (the majority on men) and have involved many millions of person-years of experience.

Sample sizes are now extensive in both retrospective and prospective studies. Variables observed in retrospective studies have been relatively limited; in some prospective studies, they have been more numerous and have allowed for complex analyses in which the independence of smoking as a risk factor among other risk factors has been defined. Autopsy and experimental studies in animals have also been extended and serve to clarify earlier issues.

The 1979 Report includes the following conclusions:

1. The data collected from Western countries, particularly the United States, but also the United Kingdom, Canada, and others, show that smoking is one of three major independent risk factors for heart attack manifested as fatal and nonfatal myocardial infarction and sudden cardiac death in adult men and women. Moreover, the effect is dose-related, synergistic with other risk factors for heart attack, and of stronger association at younger ages.

2. Smoking cigarettes is a major risk factor for arteriosclerotic peripheral vascular disease and is strongly associated with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta.

3. The data establish adequately that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries than is found among nonsmokers. The effect is dose-related.

4. Epidemiologic data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive.

5. Smoking increases the possibility of a heart attack recurrence among survivors of a myocardial infarction.

6. In acute experiments on arteriosclerotic patients with angina pectoris or with intermittent claudication of peripheral vascular disease, smoking or exposure to carbon monoxide reduces the patient's established threshold for the precipitation of angina or claudication. Both nicotine and carbon monoxide (CO) aggravate exercise-induced angina.

7. Women who smoke and use oral contraceptives are at a significantly elevated risk for fatal and nonfatal myocardial infarction. A synergistic role of cigarette smoking and oral contraceptive use is suggested for subarachnoid hemorrhage.

8. Smokers of low "tar" and nicotine cigarettes experience less risk for coronary heart disease than smokers of high "tar" and nicotine cigarettes, but their risk is considerably greater than that of nonsmokers.

9. Cigarette smoking does not induce chronic hypertension. However, in the presence of hypertension as a risk factor for coronary heart

disease, smoking acts synergistically to increase the effective risk by joining the risks attributable to hypertension and to smoking alone.

10. Cigarette smoking is a major risk factor for ischemic peripheral vascular disease of arteriosclerotic type; cigarette smoking increases appreciably the risk of peripheral vascular disease in diabetes mellitus.

11. Cessation of cigarette smoking improves the prognosis of arteriosclerotic peripheral vascular disease and is advantageous to its surgical treatment.

12. Cessation of smoking reduces the risk of mortality from coronary heart disease, and after 10 years off cigarettes this risk approaches that of the nonsmoker.

13. The relationship of smoking to the incidence of stroke is not established; however, an association with subarachnoid hemorrhage has been reported in women.

In summary, for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States .

Cancer

The strongest evidence of a causal relationship between tobacco use and disease was delineated for lung cancer in the 1950's and 1960's and subjected to the rigid criteria of appraisal in the 1964 Report. In the intervening years, additional epidemiological, clinical, autopsy, and experimental studies have augmented and strengthened the earlier conclusions, particularly with regard to women smokers, for whom only preliminary data were then available.

New evidence has also accumulated since 1964 with respect to the relationships between tobacco use and cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas.

In the case of laryngeal cancer, the accumulated evidence since 1964 has strengthened, but not materially changed, the conclusions of the 1964 Report.

In the case of cancer of the oral cavity, the 1964 Report had to base its conclusions primarily on retrospective studies because of the diversity of sites, their varying incidence of tobacco exposure, and the relatively small numbers derivable in the early years of the prospective studies. These studies, unfortunately, varied in approach and either did not separate the several sites of the oral cavity or found the classes of smoking too numerous for testing their significance. Thus, the only firm judgment which could then be made was that a causal relationship exists between pipe smoking and cancer of the lip.

The 1964 Report found that an association existed between tobacco use and esophageal and urinary bladder cancer, but the Committee could not determine from the available data whether there was a causal relationship.

The 1964 Report did not address kidney or pancreatic cancer. While retrospective studies were not examined, the seven prospective studies indicated that the average mortality ratio for kidney cancer was 1.5.

Present knowledge about the relationship between smoking and the various cancers is summarized below, excerpted from the conclusions to be found in Chapter 5. As will be seen, the evidence is now overwhelming.

Lung Cancer

1. Cigarette smoking is causally related to lung cancer in both men and women.

2. The risk of developing lung cancer is increased with increasing dosages of smoking as measured by: number of cigarettes smoked per day, duration of smoking, age of initiation of smoking, degree of inhalation, "tar" and nicotine content of cigarettes smoked, and several other measurements.

3. Lung cancer mortality rates in women are increasing more rapidly than in men and, if present trends continue, will be the leading cause of cancer death in women in the next decade.

4. Use of filter cigarettes and smoking of cigarettes with lower amounts of "tar" and nicotine decrease lung cancer mortality rates among smokers; however, these rates are significantly elevated compared to rates for nonsmokers.

5. Ex-smokers experience decreasing lung cancer mortality rates which approach the rates of nonsmokers after 10 to 15 years of cessation. The residual risk of developing lung cancer in ex-smokers is proportional to the overall dosage of lifetime cigarette-smoking exposure, and inversely related to the interval since cessation.

6. Pipe and cigar smokers have lung cancer mortality rates above nonsmokers, but these rates are lower than those for cigarette smokers.

7. Certain occupational exposures can act synergistically with smoking to significantly increase lung cancer mortality rates far above those resulting from either exposure alone.

Cancer of the Larynx

8. Cigarette smoking is a significant causative factor in the development of cancer of the larynx in men and women and is directly related to several measures of dosage.

9. Pipe and cigar smokers experience approximately the same risk as cigarette smokers for cancer of the larynx.

10. There appears to be a synergistic effect between smoking and alcohol intake, as well as between asbestos exposure and smoking, for laryngeal cancer.

11. There is a substantial decrease in the risk of developing cancer of the larynx with long-term use of filter cigarettes compared to the use of nonfilter cigarettes; ex-smokers, after 10 years of cessation, have mortality rates which approximate those of nonsmokers.

Oral Cancer

12. Epidemiological studies indicate that smoking is a significant causal factor in the development of oral cancer. The risk increases with the number of cigarettes smoked per day.

13. Pipe and cigar smokers experience almost the same high risk for oral cancer as experienced by cigarette smokers.

14. A synergism exists between smoking and alcohol consumption for oral cancer.

Cancer of the Esophagus

15. Cigarette smoking is a causal factor in the development of cancer of the esophagus, and the risk increases with the amount smoked.

16. The risk of esophogeal cancer for pipe and cigar smokers is about the same as that for cigarette smokers.

17. A synergism also exists for esophageal cancer and the marked use of alcohol and cigarette smoking.

Cancer of the Urinary Bladder

18. Epidemiological studies have demonstrated a significant association between cigarette smoking and bladder cancer in both men and women.

19. Cigarette smoking acts independently and synergistically with other factors, such as occupational exposures, to increase the risk of developing cancer of the urinary bladder.

Cancer of the Kidney

20. Cigarette smoking is associated with cancer of the kidney for men. No data exist to substantiate a relationship for women.

Cancer of the Pancreas

21. Cigarette smoking is related to cancer of pancreas, and several epidemiological studies have demonstrated a dose-response relationship.

Experimental Studies

22. Experimental studies on a variety of animal models have confirmed the carcinogenic effects of tobacco smoke and its constituents on several sites including lung, larynx, esophagus, and oral cavity.

Non-Neoplastic Bronchopulmonary Diseases

Of the non-neoplastic bronchopulmonary diseases, only chronic bronchitis was judged to be causally related to cigarette smoking in the 1964 Report. In fact, cigarette smoking was then deemed the most important cause of chronic bronchitis in the U.S. and a cause of increased risk of mortality from chronic bronchitis. A relationship to pulmonary emphysema was deemed to exist, but a causal interpretation of this relationship could not then be ascribed. Cigarette smoking was then judged to exceed atmospheric pollution and environmental exposures as a cause of chronic obstructive lung disease (COLD). These diseases rank second only to coronary artery disease as a cause of Social Security-compensated disability.

In the 15 intervening years, the updating of several of the larger prospective studies and numerous retrospective and cross-sectional studies have strengthened the conclusions of the 1964 Report.

1. Cigarette smokers have a higher prevalence of chronic bronchitis and emphysema than nonsmokers and have an increased chance of dying from these diseases compared to nonsmokers. These risks are significant for both men and women who smoke, although higher rates generally exist for men than women.

2. Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related.

3. Pulmonary function abnormalities, as measured by various tests, are greater among cigarette smokers than nonsmokers.

4. Impairment of pulmonary function can be detected among smokers even in young age groups, and respiratory symptoms can be demonstrated in teenagers and adolescents who smoke.

5. Cigar and pipe smokers show higher mortality rates for chronic bronchitis and emphysema than nonsmokers, but these rates are not as great as those for cigarette smokers.

6. Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms. Cessation reduces the chance of premature death from chronic bronchitis and emphysema.

7. Although the majority of studies demonstrate a higher prevalence of pulmonary function abnormalities in smokers when compared to nonsmokers, conflicting data make it difficult to substantiate racial differences among smokers and nonsmokers.

8. Autopsy data have demonstrated more frequent abnormalities in macroscopic and microscopic lung sections among smokers compared to nonsmokers, and these effects were dose-related.

9. Several mechanisms have been suggested by which smoking might induce lung damage, including an imbalance of protease-antiprotease.

10. A wide variety of alterations in the immune system have been observed due to cigarette smoking. These alterations include macro-

phages from smokers responding abnormally to migration inhibitory factor (MIF) or antigen challenges, and T lymphocytes in smokers showing a diminished response to phytohemagglutinin (PHA), compared to those of nonsmokers. However, the role of these alterations in lung damage is unclear at this time.

11. Individuals with severe alpha-1-antitrypsin deficiency have an excess risk for developing emphysema, and the onset of symptoms is probably abbreviated in these persons by smoking. It is unclear if individuals with mild deficiency represent a group at special risk.

12. Other genetic factors may play a role in determining the risk for COLD, but these are far outweighed by the effect of cigarette smoking.

13. Certain occupations, primarily those exposing workers to dusty occupational environments, are related to COLD, and this relationship is increased further by cigarette smoking. In none of these studies are occupational effects as strong as smoking.

14. Although an increased risk of COLD due to air pollution probably exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed.

15. Childhood respiratory disease appears to be a risk factor for respiratory symptoms as an adult. However, cigarette smoking appears to be a more important factor in increasing the risk for developing these symptoms.

Interaction Between Smoking and Occupational Exposures

An extensive review of the literature on lung cancer in chromium and nickel workers and in uranium miners was prepared (*12*) for the 1964 Advisory Committee. Other studies had examined the relationships among coal gas and asbestos workers as well as in exposures to arsenic, hematite, isopropyl oil, beryllium, and copper. Significant excess lung cancer mortality was noted for chromate, nickel, coal gas and asbestos workers and for uranium miners; exposure to arsenic, hematite, beryllium, and copper remained suspect.

At the time of the 1964 report it was noted that "it must be emphasized quite strongly that the population exposed to industrial carcinogens is relatively small" (compared to the size of the smoking population), "and that these agents cannot account for the increasing lung cancer risk in the general population." It was further noted: "Of greater importance is the regrettable fact that in none of these occupational hazard studies were smoking histories obtained. Thus the contribution which smoking, as a contributory or etiologic factor, may have made to the lung cancer picture in these risk situations is unknown"(*15*).

Despite increasing recognition that smoking and occupational exposures may each contribute to the development of certain disease

states, few investigators have addressed the ways in which these two factors act together to produce disease.

This chapter has identified and illustrated six ways in which smoking may act in combination with physical and chemical agents found in the workplace to produce or increase a broad spectrum of adverse health effects. The six modes of action listed below are not mutually exclusive and several may prevail for any given agent. They may be compounded by occupational exposure to multiple chemical and physical agents.

1. Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent into the body by inhalation, ingestion, and/or skin absorption.

2. Workplace chemicals may be transformed into more harmful agents by smoking. Illustrative of this effect is the association between polymer fume fever and smokers as a result of cigarette contamination in the workplace.

3. Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent. Carbon monoxide levels in the occupational environment, for example, add to already high blood carbon monoxide levels found in smokers.

4. Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect. For example, exposure to coal dust may increase a smoker's risk of developing disease.

5. Smoking may act synergistically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influence of the agent and smoking added together. For example, cigarette smoking and exposure to asbestos may interact synergistically to greatly increase the risk of lung cancer.

6. Smoking may contribute to accidents in the workplace.

Those who have the highest risk for occupational exposures to toxic agents in general also have the highest smoking rates. Surveys have shown male blue-collar workers are much more likely to smoke than male white-collar workers. From 1920 to 1966, tobacco consumption increased as did the introduction into the workplace of chemicals with unstudied biological effects. During this same time period, the mortality rates for certain disease states associated with smoking and occupational exposures continued to increase. Some of the effects historically attributed to smoking may actually reflect interactions between smoking and occupational exposures.

Curtailment of smoking in the workplace should be accompanied by simultaneous control of occupational exposures to toxic physical and chemical agents.

Pregnancy and Infant Health

The 1964 report devoted approximately one printed page, including bibliography, to a discussion of the findings of five retrospective and two prospective studies on birth weight of infants born to mothers who smoked during pregnancy. Such infants tended to have a lower birth weight. The mechanism and its biologic significance were then not known and the findings were in some instances controversial. Since then, this area of scientific investigation has resulted in the amassing of significant data which provide many insights into the mechanisms of pathogenesis. The following conclusions are based on the work during this period:

Birth Weight and Fetal Growth

1. Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable women who do not smoke. Distribution of birth weights of smokers' babies is shifted downward, and twice as many of these babies weigh less than 2,500 grams, compared with babies of nonsmokers. There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight.

2. Birth weight is affected by maternal smoking independently of other determinants of birth weight. The more the mother smokes, the greater the baby's birth-weight reduction.

3. The ratio of placental weight to birth weight increases with increasing levels of maternal smoking. This increase may signify a response to reduced oxygen availability due to carbon monoxide and may have some survival value for the fetus.

4. There is no overall reduction in the duration of gestation with maternal smoking, indicating that the lower birth weight of smokers' infants is due to retardation of fetal growth.

5. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions; body length, chest circumference, and head circumference are smaller if the mother smokes.

6. According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11.

7. Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate directly and that fetal growth rate is not due to characteristics of the smoker rather than to the smoking, nor is it mediated by reduced maternal appetite, eating, and weight gain.

Perinatal Mortality

1. When adjustments are made for age-parity differences in mothers, their socio-economic status, and previous pregnancy histories, the risk of perinatal mortality attributable to smoking is highly significant, independent of these factors, and is dose-related.

2. Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes.

3. Although maternal smoking does not produce a lowering of mean gestational age, preterm births are increased in frequency among smokers, and a large proportion of the neonatal deaths occur among these preterm births.

4. Smoking by pregnant women contributes to the risk of their infants being victims of the "sudden infant death syndrome."

5. Maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes. Considerable literature has appeared in the area of clinical and animal experimental studies on the role of tobacco smoke, nicotine, and carbon monoxide, providing evidence for pathogenetic pathways accounting for both lower birth weight and fetal death.

6. The accumulated evidence does not support a conclusion that maternal smoking increases the incidence of congenital malformations.

Lactation and Breast Feeding

1. The epidemiologic studies on adequacy of lactation do not provide data for a conclusion on the effect of maternal smoking.

2. Although some animal studies reveal diminished milk production (but no reduction in release) following nicotine administration, human experimental studies have not thus far produced evidence for a reduction in lactation with forced smoking of large numbers of cigarettes over short periods of time.

3. There does exist a direct dose-response relationship between the number of cigarettes smoked and nicotine in breast milk.

4. Further detailed research in this area is imperative.

Peptic Ulcer Disease

The 1964 Report appraised the evidence for a relationship between tobacco use and peptic ulcer disease in five retrospective and the seven prospective studies (mortality) and concluded that only an association existed, particularly for gastric ulcers. The biological meaning of this association was not clear, particularly since studies of the effects of cigarette smoking on secretory activity and gastric motility were not consistent.

For the current report, two of the prospective mortality studies have been updated. Peptic ulcer disease mortality has continued to show excesses among smokers of cigarettes.

A number of additional studies of peptic ulcer disease and smoking were also addressed. Five of these studies showed a higher proportion of smokers among ulcer patients than among controls. Six studies showed a greater prevalence among male cigarette smokers than nonsmokers, the median ratio being 1.7. The findings in women are comparable. The majority of studies provided evidence of increased frequency of peptic ulcer disease with increases in the amount smoked.

Experimental and clinical studies of gastric and pancreatic secretion and pyloric reflux were extended in this period to resolve the mechanism of action of smoking on occurrence of peptic ulcer disease.

On the basis of the research data surveyed, it is concluded:

1. Epidemiological studies have found that cigarette smoking is significantly associated with the incidence of peptic ulcer disease and increases the risk of dying from peptic ulcer disease. This risk is, on the average, twice as high for smokers compared to nonsmokers, and appears to be greater for gastric than for duodenal ulcer disease.

2. The risk of peptic ulcer disease is dose-responsive and exists for both men and women.

3. While the pathogenetic mechanisms have not been clearly elucidated, the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship.

4. Evidence that smoking retards healing of peptic ulcers is highly suggestive.

5. Pipe smoking appears unrelated to peptic ulcer disease.

6. Experimental and clinical studies on the effect of smoking on pancreatic secretion and pyloric reflux suggest mechanisms by which peptic ulcer disease may develop.

Allergy and Immunity

Allergic manifestations to tobacco, its smoke, or its extracts were not reviewed in the 1964 report. Various studies in the late 1960's and 1970's probed the relationship of smoking to immunologic mechanisms and immune responses, not only in the acute infectious diseases, but also in several of the chronic diseases such as pulmonary disease.

The following is a summary of this research and our current understanding of this facet of human illness in relation to tobacco use.

1. Tobacco and tobacco smoke extracts have been found to act as antigens, including both precipitating and reaginic antibodies, in animals and man. These tobacco products can also sensitize lymphocytes participating in cell-mediated immune functions.

2. Tobacco and its combustion products present such an array of natural and derived components, additives, and contaminants that the precisely defined role for tobacco in immune and allergic processes cannot be delineated.

3. Several tobacco antigens have been isolated. However, epidemiologic studies on the frequency of true allergy to tobacco are inconclusive.

4. Tobacco smoke exerts a variety of effects on respiratory tract structures, and chronic smoking leads to consistent histologic changes in the respiratory tract.

(a) Evidence indicates an adverse long-term effect on the mucociliary transport mechanisms and mucus composition.

(b) The number of macrophages isolated from smokers' lung fluid is increased compared to nonsmokers.

(c) Changes in the ultrastructure of macrophages are observed in smokers.

(d) Alveolar macrophages from smokers have altered metabolism and measurable degrees of physiologic impairment.

5. Alterations in assays of cell-mediated immunity are noted locally and systemically in smokers.

6. Leukocytosis and reversible hypereosinophilia have been seen in smokers.

7. Allergic individuals, particularly those with rhinitis or asthma, may be more sensitive to the nonspecific effects of cigarette smoke than healthy individuals.

8. Because the ability to make a definitive diagnosis of tobacco allergy is complicated by the difficulty in demonstrating a cause and effect relationship between immunologic events and disease manifestations, additional evidence is required to establish a definitive role for tobacco sensitization in causing allergic disease.

Involuntary Smoking

The effects of involuntary smoking (passive or second-hand smoking) on the nonsmoker were not examined or appraised in the 1964 report but were initially discussed in the 1972 report, *The Health Consequences of Smoking*, and updated in the 1975 edition. The current report's findings in this area are summarized below. It should be understood that the literature is of recent vintage and only a limited amount of systematic information regarding the health effects of involuntary smoking on the nonsmoker is available.

1. Sidestream smoke, which comes from the lighted tip of the cigarette between puffs, has higher concentrations of some of the irritating and hazardous substances than does mainstream smoke (that smoke inhaled by the smoker).

2. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life; this effect is independent of social class, birth-weight, and parental cough and phlegm production.

3. Simple extrapolation of dose-response relationships, which are traditionally used in assessing the hazards of smoking to the smoker, cannot be employed in assessing hazards in nonsmokers.

4. Cigarette smoking in enclosed spaces can produce carbon monoxide (CO) levels well above the Ambient Air Quality Standard (9 ppm) even where ventilation is adequate.

5. Substantial proportions of the population experience irritation and annoyance when exposed to cigarette smoke. The eyes and nose are most sensitive to irritation, and such irritation increases with increasing levels of smoke contamination. Unrestricted smoking on buses and planes annoys the majority of nonsmoking passengers even under conditions of adequate ventilation.

6. Little or no physiological response to smoke was detected in healthy nonsmokers exposed to cigarette smoke. Higher heart rates detected may be due to psychological factors.

7. A slight reduction in maximum exercise capacity was noted in older nonsmokers exposed to levels of CO occasionally found in involuntary smoking situations.

8. Changes in psychomotor function, especially attentiveness and cognitive function, at levels of CO found in involuntary smoking conditions have been noted, but these effects are measurable only at the threshold of stimuli perception.

9. Levels of COHb produced by involuntary smoking situations are functionally insignificant in healthy individuals.

10. Levels of carbon monoxide which can be reached in cigarette smoke-filled environments have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. These levels of CO also have been shown to reduce the exercise time until onset of dyspnea in patients with hypoxic chronic lung disease.

Interactions of Smoking with Drugs, Food Constituents, and Responses to Diagnostic Tests

The pervasiveness of tobacco use in our society and the frequency of altered disposition and pharmacological effects of many common drugs on smokers make it apparent that cigarette smoking is one of the primary causes of drug interactions in humans. An assessment of the literature in this area provides the following conclusions:

1. Most of the experimental work in humans, animals, and tissues involving enzyme systems indicates that the dominant effect of smoking is enhanced drug disposition caused by induction of hepatic microsomal enzymes.

2. Tobacco smoke, a complex mixture of noxious materials, contains, among other compounds, enzyme inducers such as polycyclic aromatic hydrocarbons, nicotine, cadmium and some pesticides, acrolein and hydrogen cyanide.

3. The primary inducers are probably polynuclear aromatic hydrocarbons which are potent and persistent in tissues. While several of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, this enhancement is unpredictable, and the effects of cigarette smoke on other potential rate-limiting disposition processes for drugs are largely unexplored.

4. Cigarette smoking alters the pharmacologic effects of drugs or their pharmacokinetics.

5. Tobacco smoke can induce the metabolism in humans of therapeutic agents, such as phenacetin, antipyrine, theophylline, caffeine, imipramine, pentazocine, and vitamin C; examples of drugs not affected by smoking include: diazepam meperidine, phenytoin, nortriptyline, warfarin, and ethanol.

6. Tobacco smoke can modify the clinical effects of drugs.

7. Marijuana smoking may produce reactions similar to tobacco smoking since enzyme induction is also stimulated by the polycyclic aromatic hydrocarbons in marijuana smoke.

8. A woman who both smokes and uses oral contraceptives has a greater risk for myocardial infarction.

9. There is a suggestion that smoking produces a more rapid decline in influenza antibody titers after natural infection or vaccination with influenza virus.

10. Cigarette smoking appears to increase the serum carcinoembryonic antigen level in otherwise healthy individuals.

11. No information is available to indicate that the increase in body burden of trace elements by smoking has toxic effects.

12. Since tobacco smoking does affect the values of a number of clinical laboratory tests in humans, the knowledge of an individual's smoking status is important for the interpretation of such tests. Cigarette smoking increases the number of leukocytes, the red cell mass, the levels of hemoglobin and carboxyhemoglobin, the hematocrit, the mean corpuscular volume, platelet aggregation, plasma viscosity, and tensile strength of the clot; cigarette smoking decreases the serum levels of creatinine, albumin, globulin (female smokers) and uric acid (male smokers). These revert to normal levels after cessation of smoking.

Other Forms of Tobacco Use

References have already been made to the relationships between other forms of tobacco use and a number of specific diseases and cancer sites. Special attention was given in the 1973 issue of *The Health Consequences of Smoking* to the role of pipes and cigars. This attention was particularly relevant inasmuch as the 1964 Report appeared to have influenced a transient increase in consumption of cigars and pipe tobacco due to the prevailing belief that pipes and cigars were "safe."

For the present report, the summary conclusions presented here refer to men only, since the use of pipes and cigars in the United States is limited almost exclusively to them.

It can be concluded that some risk exists from smoking cigars and pipes as they are currently used in the United States, but for most diseases this is small compared to the risk of smoking cigarettes as they are commonly used.

Overall Mortality

1. Overall mortality rates among pipe or cigar smokers are slightly higher than for nonsmokers.

2. Mortality rates among smokers of pipes, cigars, or both in combination with cigarettes are intermediate between the high rates of cigarette smokers and the lower rates of those who smoke only pipes or cigars.

3. Mortality associated with combinations of pipe and/or cigar and cigarette smoking is dependent upon the level of consumption and inhalation of each.

4. A dose-response relationship exists for the several forms of tobacco use and overall mortality in terms of amount smoked, degree of inhalation, duration of smoking, and age at initiation of smoking.

Cancer

1. Prospective studies have shown that mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus are approximately equal in users of cigars, pipes, and cigarettes.

2. Although several factors appear to be involved in cancer of the lip, pipe smoking alone or in combination with other forms of smoking is causally related to lip cancer.

3. Heavy alcohol consumption in combination with heavy smoking of pipes and cigars is associated with higher rates of oral cancer than for either alcohol consumption or heavy smoking of pipes or cigars alone. There is evidence that excessive alcohol consumption may increase the pipe and cigar smoker's risk for extrinsic laryngeal cancer. A distinct synergism with heavy alcohol intake exists in esophageal cancer.

4. Cigar and pipe smokers showed the same histological changes in the larynx and esophagus at autopsy as did cigarette smokers.

5. Pipe and cigar smokers have histological abnormalities of the lung at autopsy that are intermediate in degree between nonsmokers and cigarette smokers. Some categories of pathologic changes in cigar smokers are similar to those seen in cigarette smokers.

6. The risk of pipe and cigar smokers developing lung cancer is higher than for nonsmokers, but is lower than for cigarette smokers. In the updated prospective studies, the relative risks of lung cancer for cigar and pipe smoking ranged from 1.6 to 3.4 for cigars only and from 1.8 to 8.5 for pipe only.

7. A dose-response gradient has been shown to be present in some studies.

Tumorigenic Activity of Pipe and Cigar Smoke Condensates

1. Pipe and cigar tobacco condensates have a carcinogenic potential comparable to that of cigarette condensates.

2. The alkaline smoke from pipe and cigar tobacco is usually not inhaled, and there appears to be a lower level of exposure of the harmful components of smoke than is noted with the inhalation of cigarette smoke.

Cardiovascular Diseases

1. Pipe and cigar smokers experience a small increase in coronary heart disease mortality compared to nonsmokers.

2. Similarly, pipe and cigar smokers show slight excesses of cerebrovascular death rates over nonsmokers.

Non-Neoplastic Bronchopulmonary Disease

1. Pipe and cigar smokers experience mortality rates from chronic bronchitis and emphysema that are intermediate between cigarette smokers and nonsmokers.

2. Pipe and cigar smokers have significantly more respiratory symptoms such as cough, sputum production, breathlessness, and wheezing than nonsmokers. A dose-response gradient is noted.

3. Little difference in pulmonary function was noted for pipe and cigar smokers as compared to nonsmokers.

4. Pipe and cigar smokers had far less pulmonary pathology at autopsy than did cigarette smokers.

Peptic Ulcer Disease

1. Cigar and pipe smokers experience higher death rates from peptic ulcer than nonsmokers: these rates, based on prospective mortality studies, indicated higher rates for gastric ulcer than for duodenal ulcer.

2. Retrospective and cross-sectional studies failed to find an association between pipe smoking and peptic ulcer.

Snuff and Chewing Tobacco and Oral Lesions

Snuff and chewing tobacco have not been found to increase mortality (either overall or cause-specific) in the United States. Asian studies have found an association between tobacco chewing and leukoplakia as well as oral cancer. These differences between the American and Asian studies can partially be explained by nutritional factors but are confounded by other factors such as the use of other tobacco products along with the use of snuff and chewing tobacco in the United States.

Constituents of Tobacco Smoke

Extensive research has advanced the cultivation of tobacco varieties with commercially desirable characteristics. This research has also been directed toward precursor-product relationships among specific leaf tobacco components, agronomic characteristics, cigarette and smoke constituents, and biological responses involving 151 variables. Multivariate analysis has revealed that leaf characteristics serve as markers to predict individual smoke components. Thus, there is promise of modification for more desirable qualities and use of tobacco.

Smoke Formation

1. The lighted cigarette generates about 2,000 compounds by a variety of processes including hydrogenation pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation.

2. Tobacco smoke has been separated into gas and particulate phases.

3. The gas phase components shown to produce undesirable effects include carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile N-nitrosamines, hydrogen cyanide, volatile sulfur compounds, nitriles and other nitrogen-containing compounds, volatile hydrocarbons, alcohols, aldehydes, and ketones.

4. The particulate phase consists generally of nicotine, water, and "tar". "Tar," which is the total particulate matter after subtracting moisture and nicotine, consists primarily of a wide variety of species of polycyclic aromatic hydrocarbons (PAH) to which carcinogenicity is attributed.

(a) These PAH include non-volatile N-nitrosamines, aromatic amines (regarded as being the etiologic agents in bladder cancer), isoprenoids, pyrenes, benzopyrenes, chrysenes, anthracenes, fluoranthenes, carcinogenic aza-arenes such as the acridines and carbazoles, and the mutagenic aza-arenes such as the quinolines and phenanthridines.

(b) In addition, the "tar" contains simple and complex phenols, cresols and naphthols, alkanes and alkenes, benzenes and naphthalenes, carboxylic acids, and metallic ions, as well as

radioactive compounds such as potassium-40, lead-210, polonium-210 and radium-226.

(c) The particulate phase also contains agricultural chemicals and additives as flavoring agents and humectants.

Toxic and Carcinogenic Agents

Compounds in cigarette smoke have been classified by an expert panel into:

1. Those judged most likely to contribute to the health hazards of smoking.

(a) Carbon monoxide (gas phase).

(b) Nicotine and "tar" (particulate phase).

2. Those judged as probable contributors to the health hazards of smoking.

(a) Gas phase: acrolein, hydrocyanic acid, nitric oxide and nitrogen dioxide.

(b) Particulate phase: cresols and phenol.

3. Those judged as suspected contributors to the health hazards of smoking.

(a) Gas phase: acetaldehyde, acetone, acetonitrile, acrylonitrile, ammonia, benzene, 2-3 butadione, carbon dioxide, crotononitrile, ethylamine, formaldehyde, hydrogen sulfide, methacrolein, methyl alcohol, and methylamine.

(b) Particulate phase: butylamine, dimethylamine, DDT, endrin, furfural, hydroquinone, nickel compounds, pyridine.

These compounds have been so designated not only because of their harmful actions but also because of their concentrations in tobacco smoke. Although other constituents are considered toxic, they are not present in concentrations deemed a health hazard.

A number of tumor initiators, co-carcinogens, and organ-specific carcinogens have been isolated and identified. The majority of co-carcinogens remain to be identified. The increased risk cigarette smokers have for cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic and N-nitrosamines.

Physiological Response to Cigarette Smoke

1. The smoking of a cigarette seems to satisfy a smoker's physiological and psychological needs, and it is generally accepted that nicotine is the principal constituent responsible for cigarette smokers' pharmacologic responses.

2. Nicotine causes the release of catecholamines, epinephrine and norepinephrine. Several physiologic responses are attributed to nicotine and/or catecholamines such as increased heart rate and blood

pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, oxygen consumption, coronary blood flow and arrythmias, increased mobilization and utilization of free fatty acids, hyperglycemic effects, and a decreased patellar reflex response.

3. Considerable evidence exists, although it is not uniformly accepted, that smoking patterns of chronic smokers are to a large degree dependent on the nicotine content of the cigarette and dependent on what the nicotine delivery would be when measured by the standard methodology. Smoking patterns are dependent, to varying degrees, on the type of cigarette smoked, the number of cigarettes smoked, the length of the cigarette burned, the number of puffs, and the depth and length of inhalation.

Reduction in Toxic Activity of Cigarette Smoke

1. At the present time, selective filtration of carbon monoxide has not proven feasible.

2. Charcoal filtration has proven successful in the removal of certain ciliatoxic substances from the gas phase of cigarette smoke.

3. Selected types of cellulose acetate filter tips selectively remove volatile phenols.

4. Cigarette fillers low in wax-layer components deliver smoke reduced in catechols, but there is a question as to whether selective reduction in cathechols leads to a significant reduction of the tumorigenic potential of cigarette smoke.

5. Lowering nitrate content of tobacco reduces volatile N-nitrosamines in tobacco smoke, but it has not been shown that a reduction of this compound will lead to a significant reduction in the tumorigenic potential of the smoke.

6. Experimentally, a dose-response gradient is demonstrable for "tar" application or smoke inhalation and tumor yield. A number of technical approaches, including modification of the filler, has reduced the "tar" content of smoke.

7. Similar technical approaches have reduced the nicotine content of tobacco smoke.

8. There is a possibility that nonvolatile N-nitrosamines can be reduced by addition of specific bacteria during the processing of tobacco. Selective filtration is not feasible for their removal.

9. A number of methods have led to reduction of "tar" and of toxic and tumorigenic agents in the smoke of cigarettes. Several approaches have led to the reduction of the ciliotoxicity and to selective reduction of the carcinogenicity and tumor-promoting activity of the smoke of experimental cigarettes. Many of these methods have already been incorporated in today's modified, blended U.S. cigarette.

Behavioral Aspects of Smoking

Because of the research over the past 15 years, much is now known about the health dangers of smoking. But research into reasons why the habit is so widespread and difficult to break is still in its infancy; little is known for certain, and questions far outnumber answers.

This part of the report summarizes current understanding of the biological, behavioral, and psychosocial aspects of the cigarette smoking habit and the dependence process associated with smoking. It is no exaggeration to say that smoking is the prototypical substance-abuse dependency and that improved knowledge of this process holds great promise for prevention of risk. Establishment and maintenance of the smoking habit are, obviously, prerequisite to the risk, and cessation of smoking can eliminate or greatly reduce the health threat.

Among the findings, tentative conclusions, and areas for research presented in this section are the following:

1. Nicotine, the most powerful pharmacological agent in cigarette smoke, has been proposed as the primary incentive in smoking and may be instrumental in the establishment of the smoking habit. The proposition that heavy smokers adjust their plasma nicotine levels is compatible with the observation that regular smokers commonly consume about 20 to 30 cigarettes during the smoking day (approximately one every 30 to 40 minutes) and that the biological half-life of nicotine in humans is approximately 20 to 30 minutes.

2. Recent research suggests that specific central nervous system receptor sites for nicotine can be blocked in a fashion analagous to the opiate antagonists. This phenomenon has implications for understanding the effect of nicotine on the body as well as in helping former smokers to maintain abstinence.

3. By far the most common, and clinically the most important, symptom to appear following withdrawal from tobacco is craving for tobacco. The importance of the tobacco-withdrawal syndrome is its provocative role in relapse among abstinent smokers. Abrupt and total withdrawal from tobacco is associated with a withdrawal syndrome that subsides more quickly and is no worse than that seen in partial abstinence. A partially-abstinent smoker is in a chronic state of withdrawal that typically leads to relapse and a return to baseline rates of smoking.

4. There is fragmentary evidence suggesting that the abstinence syndrome is more severe in women than in men, and it seems likely that this is at least partly responsible for lower rates of successful cessation among women.

5. Little is known about the millions of smokers who have quit on their own. It has been estimated that 95 percent of the 29 million smokers who have quit since 1964 have done so on their own.

6. Survey data show that only one-third or less of smokers motivated to quit are interested in formal programs, and only a small minority of

those who do express an interest actually attend programs when offered. It thus appears that available objective outcome data may be based on a small minority sample of smokers at large.

7. Objective data are lacking on most of the smokers who have been willing to attend formal programs. Public service clinics continue, but lack of objective outcome data precludes the evaluation of their efficacy. Similarly, proprietary programs remain virtually unmonitored and unevaluated in an objective fashion. Controlled research has yet to produce a clearly superior intervention strategy. However, rapidly accumulating and improving data now suggest that multicomponent interventions offered by intervention teams with practical knowledge regarding the smoking problem are the most encouraging.

8. Too few carefully designed and implemented longitudinal studies exist in the area of smoking in children and adolescents to allow for true evaluation of the effectiveness of many past programs developed for them.

9. Inferences about the evolution of smoking suggest that by the end of the ninth grade very few adolescents are addictive smokers; the critical level of the onset of addictive smoking appears to be in high school. Therefore, the true impact of any deterrence-of-smoking program with adolescents may not even be measurable until after the adolescent has entered high school. This problem is not unlike the recidivism encountered in virtually all smoking cessation programs.

10. Too many programs for youth have focused on information about smoking or fear of serious disease due to smoking. Adolescents are present-oriented and appear to be less influenced by messages concerning smoking that focus exclusively on long-term dangers.

11. A focus on research into prevention of the onset of addictive smoking appears to be a reasonable parallel course to follow along with efforts at control and cessation.

12. A promising new approach may be in the "inoculation" of adolescents against various pressures to smoke which apparently override their knowledge about the dangers of smoking. The approach involves strategies to resist peer pressure, emphasis on understanding of how advertising and mass media work to influence smoking, and provision of information on ways to resist the models of parents, siblings, and older students who smoke. Also included is a focus on the immediate physiological effects of smoking rather than on long-term effects.

Education and Prevention

Research strongly indicates that educators and health care providers teach youth about smoking and health as much by example as through formal instruction. But, despite a proliferation of a wide variety of educational programs aimed at youth and adults, it is not known which methods are most effective in preventing the start of smoking or in

promoting cessation. Summarized below are some of the research findings, program and experimental approaches, and needs in the areas of smoking education and prevention discussed in this part of the report.

1. Most educational programs are based on what seems reasonable rather than on sound theoretical models. It is logical to assume, for example, that young people who know about the harmful effects of cigarette smoking on health will resist smoking. Thus, many programs are based on knowledge dissemination and a health threat. However, we know that 94 percent of teenagers say that smoking is harmful to health and 90 percent of teenage smokers are aware of the health threat.

2. The trend in adult education programs is toward emphasis on personal responsibility for individual health and adoption of a health-promoting lifestyle.

3. Researchers find that "significant adults"—physicians, nurses, dentists, other health professionals, coaches, and parents—are powerful influences on teenage smoking. A nationwide survey of teenagers, for example, indicated that 72 percent of the nonsmokers identified physicians as the one group that could influence them not to start smoking; 43 percent of the smokers felt that the physician's advice would influence their decision to stop smoking.

4. Health professionals as a group have preceded the general public in improving their smoking habits; they have stopped smoking, moved to less hazardous forms of tobacco, or reduced the amount smoked.

5. Several studies of methodologies used in smoking education reported mixed results, with no method clearly predominating.

Introduction and Summary: References

(*1*) BRODERS, A.C. Squamous-cell epithelioma of the lip. A study of five hundred and thirty-seven cases. Journal of the American Medical Association 74(10): 656-664, March 6, 1920.

(*2*) BURNEY, L.E. Smoking and lung cancer—A statement of the Public Health Service. Journal of the American Medical Association 171: 1829-1837, 1959.

(*3*) CORNFIELD, J., HAENSZEL, W., HAMMOND, E.C., LILIENFELD, A.M., SHIMKIN, M.B., WYNDER, E.L. Smoking and lung cancer: Recent evidence and a discussion of some questions. Journal of the National Cancer Institute 22: 173-203, 1959.

(*4*) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Diseases. National Cancer Institute Monograph 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(*5*) HOLLAND, J.J. Dissertatio inaugur. med. chir. sistens Carcinoma labii inferioris absque sectione persanatum. In: Wolff, J. Die Lehre von der Krebskrankheit, Jena, 1911, Vol. 2, pp. 52-78.

(*6*) JAMES, G. Treatise on tobacco, tea, coffee and chocolate. (Translated from S. Paulli's Commentarius de abusu tabaci Americanorum veteri, et herbae thee Asiaticorium in Europa novo. 1665.) London, T. Osborn, 1746.

(*7*) LOMBARD, H.L., DOERING, C.R. Cancer studies in Massachusetts: Habits, characteristics, and environment of individuals with and without cancer. New England Journal of Medicine 198: 481-487, 1928.

(*8*) MILMORE, B.K., CONOVER, A.G. Tobacco consumption in the United States, 1880 to 1955. Agricultural Economic Research 8: 9-13, 1956.

(*9*) PEARL, R. Tobacco smoking and longevity. Science 87: 216-217, 1938.

(*10*) ROYAL COLLEGE OF PHYSICIANS. Smoking and Health. Summary and Report of the Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases. New York, Pitman Publishing Company, 1962,70 pp.

(*11*) SCIENCE. Smoking and Health. Joint Report of the Study Group on Smoking and Health. Science 125(3258): 1129-1133, June 7, 1957.

(*12*) SELTSER, R. Lung cancer and uranium mining. A critique. Archives of Environmental Health 10(6): 923-936, June 1965.

(*13*) SOEMMERRING, S. Th. De Morbis Vasorum Absorbentium Corporis Humani. Varrentrappii Wenneri, Traiectis ad Moenum, Publ. 1795, 105 pp.

(*14*) U.S. PUBLIC HEALTH SERVICE. A Reference Edition: 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.

(*15*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.

PART I

THE HEALTH CONSEQUENCES OF SMOKING

2. MORTALITY.

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Introduction

Cigarette smoking is the single most important environmental factor contributing to premature mortality in the United States. This preventable, premature mortality is due to increased death rates among cigarette smokers from several diseases, but primarily from ischemic heart disease, cancers of the respiratory tract, and the chronic obstructive pulmonary diseases, emphysema, and chronic bronchitis.

The world's literature on smoking and health at present consists of more than 30,000 published articles from thousands of studies conducted in every major country of the world. These data are housed in the Technical Information Center of the Office on Smoking and Health in the Department of Health, Education, and Welfare.

During the past 30 years, there have been eight large prospective epidemiological studies conducted that were specifically designed to delineate the relationship between tobacco smoking and the development of disease. Several of these studies were in progress at the time of the first report on smoking and health by the U.S. Government (*37*). Within the past 2 years, reports on long-term follow-up have been published from four of these studies, which are still in progress (*9, 19, 21, 33*). The longest follow-up comes from the study of British physicians, from which 20-year data have been published (*9*). The largest study is the American Cancer Society study of men and women in 25 States that enrolled more than one million subjects and is easily one of the largest studies of all time. Twelve-year follow-up data from this population have been published (*19*). A representative population study from Sweden includes data on men and women (*2*).

The relationship between smoking and overall mortality has been reviewed by the Department of Health, Education, and Welfare several times during the past 15 years. A report of the Advisory Committee to the Surgeon General of the Public Health Service was first published in 1964 (*37*). The subject was again reviewed in 1967, 1968, and 1978 in *The Health Consequences of Smoking* (*34, 35, 36*).

The effect of cigarette smoking on overall mortality as reported in the eight major prospective epidemiological studies is summarized in this chapter. Recently published data from these studies have resulted in numerous refinements in our understanding of smoking and overall mortality. The major conclusions drawn in 1964 still stand, but they are reinforced by the weight of evidence accumulated from these and other sources over the past 15 years. Conclusions regarding smoking and overall mortality reported in previous reports will not be presented here. The summary appearing at the end of this chapter is a synthesis of all that is currently known about smoking and overall mortality. It includes data from previous reports as well as current conclusions based on the most recently published data.

The Measures of Mortality

Overall mortality is a measure of the cumulative or total effect of a disease-causing agent on the health of a population. Overall mortality rates are particularly useful in determining the effect of agents that influence multiple organ systems and result in increased death rates from several diseases. Overall mortality is the best way to measure the sum of the risk due to cigarette smoking-related diseases. Smoking directly exposes multiple sites in the respiratory tract to the chemical constituents of tobacco smoke. This direct effect is most likely responsible for the increased mortality smokers experience from cancer of the lung, larynx, oral cavity, and esophagus, as well as the chronic obstructive diseases of the lung, emphysema, and chronic bronchitis. The more soluble compounds are absorbed into the blood stream where, unchanged or in some cases as toxic metabolites of parent compounds, they act upon susceptible tissues not directly exposed to cigarette smoke. This effect is most likely responsible for the increased mortality smokers experience from ischemic heart disease, aortic aneurysm, and cancers of the urinary bladder and pancreas. Because of these complexities, only overall mortality rates can present an accurate statement of the impact of smoking on the health of the population.

Although overall mortality is frequently used by epidemiologists and statisticians, it has little immediate application to the practice of many physicians, dentists, nurses, or other health professionals whose orientation is primarily clinical and who deal more with specific diseases and disease-specific mortality rates. Usually, when a disease-causing agent results in increased mortality for only one disease, there may be a sharp increase in the death rate for that specific disease, but there will be very little change in the overall mortality rate for the population. By contrast, cigarette smoking increases the death rates for several diseases. As a result, overall mortality rates are increased more than the disease-specific death rates for several of the diseases caused by cigarette smoking.

Overall mortality can be expressed in several ways. The most commonly used terms are listed below with a brief discussion of their significance.

1. Mortality Ratios: Obtained by dividing the death rate for a classification of smokers by the death rate of a comparable group of nonsmokers. A mortality ratio has been considered to reflect the degree to which a classification variable identifies or may account for variations in death rates. As such, it is a measure of relative risk that indicates the importance of that variable relative to uncontrolled variables—an indicator of *potential biological significance.*

2. Differences in Mortality Rates: Obtained by subtracting from the death rate for smokers, the death rate of a comparable group of nonsmokers. This measure reflects the added probability of death in a

TABLE 1.—Mortality ratios, differences in mortality rates and excess deaths by age as derived from two studies

	Age				
	35–44	45–54	55–64	65–74	75–84
U.S. Veterans Study (males)					
Total deaths	383	366	13,840	17,550	1,932
Death rates: nonsmokers	127	264	1,056	2,411	6,214
Death rates: cigarette smokers	232	728	1,819	4,032	8,417
Mortality ratio	1.83	2.76	1.72	1.67	1.36
Difference in mortality rates	105	464	763	1,621	2,257
Excess deaths as a percentage of total	33	43	21	17	8
25 State Study (males)					
Total deaths	631	5,297	8,427	8,125	3,968
Death rates: nonsmokers	210	406	1,202	3,168	7,863
Death rates: cigarette smoker	397	925	2,202	4,788	9,674
Mortality ratio	1.89	2.28	1.83	1.51	1.23
Difference in mortality rates	187	519	1,000	1,620	1,811
Excess deaths as a percentage of total	33	38	25	13	4

SOURCE: Hammond, E.C. (*17*), Kahn, H.A. (*26*).

1-year period for the smoker over that for the nonsmoker. As such, it is a measure of *personal health significance*, a means for the individual to estimate the added risk to which he or she is exposed.

3. Excess Deaths: Obtained by subtracting from the number of deaths occurring in a group of smokers, the number of deaths that would have occurred if that group of smokers had experienced the same mortality rates as a comparable group of nonsmokers. This measure is an indicator of the *public health significance* of the differences, since it measures the number of people affected and, therefore, the magnitude of the problem for society as a whole.

4. Life Expectancy: A concept that is easier to understand than to calculate. At a given age, it represents the average number of years one might be expected to live.

Table 1 illustrates the first three measures for five age groups of men from the U.S. Veterans Study and the American Cancer Society Study of Men in 25 States. Table 2 illustrates the effect of cigarette smoking on life expectancy using data from the 25-State Study and the U.S. Veterans Study. When compared to non-smokers, an average young male smoker (30 to 40 years of age) who smokes more than 40 cigarettes per day loses an estimated 8 years of life.

TABLE 2.—Estimated years of life expectancy (LE) for males at various ages by amount smoked, as derived from two studies

Cigarettes smoked per day	Age							
	30		40		50		60	
	LE	Years lost	LE	Years lost	LE	Years lost	LE	Years lost
25 State Study								
Nonsmokers	43.9	0	34.5	0	25.6	0	17.6	0
1–9	39.3	4.6	30.2	4.3	21.8	3.8	14.5	3.1
10–19	38.4	5.5	29.3	5.2	21.0	4.6	14.1	3.5
20–39	37.8	6.1	28.7	5.8	20.5	5.1	13.7	3.9
40+	35.8	8.1	26.9	7.6	19.3	6.3	13.2	4.4
	35		40		50		60	
U.S. Veterans Study								
Nonsmokers	43.5	0	38.7	0	29.4	0	20.8	0
1–10	41.0	2.5	36.3	2.4	27.5	1.9	19.0	1.8
10–20	38.7	4.8	34.1	4.6	25.2	4.2	17.2	3.6
21–39	36.7	6.8	32.0	6.7	23.4	6.0	15.8	5.0
40+	34.8	8.7	29.9	8.8	21.6	7.8	14.4	6.4

SOURCE: Hammond, E.C. (*17*), Rogot, E. (*31*).

The Major Prospective Epidemiological Studies

Below are brief outlines of the eight important prospective epidemiological studies and their results. Taken together, the eight studies encompass more than 16 million person-years of experience and over 300,000 deaths. The data are presented in Table 3. Numbers in the table have been rounded, for ease of presentation.

The British Doctors Study (*4*)

In 1951, the British Medical Association forwarded to all British doctors a questionnaire about their smoking habits. A total of 34,400 men and 6,207 women responded. With few exceptions, all men who replied in 1951 have been followed for 20 years. Further inquiries about changes in tobacco use and some additional demographic characteristics of the men were made in 1957, 1966, and 1972. More than 10,000 deaths have occurred in this population during the past 20 years.

The American Cancer Society 25-State Study (*17*)

In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women in a prospective study. All segments of the population were included except groups that could not be traced easily. A lengthy initial questionnaire was administered that contained

TABLE 3.—Outline of prospective studies of smoking and overall mortality

Authors	Doll Hill Peto Pike (*4-10*)	Hammond (*14,16-19*)	Dorn Kahn Rogot (*11,26,31,33*)	Hirayama (*21,23-25*)	Best Josie Walker (*1,13*)	Hammond Horn (*20*)	Weir Dunn Linden Breslow (*12,38*)	Cederlof Friberg Hrubec Lorich (*2*)
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 years	12 years	13 years 10 years	8 years	6 years	4 years	5–8 years	10 years
Number of deaths	10,072	150,000	87,000	21,000	11,000	12,000	4,700	4,500
Person years of experience	600,000	8,000,000	3,500,000	2,000,000	500,000	670,000	480,000	550,000

information on age, sex, race, education, place of residence, family history, past diseases, present physical complaints, occupational exposures, and various habits. Information on smoking included: type of tobacco used, number of cigarettes smoked per day, inhalation, age started smoking, and the brand of cigarettes used from which tar and nicotine content of the cigarette could be calculated. Nearly 93 percent of the survivors were successfully followed for a 12-year period.

The U.S. Veterans Study (*26*)

This study followed the mortality experience of 250,000 U.S. veterans who held Government life insurance policies in December of 1953. Almost all policy holders were white males. This group has been followed for 16 years. The most recent analysis was limited to overall mortality, as death certificates were not obtained for those who died during the last half of the study period. Smoking habits were determined only once, at the onset of the study.

Japanese Study of 29 Health Districts (*24*)

In late 1965, a total of 265,118 men and women in 29 health districts in Japan were enrolled in a prospective study. This represented from 91 to 99 percent of the population aged 40 and older in these districts. This study provides a unique opportunity to examine the relationship of cigarette smoking to death rates in a population with genetic, dietary, and other cultural differences from previously examined Western populations. At the time of the 8th year of follow-up, 11,858 deaths had occurred and there were 1,269,382 person-years of observation. The overall mortality rate for Japanese males who began smoking at a young age was quite similar to that reported for U.S. males by Hammond (*17*). Mortality ratios for most categories, however, are considerably lower than those reported for the United States, Canada, and Great Britain. This most likely reflects a lower average number of cigarettes smoked per day, an older age at initiation of smoking, or reduced inhalation of cigarette smoke among the Japanese.

In spite of these differences, the overall results of this study, including the dose-response relationships for the various diseases caused by smoking, are similar to the results of all the other major epidemiological studies. The reliability and accuracy of the methods of population selection used in other studies based on limited samples of the population are confirmed by this study based on a total population in a study area.

The Canadian Veterans Study (*1*)

Beginning in 1955, the Canadian Department of National Health and Welfare enrolled 78,000 men and 14,000 women in a study of smoking-related mortality. Information was obtained on age, detailed smoking

history, residence, and occupation. During the 6 years of follow-up, there were 9,491 deaths of males and 1,794 deaths of females. No recent follow-up has been reported.

The American Cancer Society 9-State Study (*20*)

In this study, 187,783 white males were followed for an average of 44 months. The study began in early 1952. There were 11,870 deaths in this population aged 50 to 70. The last significant report on this study was published in 1958.

California Men in Various Occupations (*12*)

This study examined the mortality experience of 68,153 men, 35 to 64 years of age, over a period of 482,658 person-years of observation. A total of 4,706 deaths occurred. These men were in nine occupational groups. The last published report from this study was in 1970.

The Swedish Study (*2*)

A probability sample of 55,000 Swedish men and women was surveyed in 1963. A 10-year follow-up on smoking-related mortality was published in 1975.

Mortality and Male Cigarette Smokers

Overall mortality rates for male cigarette smokers are significantly higher than for nonsmoking males. The mortality ratios are as low as 1.25 for Japanese males and as high as 1.83 for the males in the ACS 25-State Study. These results are shown in Table 4. Important evidence for a causal relationship between smoking and overall mortality is the demonstration of dose-response relationships. In most epidemiological studies, dosage has been measured by the number of cigarettes smoked daily at the time of entry into the study. Other dose variables include the maximum number of cigarettes smoked per day, age began smoking, the depth of inhalation, years of smoking, pack-years, tar and nicotine levels of the brand of cigarettes used, the number of puffs per cigarette, and the length of the unburned portion of the cigarette, as well as combinations of these variables into various dosage scores. All of these dosage variables have been shown in one study or another to contribute to the degree of risk involved in smoking. Several of the dosage variables as related to overall mortality are examined in this section.

Mortality and Amount Smoked

Mortality ratios for males currently smoking cigarettes only by amount smoked are presented for the eight major prospective studies in Table 4. Even males smoking one to nine cigarettes a day have a

TABLE 4.—Mortality ratios for males currently smoking cigarettes only, by amount smoked

Number of cigarettes per day	Doll (9)	Hammond (17)	Rogot (31,33)	Hirayama (25)	Best (13)	Hammond Horn (20)	Weir Dunn (38)	Cederlof (2)
	British doctors	Males in 25 States	U.S. veterans	Japanese	Canadian pensioners	Males in 9 States	California occupations	Swedish
Nonsmokers	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1-9	1.41(1-15)	1.45	1.25		1.41	1.34	1.44	1.20(1-7)
10-20	1.57(16-25)	1.75	1.51		1.56	1.70	1.79	1.40(8-15)
21-39	2.16(>25)	1.90	1.69		1.65(>20)	1.96	2.27	1.80(>16)
40+		2.20	1.89			2.23	1.83	
All smokers	1.63	1.83	1.55	1.25	1.54	1.74	1.78	1.58

TABLE 5.—Mortality ratios for male cigarette-only smokers, by number of cigarettes smoked per day and age. U.S. veterans 1954 cohort, 16-year followup

Number of cigarettes per day	Age				
	30–34	35–44	45–54	55–64	65–74
Nonsmokers	1.00	1.00	1.00	1.00	1.00
less than 10	1.94	1.44	1.44	1.20	1.15
10–20	1.27	1.79	1.64	1.49	1.30
21–39	1.76	2.23	2.10	1.67	1.42
40+	2.33	2.72	2.13	1.86	1.65
All smokers	1.52	1.95	1.83	1.53	1.32

SOURCE: Rogot, E. (*31,33*).

significant mortality ratio that varies from 1.25 to 1.45. Smokers of more than two packs of cigarettes a day have an overall mortality ratio that varies from 1.83 to 2.23.

Mortality at Different Ages

Overall mortality ratios by amount smoked at different ages for several studies are presented in Tables 5 through 8. There is a decrease in the mortality ratio with each increase in age for each smoking category. Mortality ratios are consistently more than 2.00 for heavy smokers between the ages of 30 to 50. These ratios decrease gradually with age, but are still about 1.35 for men over 75 years of age. This decline does not imply a decrease in the effect of cigarette smoking on health. Overall mortality rates increase dramatically with age in both smokers and nonsmokers. If one uses another measure of mortality and looks at the difference in death rates between smokers and nonsmokers as illustrated in Table 1, it can be seen that the difference in overall mortality rates increases with age even though the mortality ratio decreases.

The decreasing mortality ratio with age is probably due to another factor that should be considered. The population of older males who smoke two packs of cigarettes per day is probably quite different than a younger group of two-pack-a-day smokers.

Mortality by Duration of Smoking

Overall mortality ratios increase with the duration of the smoking habit. Mortality ratios by number of years smoked from two studies are presented in Tables 9 and 10. The mortality ratios remain quite low, only slightly above the rates for nonsmokers for the first 5 to 15 years of the smoking habit, and then increase more rapidly as the years

TABLE 6.—Mortality ratios for male cigarette-only smokers, by number of cigarettes smoked per day and age. Males in 25 States

Number of cigarettes per day	Age				
	35–44	45–54	55–64	65–74	75–84
Nonsmokers	1.00	1.00	1.00	1.00	1.00
1–9	**	1.84	1.53	1.50	1.36
10–19	1.36	2.26	1.92	1.65	1.55
20–39	1.91	2.41	2.05	1.71	1.26
40+	2.59	2.76	2.26	1.81	**
All smokers	1.82	2.20	1.86	1.58	1.35

SOURCE: Hammond, E.C. (*17*).

TABLE 7.—Mortality ratios for male cigarette-only smokers, by number of cigarettes smoked per day and age. Canadian pensioners

Number of cigarettes per day	Age					
	30–34	35–44	45–54	55–64	65–74	75+
Nonsmokers	1.00	1.00	1.00	1.00	1.00	1.00
1–9	0.72	1.25	1.07	1.50	1.32	1.31
10–20	1.22	1.36	1.20	1.94	1.40	1.33
20+	1.01	1.35	1.27	2.15	1.45	1.42
All smokers	0.90	1.63	1.21	1.89	1.45	1.31

SOURCE: Doll, R. (*9*).

TABLE 8.—Mortality ratios for male cigarette-only smokers, by number of cigarettes smoked per day and age. Males in nine States

Number of cigarettes per day	Age			
	50–54	55–59	60–64	65–69
Nonsmokers	1.00	1.00	1.00	1.00
1–9	1.43	1.15	1.46	1.37
10–20	1.72	1.65	1.83	1.59
21–39	2.11	1.83	2.20	1.65
40+	2.30	2.84	1.56	1.84
All smokers	1.85	1.69	1.84	1.55

SOURCE: Hammond, E.C. (*20*).

of smoking increase. Mortality ratios are as high as 1.66 for male cigarette smokers who have smoked for 35 or 40 years.

TABLE 9.—Age-adjusted mortality ratios for male cigarette-only smokers, by duration of smoking. Canadian veterans

Duration of smoking in years	Mortality ratio
Under 5	1.05
5–14	1.30
15–29	1.33
30–39	1.53
40+	1.66
All smokers	1.52

SOURCE: Best, E.W.R. (*1*)

TABLE 10.—Age-adjusted mortality ratios for male cigarette smokers who began smoking after the age of 20, by duration of smoking. U.S. veterans

Duration of smoking in years	Mortality ratio
Under 15	1.10
15–24	1.34
25–34	1.44
35+	1.66

SOURCE: Kahn, H.A. (*26*).

Mortality by Age Began Smoking

Overall mortality ratios exhibit an inverse relationship with age of initiation of the smoking habit. Table 11 displays data from the U.S. Veterans Study. Cigarette-only smokers who began smoking after the age of 25 have a mortality ratio of 1.32. For individuals who began smoking under the age of 15, the mortality ratio is 1.86. Data from the Japanese study are shown in Table 12. Again, a dose-response relationship is demonstrated but at a lower level than in the United States. When the Japanese data are broken down further "by age at start of study" and "age began smoking," as seen in Table 13, it is demonstrated that smokers who began smoking under the age of 15 have mortality ratios that are very similar to those in the United States data. Tables 14 and 15 show overall mortality ratios by "age began smoking" and "age at beginning of study" for the U.S. veterans and U.S. males in 25 States.

Overall mortality ratios by "age began smoking" and "number of cigarettes smoked per day" for the ACS Study of 25 States and the U.S. Veterans Study are presented in Tables 16 and 17. As expected,

TABLE 11.—Age-adjusted mortality ratios for male cigarette-only smokers, by age began smoking. U.S. veterans 1954 cohort

Age began smoking in years	Mortality ratio
Nonsmokers	1.00
25+	1.32
20–24	1.51
15–19	1.64
Under 15	1.86

SOURCE: Rogot, E. (*51, 53*).

TABLE 12.—Age-adjusted mortality ratios for male cigarette-only smokers, by age began smoking. Japan

Age began smoking in years	Mortality ratio
Nonsmokers	1.00
25+	1.19
20–24	1.19
Under 20	1.27

SOURCE: Hirayama, T. (*22*).

TABLE 13.—Age-adjusted mortality ratios for Japanese male cigarette smokers, by age began smoking and age at start of study

Age began smoking in years	Age at start of study		
	40–49	50–59	60–69
Nonsmokers	1.00	1.00	1.00
35+	1.53	1.08	1.02
30–34	0.89	1.11	1.29
25–29	0.91	1.17	1.19
20–24	0.82	1.16	1.19
15–19	0.92	1.31	1.29
Under 15	2.26	3.04	1.86

SOURCE: Hirayama, T. (*22*).

overall mortality ratios increase the younger a person begins smoking and the greater the number of cigarettes smoked per day.

Mortality by Inhalation of Cigarette Smoke

Inhalation of tobacco smoke is an important dosage variable. Most of the excess mortality associated with cigarette smoking results from diseases that require inhalation of smoke well into the lungs in order to

TABLE 14.—Age-adjusted mortality ratios for male cigarette-only smokers, by age began smoking and age at start of study. U.S. veterans 1954 cohort

Age began smoking in years	Age at start of study				
	30–34	35–44	45–54	55–64	65–74
Nonsmokers	1.00	1.00	1.00	1.00	1.00
25+	**	1.48	1.67	1.36	1.20
20–24	1.41	1.87	1.72	1.56	1.39
15–19	1.44	2.00	2.17	1.70	1.45
Under 15	2.00	2.18	2.25	2.02	1.42

SOURCE: Rogot, E. (*51, 53*).

TABLE 15.—Age-adjusted mortality ratios for male cigarette-only smokers, by age began smoking and age at start of study. Males in 25 States

Age began smoking in years	Age at start of study			
	45–54	55–64	65–74	75–84
Nonsmokers	1.00	1.00	1.00	1.00
30+	1.40	1.33	1.23	1.10
25–29	1.81	1.75	1.25	**
20–24	2.13	1.73	1.52	1.27
15–19	2.49	2.11	1.84	1.58
Under 15	3.01	2.26	2.00	1.59

SOURCE: Hammond, E.C. (*17*).

TABLE 16.—Age-adjusted mortality ratios for male cigarette-only smokers aged 55–64, by age began smoking and current number of cigarettes smoked per day. Males in 25 States

Age began smoking in years	Current number of cigarettes per day				
	Nonsmokers	1–9	10–19	20–39	40+
25+	1.00	1.34	1.68	1.48	1.77
15–24	1.00	1.45	1.89	2.05	2.23
Under 15	1.00	**	2.15	2.19	2.58

SOURCE: Hammond, E.C. (*17*).

expose target organs directly or through absorption of toxic substances into the circulatory system. Ischemic heart disease, lung cancer, and chronic obstructive disease are not as likely to develop in individuals who do not inhale smoke. Techniques for quantitating inhalation have been developed using carboxyhemoglobin as an index of smoke inhalation, but these methods have not been applied to studies of overall mortality. Most studies asked the smoker to report subjectively

TABLE 17.—Age-adjusted mortality ratios for males smoking cigarettes only, by amount smoked and age began smoking. U.S. veterans 1954 cohort

Age began smoking in years	Current number of cigarettes per day		
	Nonsmokers	1–20	21+
20+	1.00	1.36	1.59
Under 20	1.00	1.56	1.82

SOURCE: Rogot, E. (*31, 33*).

on his own inhalation practices. Certainly, self-reporting of inhalation is subject to considerable variation, but it may not be as inaccurate as might be presumed. Available data show the expected dose-response relationship between inhalation of cigarette smoke and overall mortality. Table 18 demonstrates that with advancing age the percentage of moderate and deep inhalers drops and the percentage of none-to-slight inhalers increases. This is consistent with increased mortality for those who inhale. It also makes the interesting point that a smoker who survives to old age is different from the younger smoker. It is likely that the lower mortality ratios experienced by older smokers are partly a reflection of the fact that they smoke in a less hazardous fashion than do younger smokers. Older smokers are less likely to inhale than younger smokers. It is also likely that they take fewer puffs per cigarette and smoke fewer cigarettes per day. If they have been faithful to their brand of cigarettes, they are likely to be smoking an "older" brand. The brand is likely to be unfiltered and more typical of the cigarettes sold 30 to 40 years ago which contained twice the tar and nicotine of the average cigarettes sold today. Tables 19, 20, and 21 show age-adjusted mortality ratios by degree of inhalation and number of cigarettes smoked per day and age at start of study for three of the large prospective studies. The overall mortality ratio is 2.80 for the moderate-to-deep inhaler who smokes 40 or more cigarettes per day. The overall mortality ratio is 2.53 for 45- to 54-year-old men who inhale deeply, but is 1.02 for noninhalers who are 75 to 84 years old. In the Canadian study, the highest mortality ratio was 2.11 for those 60 to 69 years old who reported inhaling cigarette smoke. Hammond reported a mortality ratio of 1.41 for noninhalers who are 45 to 54 years old (*15*). This suggests that cigarette smokers may underestimate the extent to which they inhale cigarette smoke.

Mortality by Tar and Nicotine Content of Cigarettes

Overall mortality increases with the tar and nicotine content of cigarette smoke. This relationship was recently examined by Hammond, et al. (*19*). In this study, tar and nicotine levels (T/N) were defined as follows: "High" T/N, 25.8–35.7 mg tar and 2.0–2.7 mg

TABLE 18.—Percent distribution of male cigarette smokers by degree of inhalation of cigarette smoke and age. Males in 25 States

Degree of inhalation	Age			
	40–49	50–59	60–69	70–79
None	3.62	6.11	11.46	19.74
Slight	10.97	13.64	20.18	25.56
Moderate	57.94	56.31	51.10	40.82
Deep	27.65	23.91	17.25	13.88
Total	100.00	100.00	100.00	100.00

SOURCE: Hammond, E.C. (*19*).

TABLE 19.—Age-adjusted mortality ratios for male cigarette-only smokers, by degree of inhalation of cigarette smoke and current number of cigarettes per day. Subjects aged 45–54 at start of study. Males in 25 States

Degree of inhalation	Number of cigarettes per day			
	1-9	10-19	20-39	40+
None-slight	1.70	1.99	2.34	2.33
Moderate-deep	1.95	2.35	2.42	2.80

SOURCE: Hammond, E.C. (*17*).

TABLE 20.—Age-adjusted mortality ratios for male cigarette-only smokers, by degree of inhalation of cigarette smoke and age at start of study. Males in 25 States

Degree of inhalation	Age at start of study			
	45–54	55–64	65–74	75–84
None	1.41	1.43	1.32	1.02
Slight	1.67	1.71	1.31	1.19
Moderate	2.06	1.68	1.53	1.10
Deep	2.53	1.88	1.68	**

SOURCE: Hammond, E.C. (*17*).

nicotine; "Medium" T/N, 17.6–25.7 mg tar and 1.2–1.9 mg nicotine; "Low" T/N, less than 17.6 mg tar and less than 1.2 mg nicotine. Table 22 shows the overall mortality ratios of male and female smokers by these tar and nicotine levels. In this instance, the mortality ratio of the "high" T/N smokers is represented as 1.00 so as to illustrate the reduction in overall mortality that occurs with lower T/N cigarettes. There is a small but statistically significant (P. less than 0.0005) reduction in the risk of dying with the use of lower T/N cigarettes. The mortality ratio was reduced to 0.91 for the "medium" T/N smokers and

TABLE 21.—Age-adjusted mortality ratios for male cigarette-only smokers, by degree of inhalation of cigarette smoke and age at start of study. Canadian veterans

Degree of inhalation	Age at start of study			
	30–39	40–49	50–59	60–69
Nonsmokers	1.00	1.00	1.00	1.00
Do not inhale	0.61	0.61	1.10	1.78
Inhale smoke	1.29	1.12	1.58	2.11

SOURCE: Best, E.W.R. (*1*).

TABLE 22.—Adjusted mortality ratios for males and females, by tar and nicotine content of cigarettes usually smoked

Sex	Mortality ratios		
	"High" T/N	"Medium" T/N	"Low" T/N
Males	1.00	0.94	0.85
Females	1.00	0.88	0.83
Total	1.00	0.91	0.84

SOURCE: Hammond, E.C. (*19*).

TABLE 23.—Adjusted mortality ratios for males and females smoking low T/N cigarettes and subjects who never smoked regularly

Sex	Mortality ratios	
	"Low" T/N	Nonsmokers
Males	1.00	0.61
Females	1.00	0.74
Total	1.00	0.66

SOURCE: Hammond, E.C. (*19*).

was further reduced to 0.84 for the "low" T/N smokers. The mortality ratios are lower for females than for males.

In a separate analysis, a comparison was also made between the mortality ratios of "low" T/N smokers and nonsmokers. These data are presented in Table 23. The mortality ratio of the "low" T/N group was designated as 1.00. Nonsmokers have overall mortality ratios that are about half those of "low" T/N smokers.

The combined data from these two tables are shown in Table 24. Here, mortality ratios are calculated using nonsmokers as the

TABLE 24.—Overall mortality ratios of cigarette smokers compared to nonsmokers, by sex and by tar and nicotine content of cigarettes usually smoked

Sex	Non-smokers	"Low" T/N	"Medium" T/N	"High" T/N
Males	1.00	1.66	1.85	1.96
Females	1.00	1.37	1.45	1.65
Total	1.00	1.52	1.64	1.80

SOURCE: Hammond, E.C. (*19*).

reference. Combining these data from two separate analyses that are not exactly comparable results in figures that are only approximate.

Hammond (*19*) also compared death rates of smokers of relatively few (1–19) "high" T/N cigarettes with those of smokers who smoked relatively large numbers (20–39) of "low" T/N cigarettes. The death rates of these two groups were very similar and the difference between them was not statistically significant.

Mortality and Female Cigarette Smokers

It is important that attention be called specifically to the mortality that females experience as a result of cigarette smoking. There has been an increase in smoking among teenage girls over the past 10 years. At present, the percentages of teenage boys smoking and teenage girls smoking are nearly identical. For some ages, there are more teenage girl smokers than boy smokers. Over the past 10 years, there has been a gradual reduction in the percentage of the adult population that is smoking. Men have quit in greater numbers than women. There has been only a modest drop in the percentage of women who are smoking. In Canada and several European countries, smoking is decreasing among men but increasing among women. In the United States, physicians, dentists, and pharmacists have been the most successful professional groups in giving up smoking, but in the past several years there has been an increase in smoking among nurses.

Several suggestions have been made as to why women do not quit smoking. It may be that women do not generally perceive smoking as a threat to their health. Lung cancer, heart attacks, and emphysema are diseases that affect men more commonly than women. Women may feel that they are in a low-risk group. Women took up smoking later than men, generally smoked filter cigarettes, and smoked fewer cigarettes per day than men. Lower overall death rates for women smokers are due to lower exposure to cigarette smoke.

Cigarette smoking for some women may be symbolic of equality with men. It is known that the smoking habits of women employed

TABLE 25.—Age-adjusted mortality ratios of female cigarette smokers, by number of cigarettes smoked per day and age. 25-State Study

Number of cigarettes per day	Age				
	35-44	45-54	55-64	65-74	75-84
Nonsmokers	1.00	1.00	1.00	1.00	1.00
1-9	0.90	0.95	0.99	1.09	1.07
10-19	0.97	1.22	1.31	1.18	1.21
20-39	1.35	1.54	1.46	1.51	**

SOURCE: Hammond, E.C. (17).

outside the home match the smoking habits of men in various occupations where men and women hold equal positions. Women with the lowest rate of smoking are housewives who at present have few male counterparts with whom to identify.

Recent surveys have shown that women are also concerned about weight gain that may accompany quitting smoking. Any significant weight gain on quitting represents an increased intake of food, but if one watches the diet on smoking cessation, weight gain can be avoided; in fact, weight loss can be achieved.

In recent years, a few investigators have studied the relationships between cigarette smoking and the development of lung cancer and coronary heart disease in women. Death rates for these diseases are similar in women and men who have similar levels of exposure to cigarette smoke; the associations are outlined in later chapters dealing with specific diseases. Overall mortality rates for women available at present are from studies initiated 10 to 20 years ago, and thus reflect the differences in accumulated exposure that were operative at that time.

Overall mortality in women varies in the same direction and in a similar degree as men for the dosage variables commonly measured. Overall mortality for women increases with the number of cigarettes smoked per day (Tables 25, 26, and 27). Table 26 shows that the overall mortality ratio is 2.19 for females smoking more than two packs a day and inhaling moderately to deeply. Table 27 demonstrates that the mortality ratio is 1.85 for females smoking more than two packs per day who began smoking between the ages of 15 and 24. Mortality ratios by "inhalation" and "age at start of study" are shown in Table 28. Noninhaling smokers have mortality ratios that are similar to nonsmokers. Females with an average age of 50 who inhale smoke deeply have a mortality ratio of 1.78.

Mortality and Ex-Smokers

There is a general recognition among smokers and nonsmokers alike that cigarette smoking is a major cause of disease and death in the

TABLE 26.—Age-adjusted mortality ratios of female cigarette smokers, by number of cigarettes smoked per day and degree of inhalation. Subjects aged 45–54 at start of study. 25–State Study

Number of cigarettes per day	Degree of inhalation of smoke	
	None-Slight	Moderate-Deep
1-9	0.85	1.04
10–19	1.27	1.17
20–39	1.41	1.58
40+	**	2.19

SOURCE: Hammond, E.C. (*17*).

TABLE 27.—Age-adjusted mortality ratios of female cigarette smokers, by number of cigarettes smoked per day and age began smoking. Subjects aged 45–54 at start of study. 25–State Study

Number of cigarettes per day	Age began smoking	
	25+	15–24
Nonsmokers	1.00	1.00
1–9	0.95	0.88
10–19	1.17	1.23
20–39	1.33	1.61
40+	**	1.85

SOURCE: Hammond, E.C. (*17*).

TABLE 28.—Age-adjusted mortality ratios of female cigarette smokers, by number of cigarettes smoked per day and degree of inhalation and age. 25–State Study

Degree of inhalation	Age				
	35–44	45–54	55–64	65–74	75–84
Nonsmokers	1.00	1.00	1.00	1.00	1.00
None	**	1.01	1.11	1.12	0.96
Slight	1.22	1.21	1.28	1.26	1.21
Moderate	1.05	1.30	1.32	1.41	**
Deep	1.40	1.78	1.64	**	**

SOURCE: Hammond, E.C. (*17*).

United States. Smokers are now asking the question: "Will it help me if I quit smoking?" Some of the first evidence concerning death rates in ex-smokers required explanation. The data from the Hammond and Horn study of men in nine States are presented in Table 29. It can be seen that the mortality ratios of ex-smokers were higher in the first year after quitting than for continuing smokers. After the first year,

TABLE 29.—Age-adjusted mortality ratios for males who are ex-smokers of cigarettes, by former amount smoked per day and years since stopped smoking. Males in nine States

Years since stopped smoking	Cigarettes formerly smoked per day	
	1–19	20+
0 (Smokers)	1.61	2.02
Under 1	2.04	2.69
1–10 years	1.30	1.82
10+ years	1.08	1.50

SOURCE: Hammond, E.C. (*20*).

however, death rates for ex-smokers fell progressively so that after 10 years the former smokers of 1 to 19 cigarettes had a mortality ratio of only 1.08.

The explanation for the higher death rates in the 1st year after quitting is found in the fact that both healthy and sick individuals quit smoking. The higher mortality ratio is experienced by those who quit because of illness and not by those who quit for better health. In the study of U.S. veterans, a differentiation was made between ex-smokers who stopped smoking on the recommendation of a doctor and those who quit for other reasons. About 10 percent of the smokers quit on doctors' orders; this group had much higher mortality ratios than those who stopped for other reasons.

These data are presented in Table 30, where the mortality ratios for ex-smokers by "years since stopping smoking," "maximum amount smoked," "age began smoking," and "reason for quitting" are examined. There is a direct relationship between mortality rates and the maximum amount smoked, an inverse relationship between mortality and "years since stopped smoking," and also an inverse relationship between mortality and "age began smoking."

A detailed analysis of the mortality experience of ex-smokers who stopped for reasons other than doctors' orders is given in Figures 1 through 4. This information is on ex-smokers, aged 55 to 64, from the 1954 cohort of the U.S. Veterans Study, who formerly smoked from 21 to 39 cigarettes per day. "Years since stopping smoking" is considered as a variable and the mortality rates are compared with those of current cigarette smokers and nonsmokers. Annual probabilities of dying are plotted on a logarithmic scale. This results in a fairly smooth and linear pattern for both smokers and nonsmokers. These lines also appear to be parallel, or perhaps to diverge slightly. This indicates an approximately constant or slightly increasing excess risk of dying

TABLE 30.—Mortality ratios of ex-smokers of cigarettes only who quit smoking on doctors orders and for other reasons, by certain dosage variables. U.S. veterans 1954 cohort, 16-year followup

Years since stopped smoking

Years since stopped	Mortality ratios: Quit for various reasons	Mortality ratios: Quit on doctors orders
<5	1.23	1.55
5–9	1.23	1.43
10–14	1.14	1.77
15–19	1.04	1.35
>19	1.06	1.16
Total	1.18	1.52

Number of cigarettes per day

No. of cigarettes per day	Mortality ratios: Quit for various reasons	Mortality ratios: Quit on doctors orders
<10	1.00	1.42
10–20	1.17	1.48
21–39	1.30	1.53
>39	1.32	1.60
Total	1.18	1.52

Age started smoking

Age began (years)	Mortality ratios: Quit for various reasons	Mortality ratios: Quit on doctors orders
<15	1.36	1.59
15–19	1.20	1.55
20–24	1.12	1.49
>24	1.15	1.34
Total	1.18	1.52

SOURCE: Rogot, E. (*33*).

among smokers, compared to nonsmokers over the 16-year period. It would be expected that the mortality experience of ex-smokers initially would be similar to that of smokers, but with the passing of time the mortality risk should move progressively closer to that of nonsmokers. Figure 1 illustrates this. For ex-smokers who quit less than 5 years prior to the beginning of the study, the mortality risk is at

first nearly identical to that of smokers. Over the years, the risk gradually falls to a position approximately halfway between that of smokers and nonsmokers. Figures 2 and 3 show that with longer periods of cessation the mortality risk continues to approach that of nonsmokers. In Figure 4, it can be seen that for ex-smokers who had been off cigarettes for 15 or more years before the start of this study, their mortality risk fluctuates about the mortality risk of nonsmokers for the entire 16-year period.

The mortality experience of British doctors who were ex-smokers is examined in Table 31. These data indicate that there are definite benefits from quitting smoking no matter how long one has smoked. After 10 to 15 years, ex-smokers have a risk of dying that is similar to that of those who have never smoked. The risk of dying from ischemic heart disease decreases rapidly immediately after stopping smoking, whereas the risk of dying from lung cancer decreases more slowly. Overall mortality measures the net benefit of quitting and, therefore, drops more slowly than do death rates for certain disease categories.

Mortality and Pipe and Cigar Smoking

Pipe and cigar smokers have mortality rates that are similar to those of cigarette smokers for cancers of the oral cavity, pharynx, larynx, and esophagus. Pipe and cigar smokers have much lower death rates than cigarette smokers for cancer of the lung, ischemic heart disease, and chronic obstructive lung disease. Since these last three disease categories account for the bulk of the excess mortality associated with cigarette smoking, pipe and cigar smokers experience overall mortality rates that are much lower than cigarette smokers. Inhalation of smoke is necessary to expose the heart and lungs to the harmful constituents found in tobacco smoke, and pipe and cigar smokers report much less inhalation of smoke than cigarette smokers. Pipe smoke and cigar smoke contain nearly all the same chemical compounds found in cigarette smoke, but pipe and cigar smoke tends to be alkaline in pH rather than acid as is cigarette smoke. Alkaline smoke is irritating to the respiratory tract. This is likely to be an important reason why pipe and cigar smokers report a much lower level of smoke inhalation than cigarette smokers.

Table 32 summarizes the mortality ratios for male smokers by the type of tobacco used for the five studies that obtained data on pipe and cigar smoking. Cigar smokers have overall mortality ratios that are from 6 to 25 percent higher than nonsmokers. Mixing cigarette smoking with pipe or cigar smoking substantially increases the mortality ratios, although they remain somewhat less than the mortality ratios of cigarette-only smokers.

Dose-response relationships between overall mortality and the amount of tobacco smoked were examined in several studies. Data

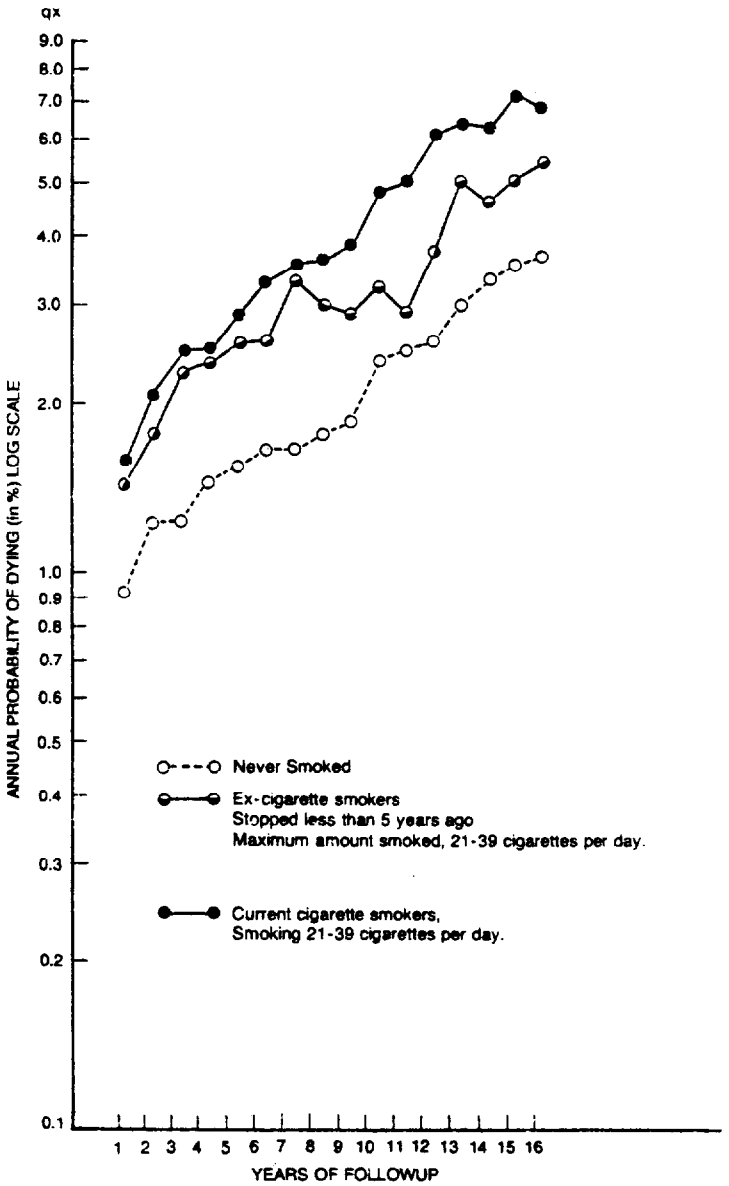

FIGURE 1.—Annual probability of dying for ex-smokers who quit smoking less than 5 years, current cigarette smokers and nonsmokers, aged 55–64, U.S. veterans 1954 cohort, 16-year follow-up

SOURCE: Rogot, E. (*55*).

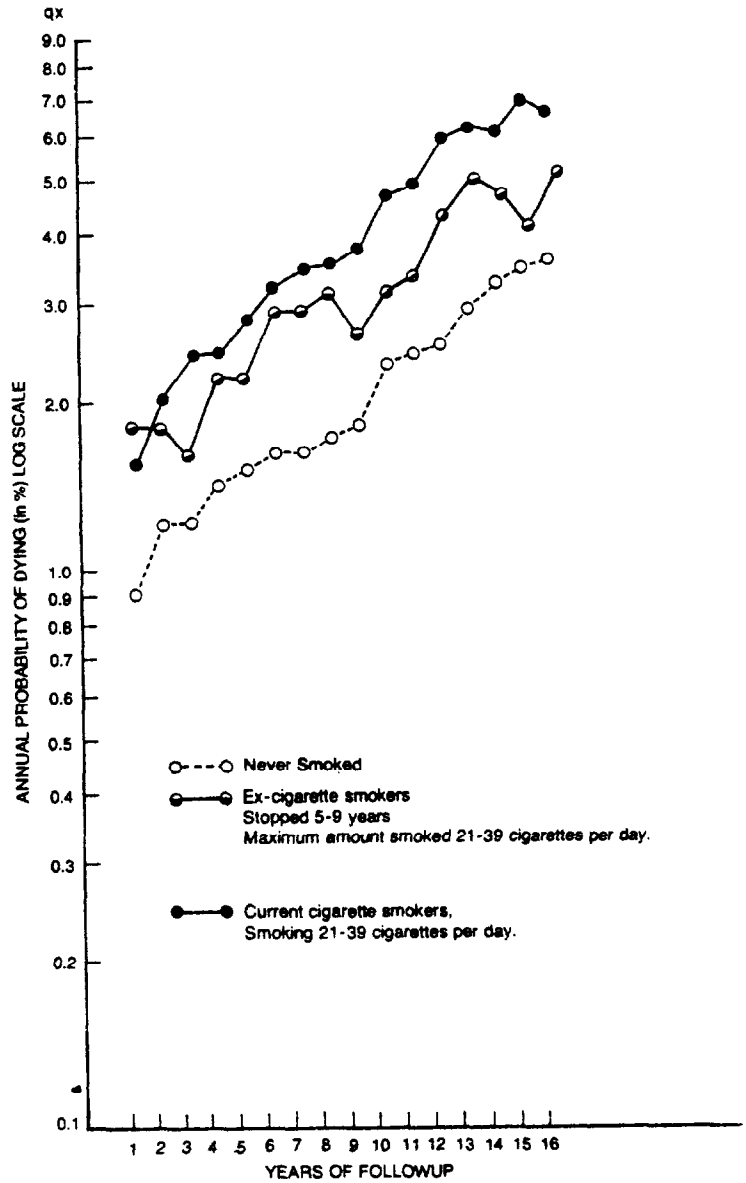

FIGURE 2.—Annual probability of dying for ex-smokers who quit smoking 5–9 years, current cigarette smokers and nonsmokers, aged 55–64, U.S. veterans 1954 cohort, 16-year follow-up

SOURCE: Rogot, E. (*55*).

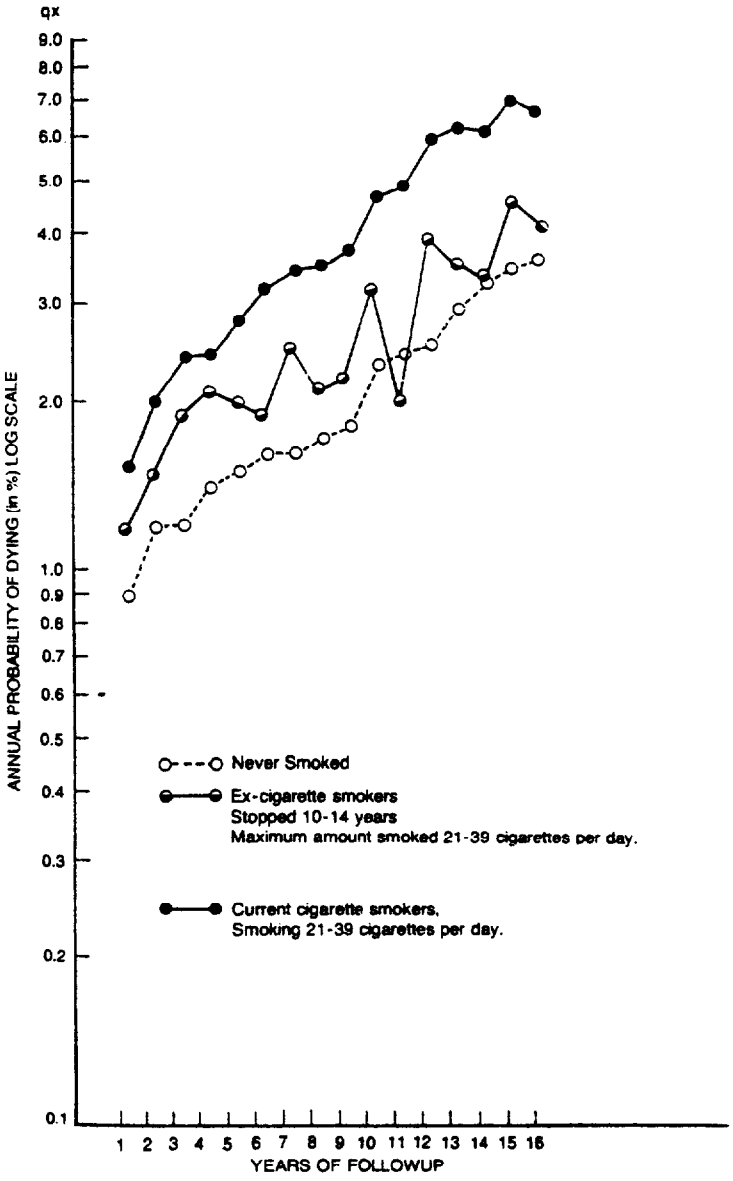

FIGURE 3.—Annual probability of dying for ex-smokers who quit 10–14 years, current cigarette smokers and nonsmokers, aged 55–64, U.S. veterans 1954 cohort, 16-year follow-up

SOURCE: Rogot, E. (*55*).

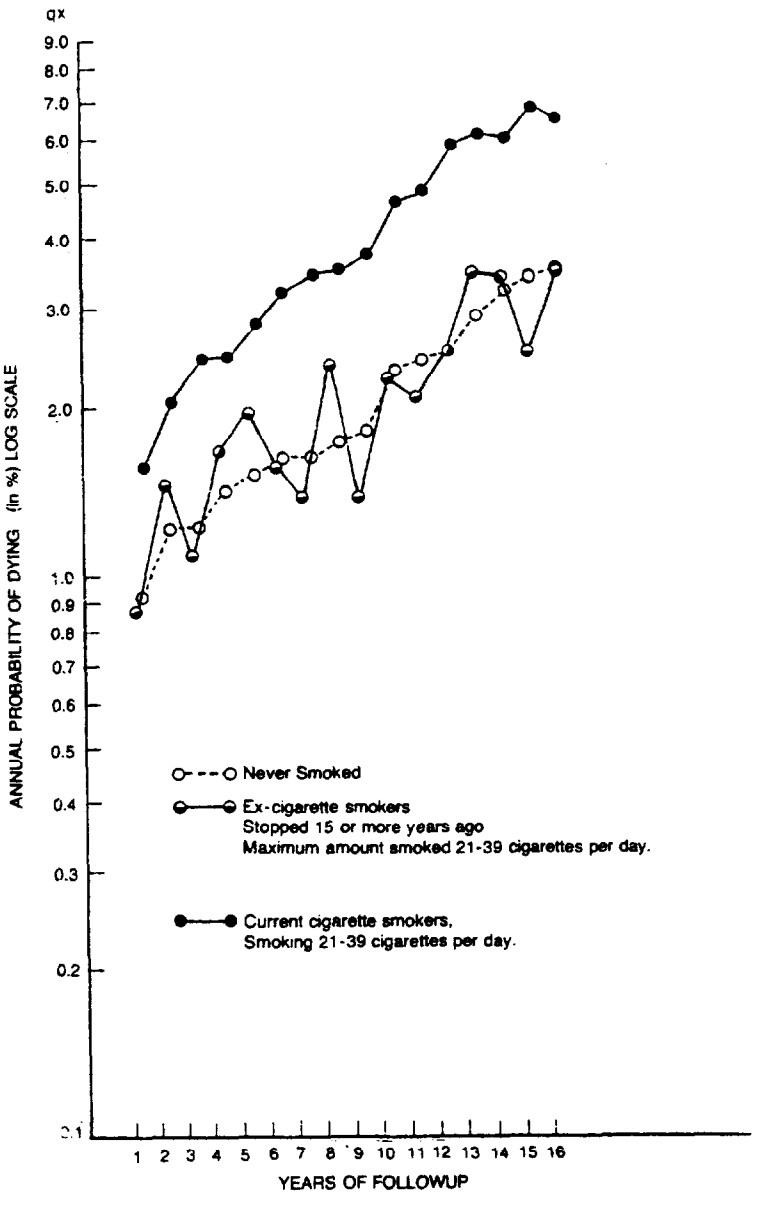

FIGURE 4.—Annual probability of dying for ex-smokers who quit 15+ years, current cigarette smokers and nonsmokers, aged 55–64, U.S. veterans 1954 cohort, 16-year follow-up

SOURCE: Rogot, E. (*55*).

TABLE 31.—Mortality ratios of ex-smokers compared to nonsmokers, by age and number of years since stopping smoking. Study of British doctors

Years since stopping smoking	Mortality ratios		
	Ages 30–64	Ages 65+	All ages
0 (Current smokers)	2.0	1.6	1.8
1–4	1.7	1.4	1.5
5–9	1.6	1.4	1.5
10–14	1.4	1.2	1.3
15+	1.1	1.1	1.1
Nonsmokers	1.0	1.0	1.0

SOURCE: Doll, R. (*8*).

TABLE 32.—Mortality ratios for male smokers, by type of tobacco used

Study	Non-smoker	Cigar only	Pipe only	Cigar & pipe	Cigarette & cigar or pipe	Cigarette only
Men in 9 States(*20*)	1.00	1.22	1.12	1.10	1.43	1.68
British Doctors(*4*)	1.00	**	**	1.09	1.31	1.73
Canadian Veterans(*1*)	1.00	1.06	1.05	0.98	1.13	1.54
U.S. Veterans(*26*)	1.00	1.16	1.07	1.08	1.51	1.55
Males in 25 States(*17*)	1.00	1.25	1.19	1.01	1.57	1.86

from the study of men in nine States, Canadian veterans, and the ACS 25-State Study are presented in Tables 33 through 35. There is a dose-response relationship evident for cigar smoking that is small but found consistently. There was no clear dose-response relationship for pipe smoking. Data from the U.S. Veterans Study are presented in Tables 36 through 39. Again, there appears to be a dose-response relationship for cigar smoking, both for the number of cigars smoked per day and for the age began smoking cigars. For pipe smokers, a dose-response relationship was found for the number of pipefuls per day, but not for the age began smoking.

The U.S. Veterans Study (*31*) contains the most detailed information on pipe, cigar, and cigarette smoking in various combinations and in various sequences. These data on mortality ratios are shown in Table 40 and have been arranged by "increasing risk of mortality." The first section shows the mortality experience of current cigarette smokers by the present, past, or nonuse of pipes and cigars. Cigarette smokers who have the lowest mortality ratio of 1.21 are those who also currently smoke both pipes and cigars. Current cigarette smokers who formerly smoked pipes and cigars have a mortality ratio of 1.48, which is only

TABLE 33.—Age-adjusted mortality ratios for male cigar and pipe smokers, by amount smoked. Males in nine States

Type and amount smoked	Mortality ratio
Nonsmokers	1.00
Cigar only	
1–4 per day	1.03
4+ per day	1.24
All cigar smokers	1.09
Pipe only	
1–10 pipefuls per day	1.05
10+ pipefuls per day	1.19
All pipe smokers	1.09

SOURCE: Hammond, E.C. (*20*).

TABLE 34.—Age-adjusted mortality ratios for male cigar and pipe smokers, by amount smoked. Canadian veterans

Type and amount smoked	Mortality ratio
Nonsmokers	1.00
Cigar only	
1–2 per day	1.14
3–10 per day	1.19
Pipe only	
1–10 pipefuls per day	1.01
10+ pipefuls per day	1.00

SOURCE: Best, E.W.R. (*1*).

slightly below the mortality ratio of 1.55 of cigarette-only smokers who have never smoked pipes or cigars.

The second section of Table 40 shows that the mortality ratios of current cigar smokers are slightly decreased among those also currently smoking pipes and significantly increased among those also currently smoking cigarettes. The third section shows that pipe smokers with the lowest mortality are those who have never smoked cigarettes or cigars. Mortality ratios increase slightly with the addition of current cigar smoking and jump moderately with the addition of current cigarette smoking.

TABLE 35.—Age-adjusted mortality ratios for male cigar and pipe smokers, by amount smoked. Males in 25 States

Type and amount smoked	Mortality ratio
Nonsmokers	1.00
Cigar only	
1–4 per day	1.03
4+ per day	1.18
All cigar smokers	1.09
Pipe only	
1–9 pipefuls per day	1.08
9+ pipefuls per day	0.92
All pipe smokers	1.04

SOURCE: Hammond, E.C. (*17*).

TABLE 36.—Age-adjusted mortality ratios of current smokers of cigars only, by amount smoked. U.S. veterans 1954 cohort, 16–year followup

No. of cigars per day	Mortality ratio
Nonsmokers	1.00
1–2	1.11
3–4	1.13
5–8	1.22
9+	1.39
Total	1.16

SOURCE: Rogot, E. (*55*).

TABLE 37.—Age-adjusted mortality ratios of current smokers of cigars only, by age began smoking. U.S. veterans 1954 cohort, 16–year followup

Age began (years)	Mortality ratio
Nonsmokers	1.00
<15	1.22
15–19	1.23
20–24	1.16
>24	1.13
Total	1.16

SOURCE: Rogot, E. (*55*).

Mortality by Cause of Death

The underlying cause of death was obtained from the death certificate

TABLE 38.—Age-adjusted mortality ratios of current smokers of pipes only, by amount smoked. U.S. veterans 1954 cohort, 16-year followup

No. of pipefuls	Mortality ratio
Nonsmokers	1.00
<5	0.93
5–9	1.12
10–19	1.08
>19	1.21
Total	1.07

SOURCE: Rogot, E. (*55*).

TABLE 39.—Age-adjusted mortality ratios of current smokers of pipes only, by age began smoking. U.S. veterans 1954 cohort, 16-year followup

Age began years	Mortality ratio
Nonsmokers	1.00
<15	1.04
15–19	1.12
20–24	1.06
>24	1.06
Total	1.07

SOURCE: Rogot, E. (*55*).

in each of the eight prospective studies. These were classified according to the International Statistical Classification of Diseases, Injuries, and Causes of Death. The mortality ratios of current cigarette smokers by cause of death in the prospective epidemiological studies are presented in Table 41. The causes of death have been grouped into four categories: cancers, cardiovascular diseases, respiratory diseases, and other conditions.

Mortality ratios for the "all cancers" category are about twice as high in smokers as in nonsmokers. Accordingly, cigarette smokers are about twice as likely as nonsmokers to die of cancer. The highest mortality ratio for malignancies is for lung cancer, followed by cancer of the larynx, oral cavity, esophagus, urinary bladder, and the pancreas. Cigarette smoking has been established as a major cause in the development of these cancers. There are associations between cigarette smoking and cancer of the kidney and stomach, but further research is needed to determine the exact nature of this association. Cancer of the intestines and rectum do not appear to be related to cigarette smoking.

TABLE 40.—Age-adjusted mortality ratios of males smoking cigarettes, pipes, and cigars in various combinations and at various times. U.S. veterans 1954 cohort

Current cigarette smokers by use of other types of tobacco

Cigars	Pipes	Mortality ratio
Current	Current	1.21
Never	Current	1.28
Current	Never	1.30
Current	Former	1.33
Former	Current	1.36
Never	Former	1.47
Former	Former	1.48
Former	Never	1.53
Never	Never	1.55

Current cigar smokers by use of other types of tobacco

Cigarettes	Pipes	Mortality ratio
Never	Former	1.10
Former	Former	1.10
Never	Current	1.10
Former	Current	1.13
Never	Never	1.16
Current	Current	1.21
Former	Never	1.23
Current	Never	1.30
Current	Former	1.33

Current pipe smokers by use of other types of tobacco

Cigarettes	Cigars	Mortality ratio
Never	Never	1.07
Never	Current	1.10
Former	Never	1.10
Never	Former	1.11
Former	Current	1.14
Former	Former	1.14
Current	Current	1.21
Current	Never	1.28
Current	Former	1.36

SOURCE: Rogot, E. (*55*).

The mortality ratio for the "all cardiovascular disease" category is about 1.6. Coronary heart disease is the most important cause of cigarette smoking-related mortality. The mortality ratios for coronary heart disease in the eight studies varied from 1.3 to 2.03. Although the mortality ratio for coronary heart disease is considerably lower than for lung cancer, it results in a greater excess mortality because coronary heart disease is the most common cause of death in the

TABLE 41.—Mortality ratios of current cigarette-only smokers, by cause of death in eight prospective epidemiological studies

	British Doctors (3)	Males in 25 States 45–64 (17)	Males in 25 States 65–79 (17)	U.S. Veterans (26)	Japanese Study (24)	Canadian Veterans (1)	Males in 9 States (20)	Swedish Males (2)	Swedish Females (2)	California Occupations (12)
All cancers[1] (140-205)	- - -	2.14	1.76	2.21	1.62	- - -	1.97	- - -	- - -	- - -
Cancer of lung and bronchus (162-163)	14.0	7.84	11.59	12.14	3.64	14.2	10.73	7.0	4.5	15.9
Cancer of larynx (161)		6.09	8.99	9.95	13.59		13.10	- - -	- - -	- - -
Cancer of buccal cavity (140-141)	13.0			4.09	7.04	3.9	2.80	- - -	- - -	1.0
Cancer of pharynx (145-148)		9.90	2.93	12.54	2.81		- - -	- - -	- - -	- - -
Cancer of esophagus (150)	4.7	4.17	1.74	6.17	2.57	3.3	6.60	- - -	- - -	0.7
Cancer of bladder and other (181)	2.1	2.20	2.96	2.15	0.98	1.3	2.40	1.8	1.6	6.0
Cancer of pancreas (157)	1.6	2.69	2.17	1.84	1.83	2.1	- - -	3.1	2.5	- - -
Cancer of kidney (180)	- - -	1.42	1.57	1.45	1.11	1.4	1.50	- - -	- - -	- - -
Cancer of stomach (151)	- - -	1.42	1.26	1.60	1.51	1.9	2.30	0.9	2.3	0.8
Cancer of intestines (152-153)	- - -			1.27	1.27	1.4	0.50	- - -	- - -	0.9
Cancer of rectum (154)	2.7	1.01	1.17	0.98	0.91	0.6	0.80	- - -	- - -	1.0
All cardiovascular diseases (330-334, 400-468)	- - -	1.90	1.31	1.75	- - -	- - -	1.57	- - -	- - -	- - -
Coronary heart disease (420)	1.6	2.03	1.36	1.74	1.96	1.6	1.70	1.7	1.3	2.0
Cerebrovascular lesions (330-334)	1.3	1.38	1.06	1.52	1.14	0.9	1.30	1.0	1.1	1.8
Aortic aneurysm (nonsyphilitic) (451)	6.6	2.62	4.92	5.24	- - -	1.8	- - -	1.6	- - -	- - -
Hypertension (440-447)	- - -	1.40	1.42	1.67	2.51	1.6	1.20	1.3	1.4	1.0
General arteriosclerosis (450)	1.4	- - -	- - -	1.86	- - -	3.3	2.00	2.0	2.0	- - -
All Respiratory Disease (non-neoplastic)	- - -	- - -	- - -	- - -	- - -	- - -	2.85	- - -	- - -	- - -
Emphysema and/or bronchitis	24.7	- - -	- - -	10.08	- - -	- - -	2.30	1.6	2.2[2]	4.3
Emphysema without bronchitis (527.1)	- - -	6.55	11.41	14.17	- - -	7.7	- - -	- - -	- - -	- - -
Bronchitis (500-502)	- - -	- - -	- - -	4.49	- - -	11.3	- - -	- - -	- - -	- - -
Respiratory tuberculosis (001-008)	5.0	- - -	- - -	2.12	1.27	- - -	- - -	- - -	- - -	- - -
Asthma (241)	- - -	- - -	- - -	3.47	- - -	- - -	- - -	- - -	- - -	- - -
Influenza and pneumonia (480-493)	1.4	1.86	1.72	1.87	- - -	1.4	2.60	- - -	- - -	2.4
Certain other conditions										
Stomach ulcer (540)	2.5	4.06	4.13	4.13	2.06	- - -	- - -	- - -	- - -	- - -
Duodenal ulcer (541)		2.86	1.50	2.98		6.9	2.16	- - -	- - -	0.5
Cirrhosis (581)	3.0	2.06	1.97	3.33	1.35	2.3	1.93	2.4	0.8	4.0
Parkinsonism (350)	0.4	- - -	- - -	0.26	- - -	- - -	- - -	- - -	- - -	- - -
All causes	1.64	1.88	1.43	1.84	1.22	1.52	1.70	1.4	1.2	1.78

[1]Numbers in parentheses represent ICD (International Classification of Diseases) codes.
[2]Includes emphysema, bronchitis, and asthma.

United States. There are several important risk factors for the development of coronary heart disease, including cigarette smoking, hypertension, and high blood cholesterol. None appears to be more important than cigarette smoking. Cigarette smoking does not appear to be a significant cause of hypertension or elevated serum cholesterol, but there is an adverse synergism between these risk factors that greatly increases the risk of ischemic heart disease for individuals who have multiple risk-factors. There is a strong and, most likely, causal relationship between cigarette smoking and death from aortic aneurysm (nonsyphylitic). General arteriosclerosis is also associated with cigarette smoking.

Of the non-neoplastic respiratory diseases, cigarette smoking is most strongly associated with emphysema and chronic bronchitis. Because of difficulty in differentiating between these diseases, and since they commonly coexist in an individual, they are frequently combined and called chronic obstructive lung disease (COLD). It is clear that cigarette smoking is the major cause of COLD. Certain industrial exposures result in COLD, and in these situations an adverse synergism with cigarette smoking exists, creating premature disability and death primarily among cigarette smokers in these industries. Asthma is not commonly caused by cigarette smoking, but this condition is seriously aggravated by cigarette smoking. Deaths from infectious pulmonary diseases such as pneumonia and influenza are more common in cigarette smokers than in nonsmokers.

The mechanisms responsible for the increased mortality from stomach and duodenal ulcers among cigarette smokers are not clearly understood. The association of cigarette smoking with cirrhosis is an indirect one. There is a strong correlation of cigarette smoking with the use of alcoholic beverages, which in turn cause cirrhosis. There is a significant negative association between cigarette smoking and parkinsonism; the cause of this association is not known.

The Constitutional Hypothesis, Social, and Environmental Factors

Certain critics have advanced various hypotheses in an attempt to dismiss cigarette smoking as a cause of mortality. The constitutional hypothesis and social and various environmental factors have been raised as explanations of the mortality trends that have been observed to be associated with cigarette smoking.

The constitutional hypothesis holds that people with certain genetically-acquired constitutional makeups are more likely to develop certain diseases and are also more likely to smoke cigarettes. This hypothesis maintains that the relationship between cigarette smoking and certain diseases is largely fortuitous.

Data from the United States and Swedish Twin Registries have been examined to try to clarify the constitutional hypothesis. Cederlof, et al. (*3*) have published the most extensive data available on the interactions of smoking, environment, and heredity in the development of disease. Comparisons were made between smoking discordant monozygotic (identical) pairs and smoking discordant dizygotic (fraternal) pairs, and between unmatched twin pairs and matched twin pairs. When smoking and overall mortality are examined, treating all twins as "unrelated" individuals, a strong correlation is found. The group smoking more than 10 cigarettes per day has a mortality ratio of about 2.0 compared to nonsmokers. This is true for both men and women in all age groups.

When smokers and nonsmokers among the dizygotic pairs were compared, a mortality ratio of 1.45 for males and 1.21 for females was observed. Corresponding mortality ratios for the monozygotic pairs were 1.5 for males and 1.22 for females. Commenting on the constitutional hypothesis and lung cancer, the authors observed that "the constitutional hypothesis as advanced by Fisher and still supported by a few, has here been tested in twin studies. The results from the Swedish monozygotic twin series speak strongly against this constitutional hypothesis" (*3*).

Preston (*27-30*) has published several articles in which he examined the excess mortality—above predicted values for men and women—that has occurred in the United States and other countries. Genetic, social, and environmental factors were analyzed in an attempt to explain this phenomenon. The genetic and social hypothesis received some support from correlation analysis; however, the correlations were weak and became trivial when cigarette smoking was taken into consideration. Preston observed: "Rather than representing victimization by nature or by hostile social forces, the current abnormal rates of dying among older males appear to be largely self-imposed and avoidable" (*28*).

Social, genetic, and environmental arguments are also weakened by the observation that epidemiological studies of the effects of cigarette smoking have been conducted in many countries on every major continent and among peoples of diverse social and cultural backgrounds who are exposed to a variety of environmental factors—all with similar results. Cigarette smoking causes the same diseases, and the same dose-response relationships are found wherever the effects of cigarette smoking are studied.

Summary of Overall Mortality Related to Smoking

The following conclusions summarize the relationships that have been established between smoking and overall mortality. Some conclusions were drawn 15 years ago; others are based on data that have

accumulated in the interval since publication of the first Surgeon General's Report.

1. The overall mortality ratio for all smokers of cigarettes is about 1.7 compared to nonsmokers.

2. Life expectancy is significantly shortened by cigarette smoking. A 30-year-old, two-pack-a-day smoker has a life expectancy that is 8.1 years shorter than his nonsmoking counterpart.

3. Overall mortality ratios increase with the amount smoked. The mortality ratio is 2.0 for the two-pack-a-day smoker as compared to nonsmokers.

4. Overall mortality ratios for smokers are highest at younger ages and decline somewhat with increasing age. This reflects a relative decrease of the impact of smoking on health as death rates in general increase with age. This is a relative effect. The actual number of excess deaths attributable to cigarette smoking increases with age.

5. Overall mortality ratios are proportional to the duration of cigarette smoking. The longer one smokes, the greater the risk of dying.

6. Overall mortality ratios are higher for those who began smoking at a young age as compared to those who began smoking later.

7. Overall mortality ratios are higher for those who report they inhale smoke than for those who do not inhale.

8. Overall mortality ratios increase with the tar and nicotine content of the cigarette. Overall mortality ratios of low tar and nicotine (less than 1.2 mg nicotine and less than 17.6 mg tar) cigarette smokers are 50 percent higher than for nonsmokers.

9. Overall mortality ratios for female smokers are somewhat less than for male smokers. This probably reflects differences in exposure to cigarette smoke, such as starting smoking later, smoking cigarettes with lower tar and nicotine content, and smoking fewer cigarettes per day than men.

10. Women demonstrate the same dose-response relationships with cigarette smoking as men. An increase in mortality occurs with an increase in the number of cigarettes smoked per day, an earlier age of beginning cigarette smoking, a longer duration of smoking, inhalation of cigarette smoke, and a higher tar and nicotine content of the cigarette. Women who have smoking characteristics similar to men experience mortality rates similar to men.

11. Ex-smokers experience overall mortality ratios that decline as the number of years off cigarettes increases. After 15 years, the overall mortality ratios of ex-smokers are similar to those of individuals who have never smoked.

12. Ex-smokers have overall mortality ratios that are directly proportional to the number of cigarettes the person used to smoke.

13. Ex-smokers have overall mortality ratios that are inversely related to the age at which the person began to smoke.

14. Ex-smokers who were ill when they quit smoking have higher mortality rates than ex-smokers who quit for other reasons.

15. Regardless of how long or how much an individual has smoked, there is a decrease in overall mortality when the person quits smoking, provided the person is not ill at the time of quitting.

16. Overall mortality ratios for cigar-only smokers as a group are somewhat higher than for nonsmokers.

17. Overall mortality ratios for cigar smokers increase with the number of cigars smoked per day.

18. Overall mortality ratios for cigar smokers are inversely proportional to the age at which the individual began smoking cigars.

19. Overall mortality ratios for pipe-only smokers as a group are only slightly higher than for nonsmokers.

20. Overall mortality ratios of men who smoke cigarettes in combination with pipes and cigars are intermediate between those who smoke pipes or cigars only and those who smoke only cigarettes.

Summary of Smoking and Mortality by Cause of Death

1. Mortality ratios are particularly high for a number of diseases associated with smoking. These include:

a. Cancer of the lung
b. Chronic obstructive lung diseases, emphysema, and chronic bronchitis
c. Cancer of the larynx
d. Cancer of the oral cavity
e. Cancer of the esophagus
f. Ischemic heart disease
g. Cancer of the urinary bladder
h. Cancer of the pancreas
i. Aortic aneurysm (nonsyphilitic)
j. Ulcers of the stomach and duodenum

2. Coronary heart disease is the chief contributor to the excess mortality associated with cigarette smoking.

3. Lung cancer is the second leading contributor to excess mortality associated with cigarette smoking.

4. Chronic obstructive lung disease is the third leading contributor to excess mortality associated with cigarette smoking.

5. Pipe smoking and cigar smoking are associated with elevated mortality ratios for cancers of the upper respiratory tract, including cancer of the oral cavity, the larynx, and the esophagus.

Mortality: References

(1) BEST, E.W.R., JOSIE, G.H., WALKER, C.B. A Canadian study of mortality in relation to smoking habits: A preliminary report. Canadian Journal of Public Health 52: 99-106, March 1961.

(2) CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity. A Ten Year Follow-up in a Probability Sample of 55,000 Swedish Subjects Age 18 to 69. Part I and II. Stockholm, Sweden, Karolinska Institute, Department of Environmental Hygiene, 1975, 201 pp.

(3) CEDERLOF, R., FRIBERG, L., LUNDMAN, T. The interactions of smoking, environment, and heredity and their implications for disease etiology. A report of epidemiological studies on the Swedish Twin Registries. Acta Medica Scandinavica, Supplement 612:7-128, September 1977.

(4) DOLL, R., HILL, A.B. Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. British Medical Journal 2: 1071-1081, November 1, 1956.

(5) DOLL, R., HILL, A.B., Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 205-268.

(6) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. Part I. British Medical Journal 1(5395): 1399-1410, May 30, 1964.

(7) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. Concluded. British Medical Journal 1(5396): 1460-1467, June 6, 1964.

(8) DOLL, R., PETO, R. Mortality among doctors in different occupations. British Medical Journal 1(6074): 1433-1436, June 4, 1977.

(9) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2(6051): 1525-1536, December 25, 1976.

(10) DOLL, R., PIKE, M.C. Trends in mortality among British doctors in relation to their smoking habits. Journal of the Royal College of Physicians 6(2): 216-222, January 1972.

(11) DORN, H.F. The mortality of smokers and nonsmokers. Proceedings of the Social Statistics Section of the American Statistical Association. Papers presented at the Annual Meeting of the American Statistical Association, Chicago, Illinois, December 27-30, 1958. Washington, D.C., American Statistical Association, 1959, pp. 34-71.

(12) DUNN, J.E., LINDEN, G., BRESLOW, L. Lung cancer mortality experience of men in certain occupations in California. American Journal of Public Health 50(10): 1475-87, October 1960.

(13) EPIDEMIOLOGY DIVISION, HEALTH SERVICES BRANCH, BIOSTATISTICS DIVISION, RESEARCH AND STATISTICS DIRECTORATE. A Canadian Study of Smoking and Health. Department of National Health and Welfare, Epidemiology Division, Health Services Branch, Biostatistics Division, Research and Statistics Directorate, 1966, 137 pp.

(14) HAMMOND, E.C. Evidence on the effects of giving up cigarette smoking. American Journal of Public Health 55(5): 682-691, May 1965.

(15) HAMMOND, E.C. Life expectancy of American men in relation to their smoking habits. Journal of the National Cancer Institute 43(4): 951-962, October 1969.

(16) HAMMOND, E.C. Smoking habits and air pollution in relation to lung cancer. In: Lee, D.H.K. (Editor). Environmental Factors in Respiratory Disease. Fogarty International Center Proceedings No. 11, New York, Academic Press, 1972. pp. 177-198.

(17) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases, National Cancer Institute Monograph 19. U.S. Department of Health, Education, and Welfare, U.S. Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(18) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Archives of Environmental Health 19(2): 167-182, August 1969.

(19) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. Environmental Research 12(3): 263-274, December 1976.

(20) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up on 187,783 men. I. Total mortality. Journal of the American Medical Association 166(10): 1159-1172, March 8, 1958.

(21) HIRAYAMA, T. Operational aspects of cancer public education in Japan. In: Summary Proceedings of the International Conference on Public Education About Cancer. UICC Technical Report Series, Volume 18, Geneva, 1975, pp. 85-90.

(22) HIRAYAMA, T. Prospective studies on cancer epidemiology based on census population in Japan. In: Bucalossi, P., Veronesi, U., Cascinelli, N. (Editors). Cancer Epidemiology, Environmental Factors. Volume 3. Proceedings of the 11th International Cancer Congress, Florence, 1974, Excerpta Medica, pp. 26-35.

(23) HIRAYAMA, T. Smoking and drinking—Is there a connection? Smoke Signals 16(7): 1-8, July 1970.

(24) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center, Research Institute, Epidemiology Division, September 1967, 14 pp.

(25) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. A report on 5 years of follow-up. Presented at the American Cancer Society's 14th Science Writers' Seminar, Clearwater Beach, Florida, March 24-29, 1972, 15 pp.

(26) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: report on 8 1/2 years of observation. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966. pp. 1-125.

(27) PRESTON, S.H. The age-incidence of death from smoking. Journal of the American Statistical Association 65(331): 1125-1130, September 1970.

(28) PRESTON, S.H. An international comparison of excessive adult mortality. Population Studies 24(1): 5-20, March 1970.

(29) PRESTON, S.H. Mortality differentials by social class and smoking habit. Social Biology 16(4): 280-289, December 1969.

(30) PRESTON, S.H. Older male mortality and cigarette smoking. A demographic analysis. Institute of International Studies, Berkeley, California, University of California, 1970, 150 pp.

(31) ROGOT, E. Smoking and General Mortality Among U.S. Veterans, 1954-1969. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Heart and Lung Institute, Epidemiology Branch, DHEW Publication No. (NIH) 74-544, 1974, 65 pp.

3. MORBIDITY.

CONTENTS

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Introduction

For many years, researchers have been accumulating evidence of the relationship between cigarette smoking and mortality, as well as data on the relationship between smoking and the prevalence of selected chronic diseases. These findings are presented in detail elsewhere in this report. It has been only recently that data have also become available that indicate a relationship, although a statistical relationship and not an established causal relationship, between cigarette smoking and disability and other health indicators. This chapter of the report will present some of these data based on surveys conducted by the National Center for Health Statistics (NCHS).

Past Studies

One of the few sources of national data on cigarette smoking and health characteristics, and the only data set based on a large national sample, is the National Health Interview Survey. This is a continuous survey conducted by NCHS each year since 1957. Interviews are conducted in a national probability sample of approximately 40,000 households, with a new sample selected each year. Information is obtained on a wide range of health characteristics, including incidence of acute illnesses and injuries, prevalence of selected chronic diseases, short- and long-term disability associated with illness and injuries, utilization of health services, and related health topics such as health insurance coverage, usual sources of medical care, and use of prescription medicine. One of the topics on which data have been periodically collected is cigarette smoking behavior. Some data on cigar and pipe smoking have also been collected.

Shortly after the Surgeon General's first report, *Smoking and Health*, was published in 1964, NCHS began collecting information on smoking as a part of the Health Interview Survey. The result of this effort was a report, *Cigarette Smoking and Health Characteristics* (*14*), which was the first such study based on a national probability sample. While several significant studies had been conducted earlier, such as those by Hammond and Horn (*5*, *6*), they were, for the most part, not based on scientifically designed samples, and were therefore subject to the criticism that the findings could not be generalized to the total population. NCHS's first report on smoking, based on the fiscal year 1965 survey, presented data on the relationships between cigarette smoking, the incidence of selected acute illnesses, and the prevalence of selected chronic diseases, as well as information on the relationship between smoking and measures of disability, such as restricted activity days, bed days, and work-loss days.

The data showed, for example, that male cigarette smokers were almost 2 1/2 times more likely to report chronic bronchitis or emphysema than were those who had never smoked, and almost 60

TABLE 1.—Age-specific ratios[1] of prevalence rates of chronic conditions for persons who had ever smoked to persons who had never smoked, by sex, age, and selected chronic conditions: United States, July 1964 to June 1965

Selected chronic conditions	Male				Female			
	All ages, 17+ years	17–44 years	45–64 years	65+ years	All ages, 17+ years	17–44 years	45–64 years	65+ years
	Ratio							
All chronic conditions	1.09	1.27[2]	1.17	1.09	0.90	1.26	1.02	0.99
Heart conditions (excluding rheumatic heart disease)	1.00	*	1.45	1.06	0.47	1.33	0.92	0.92
Arteriosclerotic heart disease including coronary disease	1.50	†	1.80	1.22	0.75	†	1.63	1.61
Hypertension without heart involvement	0.91	1.25	0.86	0.95	0.57	1.17	0.75	0.89
Chronic bronchitis and/or emphysema	2.30	*	*	2.67	2.38	3.43	2.86	2.16
Chronic sinusitis	1.35	1.38	1.31	1.34	1.25	1.34	1.19	1.22
Peptic ulcer	2.00	2.38	1.88	1.59	1.56	1.82	1.52	2.35
Arthritis	0.95	1.64	0.99	1.06	0.63	1.32	0.89	0.97
Hearing impairments	0.88	1.31	1.06	0.97	0.55	1.05	1.02	0.75
All other chronic conditions	1.07	1.19	1.15	1.08	0.95	1.23	1.03	0.99

[1]Prevalence rate of "ever smokers" divided by prevalence rate of "never smokers."
[2]Example: 1.27 = 82.9/65.4.
*Figure does not meet standards of reliability or precision.
†Quantity zero.
SOURCE: Wilson, R.W. (*14*).

percent more likely to report arteriosclerotic heart disease (Table 1). Among the heaviest smokers the relationships were even stronger. For example, women who smoked between one and two packs a day reported chronic bronchitis or emphysema almost five times more frequently than did women who had never smoked (Table 2). In addition, former smokers, particularly among the males, reported higher rates of chronic illnesses than did the current smokers. Data were not available to further analyze illness rates by the reason people stopped smoking, i.e., the category of former smokers is composed of both those who stopped *because* of poor health and those who stopped to *avoid* poor health.

Data from this study also indicated that people who had ever smoked cigarettes also had a higher incidence of acute illnesses than did people who had never smoked. The age-adjusted incidence of acute conditions

TABLE 2.—Ratios of age-adjusted[1] prevalence rates of chronic conditions for persons 17 years old and older who have ever smoked, to persons who have never smoked, by cigarette smoking status, number of cigarettes smoked per day for present smokers—heaviest amount, sex, and selected chronic conditions: United States, July 1964 to June 1965

Sex and selected chronic conditions	Cigarette smoking status			Present smokers			
	Persons who ever smoked	Former smokers	Present smokers	Number of cigarettes smoked per day–heaviest amount			
				Under 11	11–20	21–40	41 and over
Male	Ratio[2]						
All chronic conditions	1.17	1.26	1.13	0.92	1.04	1.30	1.54
Heart conditions (excluding rheumatic heart disease)	1.22	1.44	1.12	0.93	1.07	1.29	1.71
Arteriosclerotic heart disease, including coronary disease	1.67	2.22	1.56	*	1.44	2.11	*[3]
Hypertension without heart involvement	1.02	1.07	1.00	0.93	0.88	1.20	1.27
Chronic bronchitis and/or emphysema	2.40	2.50	2.40	*	2.30	3.10	4.10
Chronic sinusitis	1.34	1.40	1.30	0.93	1.22	1.57	1.78
Peptic ulcer	1.92	1.75	1.96	1.25	1.92	2.17	2.75
Arthritis	1.07	1.24	0.99	0.97	0.87	1.16	1.16
Hearing impairments	1.06	1.14	1.04	0.98	0.94	1.14	1.34
All other chronic conditions	1.13	1.23	1.09	0.90	1.01	1.25	1.50
Female							
All chronic conditions	1.12	1.23	1.09	0.88	1.05	1.39	2.00
Heart conditions (excluding rheumatic heart disease)	0.91	1.26	0.81	0.65	0.81	1.05	*
Arteriosclerotic heart disease, including coronary disease	1.29	*	0.86	*	*	*	*
Hypertension without heart involvement	0.86	0.98	0.83	0.86	0.76	0.90	*
Chronic bronchitis and/or emphysema	2.83	2.17	3.17	1.33	3.33	4.92	9.67
Chronic sinusitis	1.26	1.32	1.24	0.97	1.26	1.56	1.74
Peptic ulcer	1.63	1.63	1.56	1.25	1.56	2.13	*
Arthritis	0.99	1.12	0.98	0.86	0.97	1.11	1.68
Hearing impairments	0.93	0.97	0.90	0.72	0.91	1.14	*
All other chronic conditions	1.12	1.25	1.09	0.89	1.04	1.41	2.08

[1]Adjusted by the indirect method to the age distribution of the total civilian, noninstitutional population of the United States.

[2]Prevalence rate for given smoking category divided by prevalence rate for "never smokers." Ratios of 1.00 = same as "never smoked."

[3]Even though the asterisks in this column replace figures with large sampling errors, each of the six of the replaced ratios were larger than the ratios for the lower smoking amounts.

*Figure does not meet standards of reliability or precision.

SOURCE: Wilson, R.W. (*14*).

for persons who had ever smoked was 14 percent higher among men and 21 percent higher among women than among people who had never smoked cigarettes (Table 3). As with chronic conditions, the former smokers reported higher rates of acute illness than did the present smokers.

However, just as the earlier studies were subject to criticism because of their sample designs, this study was criticized because the disease information came from reporting in household interviews rather than from physician examination. Methodological studies on the accuracy of the reporting of disease in which medical records are compared with household interview data have indicated a wide range of reporting completeness depending on the nature and the seriousness of the specific disease (*7*).

Another indication of morbidity is the impact of illness on the individual. Two of the indicators routinely collected in the Health Interview Survey are the number of days lost from work as a result of illness or injury and the number of days which a person had to spend in bed as a result of illness or injury. These indicators are independent of a physician's diagnosis and require only that a respondent attribute the disability to an illness or injury, although the data can also be analyzed by specific disease categories. The data collection procedure requires that respondents recall days spent in bed or days lost from work only for the 2-week period prior to the week of the interview, thus reducing memory loss. The data on work-loss days apply to currently employed persons only and do not reflect long-term work loss from unemployment or early retirement as a result of illness or injury.

The age-adjusted data from the 1965 Health Interview Survey indicated that there were about 15 percent more bed-disability days among current smokers than among people who had never smoked cigarettes, and about a third more bed disability days among the former smokers than among those who had never smoked (Table 4). The levels of bed-disability days tended to increase as the number of cigarettes smoked increased, as measured by the heaviest amount smoked.

The number of work-loss days among both current and former cigarette smokers was markedly higher than among workers who had never smoked. The age-adjusted rate of work loss was 33 percent higher for male current smokers, 45 percent higher for female current smokers, and 42 percent higher for both male and female former smokers. As with disease and bed-day differentials, the heaviest smokers reported the highest rates of work loss. These data were used by the Public Health Service in its early national public education and antismoking campaigns. The campaigns included television spots that noted there were an estimated 77 million "excess" work-loss days associated with cigarette smoking; that is, if the smokers had the same rate of work loss as did those workers who had never smoked, there

TABLE 3.—Ratios of age-adjusted[1] incidence of acute conditions for persons 17 years old and older who have ever smoked, to persons who have never smoked, by cigarette smoking status, number of cigarettes smoked per day for present smokers—present amount, sex, and selected acute conditions: United States, July 1964 to June 1965

Sex and selected acute conditions	Cigarette smoking status			Present smokers			
	Persons who ever smoked	Former smokers	Present smokers	Number of cigarettes smoked per day—present amount			
				Under 11	11–20	21–40	41 and over
Male				Ratio[2]			
All acute conditions	1.14	1.23	1.11	1.02	1.11	1.23	1.21
Infective and parasitic diseases	1.21	1.36	1.16	*	1.24	1.59	*
Upper respiratory conditions	1.03	1.22	0.96	0.98	0.98	0.92	*
Influenza	1.25	1.36	1.22	1.22	1.19	1.28	*
Other respiratory conditions	1.62	*	1.54	*	*	*	*
Digestive system conditions	1.05	1.13	1.03	*	0.90	1.41	*
Injuries	1.25	1.03	1.32	1.00	1.35	1.56	*
All other acute conditions	1.06	1.35	0.95	1.08	0.85	1.11	*
Female							
All acute conditions	1.21	1.26	1.21	1.18	1.20	1.31	*
Infective and parasitic diseases	1.35	1.62	1.29	1.26	1.04	2.29	†
Upper respiratory conditions	1.26	1.20	1.27	1.29	1.28	1.26	*
Influenza	1.13	1.28	1.09	1.23	1.03	0.99	*
Other respiratory conditions	1.68	*	1.74	*	*	*	*
Digestive system conditions	1.07	*	1.04	0.78	1.05	*	*
Injuries	1.14	1.04	1.17	0.89	1.40	*	*
All other acute conditions	1.22	1.31	1.19	1.29	1.15	1.13	*

[1]Adjusted by the indirect method to the age distribution of the total civilian, noninstitutional population of the United States.

[2]Incidence rate for given smoking category divided by incidence rate for "never smokers."

*Figure does not meet standards of reliability or precision.

†Quantity zero.

SOURCE: Wilson, R.W. (*14*).

would have been 77 million fewer days lost from work (*13*). This represented 19 percent of all work-loss days from illness at that time. More recent data are presented below.

TABLE 4.—Ratios of age-adjusted[1] number of days of disability per person 17 years old and older per year who have ever smoked, to persons who have never smoked, by number of cigarettes smoked per day for present smokers—heaviest amount, type of days of disability, smoking status, and sex: United States, July 1964 to June 1965

Type of disability days, smoking status, and sex	Total smokers	Present smokers			
		Number of cigarettes smoked per day–heaviest amount			
		Under 11	11–20	21–40	41 and over
		Ratio[2]			
Days of work loss[3]					
Present smokers					
Male	1.33	0.87	1.35	1.41	1.65
Female	1.45	1.09	1.57	1.83	2.74
Former smokers					
Male	1.41	1.28	1.26	1.70	2.17
Female	1.43	1.34	1.66	1.72	*
Days of bed Disability					
Present smokers					
Male	1.14	0.98	1.20	1.16	1.49
Female	1.17	0.92	1.09	1.59	2.63
Former smokers					
Male	1.31	1.27	1.24	1.45	1.65
Female	1.39	1.09	1.61	1.49	4.57

[1]Adjusted by the indirect method to the age distribution of the total civilian, noninstitutional population of the United States.

[2]Days of disability of given smoking category divided by days of disability of "never smokers."

[3]Days of work loss reported for currently employed persons only.

*Figure does not meet standards of reliability or precision.

SOURCE: Wilson, R.W. (*14*).

The following year NCHS also collected data on smoking and published a report, *Changes in Cigarette Smoking Habits Between 1955 and 1966* (*1*), which compared the 1966 data with similar data collected earlier as a part of the Current Population Survey conducted by the Bureau of the Census (*4*). The Census data, however, did not include any health-related information. NCHS continued to monitor cigarette smoking levels, but with no health data, in 1966, 1967, and 1968

through supplemental questions in the Current Population Survey. The 1970 Health Interview Survey contained many of the same smoking and health questions as the 1965–1966 surveys, with the exception that data were not collected on all chronic diseases, but only on respiratory disease. These data again showed increased reporting of selected respiratory diseases and more work loss among smokers than among those who had never smoked (*15*). In addition, the data continued to document the decline in the proportion of cigarette smokers, particularly among males, where the drop was from 51.0 percent in 1965 to 43.2 percent in 1970 (*10*). Smoking data were again collected in 1974 in conjunction with a special set of questions on hypertension (*9*). Smoking questions were also asked on the 1976 and 1977 Health Interview Surveys.

Most large scale studies on smoking and health have tended to investigate the role of smoking independently of other behavioral variables, such as alcohol consumption and other life style factors, occupational and environmental hazards, and certain psychological factors. These variables are known to be related to health status and many are also related to smoking habits. Thus it may well be that the elimination of smoking without any changes in the other factors will have only a partial impact on health status. The data collected on the 1977 survey were a part of a series of questions developed by Belloc and Breslow for a study in Alameda County, California, on health behavior, including such life-style factors as amount of sleep, eating breakfast, eating between meals, physical activity, smoking and drinking practices, and weight. It was found that persons with a number of "good health habits" live considerably longer than those with "poor health habits" (*2*).

Recent Studies

Questions on cigarette smoking behavior which were added to the July-December period of the 1978 Health Interview Survey will be continued through December 1979. These questions for the first time include information needed to determine tar and nicotine as well as carbon monoxide (CO) levels. While national surveys on adult smoking behavior conducted earlier by the National Clearinghouse on Smoking and Health had inquired about brand names to determine tar and nicotine levels, they did not include data on health characteristics.

NCHS has recently completed the first cycle of the Health and Nutrition Examination Survey, in which a large national probability sample of persons was brought to mobile examination units for a very extensive physical examination, including tests for cardiovascular and pulmonary diseases (e.g., chest x-ray, EKG, spirometry and single breath carbon monoxide diffusion) as well as a number of biochemical tests. Examinees were also asked about their smoking habits (*8*). While

TABLE 5.—Days of bed disability per person 17 years old and older, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
	Days per person per year			
Male				
17+	6.1	6.7	6.1	5.1
17–44	4.2	5.3	3.6	2.9
45–64	6.5	8.0	5.1	6.5
65+	13.9	12.9	13.2	12.4
Female				
17+	8.7	7.9	9.3	8.6
17–44	6.6	6.9	6.8	6.1
45–64	9.6	9.3	9.4	9.1
65+	13.9	10.3	18.4	13.6

Note: Actual number of bed-disability days	=	1,076,131,000
Expected number of bed-disability days if all persons had same rate as persons who never smoked	=	930,237,000
Excess bed-disability days	=	145,894,000

SOURCE: Wilson, R.W. (*16*).

the smoking data have not yet been fully analyzed, this study will provide a valuable source of information on smoking and health.

A second cycle of the Health and Nutrition Examination Survey is currently in the field (1976–1980) and also includes questions on smoking habits as well as data on carboxyhemoglobin, an indicator of CO in the blood. These data will be helpful in assessing the accuracy of self-reported cigarette smoking levels.

Disability data from the 1974 Health Interview Survey provide results very similar to those found a decade earlier. They indicate that smokers in all age and sex groups, except for women over age 65, report more days in bed due to illness than do persons who have never smoked (Table 5). If the number of excess bed days is calculated, as it was for the earlier antismoking campaigns, it is estimated that there were almost 150 million (145,894,000) excess bed days among smokers and former smokers. This type of calculation assumes that smokers and former smokers would experience the same rate of bed disability if they did not smoke as did those who had never smoked cigarettes.

Currently employed smokers also report more days lost from work as a result of illness and injury than do employed persons who have never smoked (Table 6). If "excess" work-loss days are calculated for

TABLE 6.—Days lost from work per year due to illness and injury, per currently employed person 17 years old and older, by smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
		Days per person per year		
Male				
17+	4.5	5.1	5.0	3.4
17–44	4.2	5.5	4.2	3.0
45–64	5.0	4.5	5.5	4.4
65+	3.8	0.3	7.9	*
Female				
17+	4.8	5.6	*	4.5
17–44	4.6	5.3	*	4.3
45–64	5.6	6.5	*	5.4
65+	0.9	*	*	*

*Figure does not meet standards of reliability or precision.

Note: Actual number of work-loss days	=	379,389,000
Expected number of work-loss days if all workers had the same rate as workers who never smoked	=	298,021,00
Excess work-loss days	=	81,368,000

SOURCE: Wilson, R.W. (*16*).

employed persons under 65 years of age, there would have been an estimated 81,368,000 "excess" work-loss days among smokers and former smokers, accounting for over 21 percent of all work-loss days. This is about the same proportion as a decade ago.

Another measure of the impact of illness is whether a person is limited in major activity, such as work or keeping house, or limited in other activities such as social or recreational activities as a result of chronic illness. This is a measure of long-term chronic disability as opposed to the bed-days and work-loss indicators that can result from both short-term acute illness or injury and chronic disease. For most age and sex groups, a higher proportion of current smokers and former smokers report they have a limitation of activity than do persons who have never smoked, although the differences are not always striking (Table 7). One factor that may attenuate these differences is the higher mortality rate for persons who have smoked cigarettes. One of the major causes of mortality that has been shown to be related to cigarette smoking, heart disease, is also one of the major causes of limitation of activity. Since the above findings were obtained from

TABLE 7.—Percent of persons with chronic condition(s) causing limitations of activity, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	18.6	17.3	22.4	18.9
17–44	8.8	9.8	9.4	8.0
45–64	23.7	26.2	24.7	22.3
65+	45.8	46.3	49.2	44.7
Male				
17+	18.7	18.7	23.5	17.3
17–44	9.0	10.0	8.8	8.4
45–64	23.7	27.8	23.8	20.0
65+	51.0	52.5	50.9	51.4
Female				
17+	18.4	15.8	20.6	19.7
17–44	8.6	9.5	10.2	7.8
45–64	23.8	24.4	26.5	23.1
65+	42.1	37.4	44.6	42.6

SOURCE: Wilson, R.W. (*16*).

interview surveys, there is a selection process by mortality that removes a certain number of smokers and former smokers from the data base. In addition, the group of former smokers is made up of two very different kinds of people—those who quit smoking before there was any noticeable deleterious impact on their health and those who quit smoking because of poor health. There are some recent data from the Health Interview Survey, although not yet fully analyzed, that indicate whether the respondent quit smoking because of a specific condition.

Respondents in the Health Interview Survey were asked whether they perceived their health to be excellent, good, fair, or poor. Although the differences are not large, there is a tendency for higher proportions of former smokers and of those who have never smoked to report their health status as excellent (Table 8). For example, among males 17 to 44 years old, about 53 percent of the present cigarette smokers said their health was excellent compared with about 60 percent for both the former smokers and those who had never smoked.

The data also indicate that smokers and former smokers are more likely to be hospitalized in the year prior to the interview than are persons who have never smoked (Table 9). However, the data have not

TABLE 8.—Percent of persons 17 years old and older, who perceive their health to be "excellent," by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both Sexes				
17+	42.7	41.5	43.0	42.8
17–44	51.3	47.7	55.4	53.1
45–64	34.0	32.6	36.7	32.0
65+	27.1	24.7	26.5	28.2
Male				
17+	46.8	44.1	44.0	52.0
17–44	56.7	52.9	59.9	60.8
45–64	36.9	32.3	38.0	40.9
65+	25.5	19.2	25.4	30.0
Female				
17+	39.0	38.7	41.2	38.7
17–44	46.3	42.0	49.2	48.7
45–64	31.3	33.0	34.1	28.9
65+	28.3	32.4	29.3	27.7

SOURCE: Wilson, R.W. (*16*).

been analyzed to determine if this increased hospitalization is for diseases usually associated with smoking.[1]

While smokers tended to report more hospitalizations than did persons who had never smoked, there was no tendency for smokers to report more frequent visits to physicians than those who had never smoked, although former cigarette smokers reported the largest proportion with five or more physician visits during the past year (Table 10).

Respondents in the 1974 Health Interview Survey were also asked whether they had ever tried to quit smoking, whether a doctor had advised them to quit, and whether they had been advised to quit because of specific health conditions. Just under a quarter of all persons who had ever smoked reported that they had been advised by a doctor at one time or another to stop smoking (Table 11). Surprisingly, at least from a public health point of view, at those ages at which the effects of smoking often begin to manifest themselves, 45 to 64, less than one-third of the smokers reported that they had been advised by their physicians to stop smoking. This would appear to indicate a need

[1]There are many types of analyses that could be performed on these data that have not been done because of differing priorities and lack of resources. For example, one interesting area of investigation that was begun, but not completed because of the apparent complexities of the issue, is the relationship between cigarette smoking, health variables, and weight. However, NCHS does make available to researchers public-use data tapes from the various surveys, so that they can conduct their own analyses (*12*).

TABLE 9.—Percent of persons 17 years old and older, with one or more hospital episodes in the year prior to interview, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	13.1	13.5	14.4	12.7
17–44	12.3	13.8	11.7	12.0
45–64	12.9	12.3	15.1	12.1
65+	16.5	16.5	19.7	15.3
Male				
17+	10.2	10.5	12.8	8.3
17–44	7.0	8.6	8.0	5.3
45–64	13.1	12.4	14.5	12.5
65+	17.4	19.0	18.5	14.9
Female				
17+	15.7	16.9	17.5	14.7
17–44	17.2	19.5	16.8	15.9
45–64	12.8	12.3	16.2	12.0
65+	15.8	12.9	23.1	15.4

SOURCE: Wilson, R.W. (*16*).

not only for increased public education, but also for increased educational programs among health professionals. About two-thirds of all present smokers had tried to stop smoking at some time (Table 12).

Since detailed smoking history information was not obtained, it is difficult with these data to determine the more precise relationships between illness, physicians' advice to stop smoking, and actual attempts to stop. Some of the studies conducted in the past by the National Clearinghouse for Smoking and Health and reported elsewhere in this report have attempted to investigate these relationships as well as some of the more attitudinal and psychological aspects of smoking.

Respondents to the Health Interview Survey were asked if a doctor had ever told them they had heart trouble. Among persons under 65 years of age, a larger proportion of both present smokers and former smokers had been told that they had heart trouble compared with persons who had never smoked (Table 13). For example, 15 percent of the male former smokers aged 45 to 64 had been told they had heart trouble compared to 10 percent of those who had never smoked. There is some difficulty interpreting the data for persons over 65 years old, where a higher proportion of those who had never smoked report heart

TABLE 10.—Percent of persons 17 years old and older, with five or more physician visits in the year prior to interview, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	24.8	23.7	27.0	26.1
17–44	22.0	23.0	23.4	22.3
45–64	25.5	24.3	26.4	27.2
65+	34.2	27.0	37.1	34.9
Male				
17+	17.9	16.9	22.9	17.3
17–44	13.4	14.1	16.1	13.1
45–64	21.3	20.7	24.1	20.8
65+	30.2	24.8	33.5	30.4
Female				
17+	30.8	31.3	34.5	30.0
17–44	29.9	32.9	33.5	27.6
45–64	29.2	28.3	31.1	29.4
65+	37.0	30.1	46.8	36.3

SOURCE: Wilson, R.W. (*16*).

trouble, since many of the smokers with heart trouble have already died.

Of those smokers who have been advised by a doctor to stop, about 28 percent were advised to stop because of respiratory disease. About 23 percent of the smokers 65 and older were advised to stop because of circulatory problems, but this proportion drops for the younger smokers. Hardly any smokers reported they were advised to stop because of cancer. However, these data on cancer are also misleading; since the survival rate for lung cancer is relatively low, many smokers would not live long enough to report that the doctor had told them to stop smoking.

The first cycle of the Health and Nutrition Examination Survey contained a number of questions that, when combined, formed an Index of General Psychological Well-Being.[2] This measure provides data on another dimension of the relationship between cigarette smoking and health. In general, current cigarette smokers were found

[2] The Index of General Psychological Well-Being is composed of 18 items with a total of 128 response options. The response option for each item that indicates the greatest distress is scored zero. Some of the items and their response options also permit representations of high-level positive well-being. The total index scores range from 0 thru 110, with low scores indicating distress and high scores indicating positive well-being. Generally positive affect is represented by scores above 78 and marginal well-being by scores of 73 to 77. The median score for the population estimates of adults, 25 to 74 years old, was between 83 and 84 (*5*).

TABLE 11.—Percent of persons 17 years old and older who have ever smoked and who were ever advised by a physician to stop smoking, by smoking status, sex, and age: United States 1974

Smoking status and sex	All ages 17+	17–44	45–64	65+
Total ever smoked				
Both sexes	23.9	19.6	29.2	30.1
Male	23.5	17.8	29.2	32.4
Female	24.4	21.8	29.2	25.3
Former smoker				
Both sexes	21.3	14.2	26.3	28.2
Male	22.7	13.5	28.0	29.6
Female	18.9	15.0	22.6	24.2
Present smoker				
Both sexes	25.2	21.5	31.1	32.6
Male	24.0	19.4	30.2	37.0
Female	26.6	23.9	32.1	26.2

SOURCE: Wilson, R.W. (*16*).

TABLE 12.—Percent of present cigarette smokers 17 years old and older who have tried to stop smoking, by sex and age: United States, 1974

Sex	All ages 17	17–44	45–64	65+
Both sexes	64.7	66.0	62.8	61.1
Male	66.0	66.7	65.1	63.3
Female	63.3	65.3	60.2	57.9

SOURCE: Wilson, R.W. (*16*).

to have a slightly lower level of well-being than were nonsmokers. Heavy smokers (more than 1 1/2 packs a day) under 65 years of age report the lowest levels of general well-being and report mean levels of general well-being at marginal levels or lower.

Conclusions

The available evidence in the relationship between cigarette smoking and illness and disability has increased markedly since the first

TABLE 13.—Percent of persons 17 years old and older who have been told by a doctor that they had heart trouble, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	9.0	7.8	12.9	9.4
17–44	4.2	4.8	4.7	4.1
45–64	11.1	11.6	14.9	9.9
65+	22.9	17.9	28.5	23.3
Male				
17+	8.9	8.2	13.8	8.4
17–44	3.8	4.5	4.7	3.6
45–64	12.0	13.0	15.2	10.0
65+	24.5	18.6	28.5	26.5
Female				
17+	9.0	7.4	11.4	9.9
17–44	4.6	5.1	4.9	4.4
45–64	10.3	10.0	14.3	9.9
65+	21.8	16.8	28.5	22.4

SOURCE: Wilson, R.W. (*16*).

Surgeon General's report was issued, largely as a result of data collected from national probability surveys conducted by NCHS. These data range from the standard health indicators, such as measures of chronic and acute illness and measures of disability days, to less commonly used indicators of lifestyles. The results of analysis performed on these data vary from the more frequently reported findings on disability to data from the Index of General Psychological Well-Being, first reported in this chapter.

The findings tend to be consistent with the large amount of evidence on the relationship between cigarette smoking and mortality, i.e., people who smoke cigarettes report more illness and disability than people who have never smoked cigarettes. While many studies show a reduction in the risk of mortality among former cigarette smokers, data on disability and illness often show continued high risk for former smokers, indicating both a lack of refinement in the current data to distinguish between types of former smokers as well as the fact that once certain diseases occur they do not go away.

The most important aspect of these data collected by NCHS lies not in the substantive analysis prepared by the NCHS staff, but in the

analytic potential of the data to other researchers in the smoking area through the use of NCHS's public-use data tape program.

Morbidity: References

(1) AHMED, P.I., GLEESON, G.A. Changes in Cigarette Smoking Habits Between 1955 and 1966. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Center for Health Statistics, Series 10, No. 59, PHS Publication No. 1000, April 1970, 33 pp.

(2) BELLOC, N.B. Relationship of health practices and mortality. Preventive Medicine 2: 67-81, 1973.

(3) FAZIO, A.F. A Concurrent Validational Study of the NCHS General Well-Being Schedule. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics, Series 2, No. 73, DHEW Publication No. (HRA) 78-1347, September 1977, 53 pp.

(4) HAENSZEL, W., SHIMKIM, M.B., MILLER, H.P. Tobacco Smoking Patterns in the United States. Public Health Monograph No. 45. U.S. Department of Health, Education, and Welfare, Public Health Service, PHS Publication No. 463, 1956, 111 pp.

(5) HAMMOND, E.C. Smoking in relation to death rates of one million men and women. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(6) HAMMOND, E.C., HORN, D. Smoking and death rates - Report on 44 months of follow-up of 187,783 men. Journal of the American Medical Association 166(10): 1159-1172, 1958.

(7) MADOW, W.G. Net Differences in Interview Data on Chronic Conditions and Information Derived From Medical Records. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Center for Health Statistics, Series 2, No. 57, DHEW Publication No. (HSM) 73-1331, June 1973, 58 pp.

(8) MILLER, H.W. Plan and Operation of the Health and Nutrition Examination Survey: United States, 1971-1973. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics, Series 1, Nos. 10a, 10b, DHEW Publication No. (HSM) 73-1310, February 1973, 123 pp.

(9) MOSS, A.J., SCOTT, G. Characteristics of Persons with Hypertension: United States, 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Series 10, No. 121, DHEW Publication No. (PHS) 79-1549, 1979. (In press)

(10) NATIONAL CENTER FOR HEALTH STATISTICS. Cigarette smoking: United States, 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Center for Health Statistics. Monthly Vital Statistics Report 21(3)(Supplement), June 2, 1972, 8 pp.

(11) NATIONAL CENTER FOR HEALTH STATISTICS. Health, United States, 1976-1977. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics, National Center for Health Services Research, DHEW Publication No. (HRA) 77-1232, 1977, 441 pp.

(12) NATIONAL CENTER FOR HEALTH STATISTICS. Standardized Micro-Data Tape Transcripts. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, DHEW Publication No. (PHS) 78-1213, June 1978, 36 pp.

(13) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Smoking and Illness. U.S. Department of Health, Education, and Welfare, Public Health Service, Bureau of Disease Prevention and Environmental Control, National Center for Chronic Disease Control, National Clearinghouse for Smoking and Health, PHS Publication No. 1662, July 1967, 6 pp.

(14) WILSON R.W. Cigarette Smoking and Health Characteristics. United States, July 1964-June 1965. U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics, Series 10, No. 34, PHS Publication No. 1000, May 1967, 64 pp.

(15) WILSON R.W. Cigarette smoking, disability days and respiratory condition. Journal of Occupational Medicine 15(3): 236-240, March 1973.

(16) WILSON R.W. Testimony presented at Regional Forum sponsored by the National Commission for Smoking and Public Policy. Philadelphia, June 16, 1977, 27 pp.

4. CARDIOVASCULAR DISEASES.

National Heart, Lung, and Blood Institute

CONTENTS

LIST OF TABLES

Atherosclerosis

Most studies of the pathology of atherosclerosis have been based on autopsies of coroner's or hospital populations in which only a limited fraction of decedents have been examined. They have been valuable for an understanding of the pathogenesis and complications of atherosclerosis. Such studies cannot be taken to represent the prevalence of atherosclerosis in the general population. Studies which attempt to minimize selection bias at autopsy by examining the great majority of decedents in a defined population are rare (*66, 114*).

The most extensive and comprehensive autopsy study that has been conducted is the International Atherosclerosis Project, which collected data from 15 cities in 14 countries and recorded more than 21,000 autopsies according to a standardized protocol and method of evaluation (*85*). The study found a remarkably frequent occurrence of atherosclerotic lesions in the United States; detailed international or geographic differences in the severity of atherosclerosis; raised the issue of whether childhood atherosclerosis evolves into adult forms of atherosclerosis; and documented that, on the average, there are more frequent and extensive coronary plaques in cases with coronary heart disease than in comparison cases regardless of age, sex, geographic location, or race. Approximately the same prevalence and extent of advanced atherosclerosis were seen in coronary heart disease cases regardless of age, sex, and, with few exceptions, of geographic location. While individuals may show considerable variability in the severity of atherosclerosis, the conclusion is that coronary atherosclerosis is of primary importance in the development of coronary heart disease in a population (*133*). Another extensive study in five towns in Europe has been reported by the World Health Organization (WHO) (*66*).

The Nature of Atherosclerosis in Man

Information about atherosclerosis in man derives from pathological studies and from associations observed in clinical or epidemiological studies.

The lesion or plaque is a cellular proliferation in the arterial intima. It contains chiefly smooth muscle cells, but also fibrocytes and cells typical of chronic inflammation. Lipid is commonly present along with cellular products such as collagen, elastic tissue, glycosaminoglycans, and cellular debris from necrosis. Elements of thrombus are common both in and on the plaque. Focal calcification is frequent. Thus, a highly variable and complex range of lesions can be considered under the term atherosclerosis.

The concept of the development of lesions is a synthetic one derived from the observation of many lesions rather than from the actual observation of a single lesion over time. At present, there is

controversy over whether the fatty streaks seen in childhood are the precursors of the more fibrous, raised, and complex adult lesions, or whether some or many adult lesions arise independently of fatty streaks (which also occur in adult life) (*89*). The usual prevalence of atherosclerotic lesions in adult life is such that the aorta and carotid arteries are affected about a decade before the coronary arteries and cerebral arteries, and the latter are affected a decade in advance of the arteries of the leg. However, such relationships are not constant; individual variations are common and, indeed, specific clinical syndromes of localized atherosclerosis are recognized.

Atherosclerotic plaques distort and narrow the calibre of the affected arteries. This reduces the flow of blood through them and creates the condition called ischemia. When ischemia becomes severe, the organs and tissues deprived of blood no longer function properly and clinical disease occurs in the form of coronary heart disease, stroke, or peripheral vascular disease. The occurrence of severe ischemia may arise because of the enlargement of plaques, or it may be precipitated by the development of thrombosis (clot) on plaques, or by other complications that can affect them. The various diseases resulting from ischemia are considered subsequently in this chapter.

Conditions that predispose to the onset of disease in the future, increasing the risk of its occurrence, are spoken of as "risk factors". The concept of risk factors arose from clinical experience with cardiovascular disease, particularly coronary heart disease, rather than with atherosclerosis itself. Prospective population studies such as those considered in the Pooling Project (*107*) further developed the predictive value of selected factors such as cigarette smoking and levels of blood pressure and cholesterol.

Risk factor associations for atherosclerosis as distinct from coronary heart disease are limited in their documentation. The International Atherosclerosis Project (*85*), dealing with autopsy data, concluded that the severity of atherosclerosis is closely associated with the proportion of total calories derived from saturated fat in the diet of the population, with the serum cholesterol levels measured in the population, and with hypertension. The association with smoking was not examined. The WHO (*66*) study documented the association of a number of disease states and conditions with the extent and severity of atherosclerosis. A recent report has described the associations between several variables measured during life and the extent of atherosclerosis of the aorta and coronary arteries seen at autopsy in Japanese-Americans participating in a prospective cardiovascular risk factor study (*112*). Statistically independent associations were found by multivariate analysis between aortic atherosclerosis and age at death, cigarettes smoked per day, serum cholesterol concentration, and blood pressure level. Coronary atherosclerosis was related to relative body

weight, cigarettes smoked per day, and serum cholesterol concentration.

Models of experimental atherosclerosis in species as different as birds, rodents, dogs, swine, and nonhuman primates have been developed. The majority of these models have been induced by feeding saturated fat or cholesterol leading to fat-rich plaques that resemble the fatty streaks of childhood or the very fat-laden plaques occasionally seen in adult life. Other experimental techniques of inducing lesions are: the use of physical injury to arteries leading to acute proliferative plaque development with little or no lipid accumulation; the induction of intimal thrombi with their tissue organization yielding fibro-fatty plaques; immunologic vascular injury with lipid or cholesterol feeding; and, recently (in chickens), viral infection. Among different species of nonhuman primates, the same dietary regimen will produce characteristically a somewhat different distribution of plaques in the arterial tree. Different experimental diets will produce lesions that are characteristically more fatty or more fibrous. Spontaneous fibrous or fibro-fatty plaques occur in many species including birds, rabbits, swine, and nonhuman primates. The enhancement of spontaneous atherogenesis in chickens by polycyclic hydrocarbons has been reported (*1*). A strong genetic control exists in pigeons both for the expression of experimental atherosclerosis and for its localization predominantly either in the aorta or in the coronary arteries. Thus, there is a wide variety of experimental and spontaneous animal models available with which to study atherogenesis.

A huge body of literature deals with the pathogenesis of human and experimental atherosclerosis. Several recent reviews provide a detailed and critical consideration of current concepts (*3,21,22,84,89, 117,119,126,155,156*). The various interrelationships of different pathogenetic processes such as cellular proliferation, lipid accumulation, and thrombotic phenomena are not fully understood. Nevertheless, it is possible to synthesize available data into a frequently explored major working hypothesis of the initial stages of atherogenesis based on extensive experimental data (see particularly *117,155,156*) that support the pathogenetic concept that the arterial endothelium functions normally to separate the intima and media from the blood. The hypothesis holds that local injury results in failure of this barrier function or in loss of endothelial cells and exposure of the subendothelium to whole plasma and to blood platelets. Platelets and plasma contain growth factors capable of inducing smooth muscle cells in the intima and adjacent media to multiply. This loss of barrier function also allows macromolecules such as fibrinogen and very low density (VLDL), intermediate, low density (LDL), and high density (HDL) lipoproteins freer access to the vessel wall. More lipid is internalized by intimal smooth muscle cells and macrophages than their lysosomal digestive systems can catabolize, and they become overloaded with fat

and cholesterol. The amount of sterol externalized metabolically by such cells may exceed the local capacity of HDL to accept and transport it away. Cellular necrosis occurs and both intracellular and structural lipids spill into the extracellular compartment of the intima where they contribute to the lipid burden. The sequence in this hypothesis is endothelial injury, impaired barrier function, and subendothelial exposure to plasma and to platelets, followed by cellular metabolic overload, failed homeostasis, cellular proliferation, and necrosis. In addition, the stigmata of mild chronic inflammation occur promptly, and appearances suggestive of a migration of smooth muscle cells to the lesion are seen. Local cellular production of glycosaminoglycans, collagens, and elastin follows. Progression of the lesions can be through a continuation or cyclical repetitions of the same processes or by thrombosis. Thrombosis, necrosis, calcification, hemorrhage, and ulceration may further complicate the lesion. A large number of agents are suspected to be capable of injuring endothelium and altering its barrier function. It should be noted that the foregoing views are derived from animal experimentation but appear to be congruent with the nature of atherosclerosis in humans.

A novel theory of atherogenesis has been proposed recently that does not necessarily contradict the concepts stated above, but which designates a prior abnormality of the smooth muscle cells that proliferate to form plaques. It has been found that the cells that constitute individual fibrous atherosclerotic plaques in adults are homogenous for an isoenzyme marker. That is, each plaque must either be monoclonal or initially polyclonal with the development of a monotypic character as it has developed (*21*, *22*, *104*, *105*, *135*). If the correct interpretation is that plaques are monoclonal, it is necessary to consider whether this represents a mutation or transformation of vascular cells leading to a local proliferation analogous to benign smooth muscle cell neoplasia. In this view, environmental agents capable of inducing somatic cell mutation, including mutagens derived from tobacco, could be fundamental to the pathogenesis of atherosclerotic plaques, and might cause the primary cellular changes facilitating other conventional risk factors or agents to produce lesions in man. At the present time, data to settle the validity of these interpretations are not available.

The Effect of Smoking on Atherogenesis

Autopsy studies in which smoking behavior has been recorded are not common. Table 19 (pp. 49-51) of the 1976 reference edition of the report, *The Health Consequences of Smoking* (*138*), lists several investigations into this aspect of smoking. This table is reproduced below as Table 1.

These investigations compare, within their particular group of study cases, smokers with nonsmokers and different levels of smoking,

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Severity of aortic sclerosis			Conclusions	Comments
				Above average	Average	Below average		
Wilens and Plair, 1962, U.S.A.	989 consecutive male autopsies at New York City VA hospitals.	Routine clinical records of previous and present admissions.	NS	9.9(161)	60.2	29.8	The authors conclude that in 60 percent of cases, the degree of sclerosis at autopsy was commensurate with age of patient, regardless of smoking habits. In the remaining 40 percent there is evidence that cigarette smoking may be associated with an above-average degree of aortic sclerosis.	Smoking data unavailable for 120 cases. Each aorta specimen given an "atherosclerotic age" by comparison with a standard. If "atherosclerotic age" was found to be 10 years more than real age, the aorta was said to show above-average sclerosis. †$p<0.001$ comparing 9.9 with 25.1 and 29.8 with 13.6.
			<20	19.1(152)	63.2	17.8		
			20–30	26.4(288)	62.5	11.1		
			>30	†25.1(199)	61.3	†13.6		

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Auerbach, et al., 1965, U.S.A.	1,372 autopsies of male patients in Orange, New Jersey, VA hospital for whom smoking habit data were available and who did not have overt CHD at death.	Interview with next of kin.	Degree of coronary artery atherosclerosis (overall age-adjusted results) No atherosclerosis / Slight / Moderate / Advanced NS ..... 5.6(69) / 57.3 / 21.8 / 15.3 Current cigarette <20 ..... 2.6(139) / 30.9 / 37.3 / 29.2 20 39 ..... 0.8(299) / 19.7 / 42.1 / 37.4 >40 ..... 0.6(144) / 18.1 / 35.4 / 45.9	The authors conclude that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers and that the percentage increased with amount of cigarette smoking. This relationship persisted even when cases were matched for age and cause of death.	
Avtandilov, 1965, Russia	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	Comparative size of mean area of atherosclerotic legions in inner coat of coronary arteries. Right coronary artery: SM / NS; Left coronary artery: SM / NS 30–39 ..... †15.5(30) / 1.3(32) / †6.3 / 2.2 40–49 ..... †23.6(34) / 11.5(27) / †15.8 / 4.4 50–59 ..... †36.3(39) / 14.8(39) / †27.9 / 9.9 60–69 ..... †31.9(32) / 23.8(36) / †26.5 / 22.5 70–79 ..... 41.9(18) / 31.7(36) / 26.1 / 35.8	The author concludes that the worst changes were found in the left and right coronary arteries with less severe changes in circumflex artery and aorta.	Causes of death 96-atherosclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at $p<0.05$ level.

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Sackett, et al., 1968, U.S.A.	893 total, including 433 male and 450 female (white) patients autopsied at Roswell Park Memorial Hospital. Represents all deaths 1956–1964 exclusive of 81 male pipe and cigar smokers and 55 incomplete files.	Patient interview on admission.	The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.	The authors conclude that among males, ". . . a large increase in the severity of aortic atherosclerosis occurred in the groups using either cigarettes only or both cigarettes and alcohol as compared with the group using neither cigarettes nor alcohol . . . there was only a small and statistically insignificant difference between the group using cigarettes alone and the group using both cigarettes and alcohol. . . ." The severity of aortic atherosclerosis increased with increasing use of cigarettes, when measured both by intensity and by duration of smoking.	

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Viel et al., 1968 Chile	1,150 males and 290 females who died violently in 1961-1964. Smoking information available only on 566 males.	Interview with relatives.	The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.	The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible."	
Strong et al., 1969 U.S.A.	747 males 20-64 years of age autopsied between 1963-1966 at Charity Hospital in New Orleans.	Interview with next of kin within 8 weeks of death.	Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).	The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers."	This report concerns only ages 25–64. No data on statistical significance provided.

	25-34	35-44	45-54	55-64
White				
NS	2(5)	19(14)	20(6)	30(11)
1-24 cigarettes/day	9(14)	17(10)	26(16)	39(7)
>25 cigarettes/day	12(9)	31(14)	26(25)	39(20)
Negro				
NS	4(14)	3(8)	16(11)	17(14)
1-24 cigarettes/day	3(39)	11(31)	14(30)	28(22)
>25 cigarettes/day	17(10)	14(17)	29(12)	16(11)

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

SOURCE: U.S. Public Health Service (*1968*).

particularly cigarettes. The trend in such data is that a history of cigarette smoking is associated in a dose-related manner with the severity or extent of aortic or coronary atherosclerosis. In some studies, the differences in atherosclerosis between smokers and nonsmokers are statistically significant. In others, the trend is congruent but not statistically significant. These autopsy studies documenting smoking behavior have generally not permitted analysis for risk factors other than smoking that might affect the severity of atherosclerosis, and have not permitted multivariate analysis common in the large prospective population studies dealing with the morbidity and mortality of heart attack.

A recent report (*132*) has provided additional information by analyzing its data in two categories according to the presence or absence of diseases associated with smoking on the one hand (emphysema, lung cancer) and coronary heart disease on the other (myocardial infarction, hypertension, diabetes, stroke). Atherosclerotic involvement of both the coronary arteries and aorta was greatest in heavy smokers and least in nonsmokers in the total sample of 1,320 men, and in each of the two categories of disease noted above. This study of men aged 25 to 64 years represents the examination at autopsy of residents of the Greater New Orleans area who died in Orleans parish from any cause. Smoking history information, generally, was obtained retrospectively from a respondent with a close knowledge of the decedent (*88*). The WHO study of five towns reported on the association between smoking and atherosclerosis only from Yalta (*79*). The study has less relevance than the New Orleans study for the United States population. It reported a positive association between raised plaques in the aorta and smoking. It failed to find a clear association between coronary artery narrowing or infarction of the heart and smoking. Calcification of plaques in the aorta and coronary arteries was related to coexisting alcohol consumption.

While data from most autopsy series are inadequate for multivariate analysis, several prospective population studies now have sufficient standard risk factor data together with autopsy findings to present preliminary analyses (*131*). A prospective study of cardiovascular risk factors among 8,000 Japanese-Americans living on the island of Oahu has recently published more extensive systematic pathological findings on the vessels in 137 autopsies from the cohort in association with prior risk factor observations. Cigarettes smoked per day were positively and independently associated with the extent of atherosclerosis affecting both the aorta and coronary arteries. The aortic regression coefficient was statistically significant at the 0.05 level and the coronary coefficient at the 0.01 level (*112*).

A recent study of autopsies from a Veterans' Administration hospital (*15*) reported that advanced coronary artery atherosclerosis

was 4.4 times as high in those smoking two packs or more per day as in those who never smoked. This study also examined the coronary arteries microscopically and found that fibrous thickening of the coronary arteries and intramyocardial small arteries was more frequent in smokers. The most marked difference between smokers and nonsmokers was found in the arterioles of the myocardium. Advanced hyaline thickening of arterioles was found in 90.7 percent of those smoking two or more packs per day, in 48.4 percent of those smoking less than one pack per day, and in none of those who never smoked regularly. The study reported on a selected series of 1,056 autopsies from which coronary arterial disease deaths, diabetes, and those with hearts weighing more than 500 g were excluded. A recent report (*98*) reaffirms the occurrence of intramyocardial small-artery sclerosis in smokers. A decrease in arteriolar muscle wall thickness in the myocardium, especially in smokers, was found that was attributed to a lower blood perfusion pressure distal to the small artery lesions noted above.

Overall, there does not appear to be substantial reason to doubt that male cigarette smokers examined at autopsy manifest more coronary and aortic atherosclerosis than nonsmokers. The effect is dose-related. Hyaline thickening of arterioles in the heart apparently is strongly associated with smoking. Specific morphological features of plaques that would be characteristic of smoking have not been delineated.

Experiments in Animals

Table A23 (pp. 116-118) of the 1976 report, *The Health Consequences of Smoking* (*138*), lists seven experiments in which nicotine had inconsistent effects on both spontaneous and diet-induced atherosclerotic lesions in rabbits. In an additional paper, Schievelbein (*120*) has reported no induction of spontaneous arteriosclerotic lesions by nicotine in rabbits, although the aortic content of free fatty acids and of calcium was reported increased in this long-term experiment. Fisher, et al. (*42*) reported no increase in atherogenic effect with small doses of nicotine in animals that were also hypertensive and fed cholesterol.

These experiments have involved the injection or oral administration of nicotine rather than inhalation and generally have employed unusually large doses of nicotine. Equivalent experiments in species such as swine or nonhuman primates that might be preferable to rabbits have apparently not been performed, nor have experiments that simultaneously involve whole smoke or carbon monoxide (CO) administration. The overall impression from available data is that nicotine does not affect atherogenesis in animals. Specific experimental data, however, are unavailable to permit a conclusion about a possible effect on experimental atherogenesis of nicotine inhaled in smoke in doses experienced chronically by smokers.

A small number of experiments involving the effect of CO on atherogenesis have been reported. Initial reports found an enhancement of atherogenesis in the aorta of cholesterol-fed rabbits (*13, 14*) and in the coronary arteries, but not the aorta, of squirrel monkeys (*148*). However, subsequent experiments (*130*) on cholesterol-fed rabbits from the same laboratory, which had earlier concluded that there was a positive effect of CO on atherogenesis, have led to the conclusion that there is no direct enhancement of cholesterol accumulation in the aorta. These more recent short-term experiments controlled dietary hypercholesterolemia by pair feeding and also studied the uptake of radioactive tracer cholesterol from the blood by the aorta. No macroscopically visible atherosclerotic lesions were seen in any animals, although the aortic free cholesterol of the animals fed cholesterol was increased in comparison with the animals receiving no cholesterol. The free cholesterol content of the aortic arch was increased significantly in the animals exposed to CO, but there were no significant differences for the thoracic aorta or for the combined segments. The aortic uptake of labeled cholesterol from the blood was not affected by CO exposure in either hypercholesterolemic or normal animals. The authors suggest that their earlier result may have been due to a relative excess of hypercholesterolemia in CO-exposed animals that had not been pair fed to maintain equal levels of plasma cholesterol. Possible effects of CO diminishing VLDL secretion and chylomicron catabolism have been discussed by Topping (*136*). Other recent studies by Davies and colleagues (*32*) failed to find that exposure of cholesterol-fed rabbits to CO for 4 hours per day yielding carboxyhemoglobin (COHb) levels of 20 percent produced any differences in the aortic content of lipids including cholesterol. The morphological extent of coronary atherosclerosis was greater in the animals exposed to CO. Malinow and associates (*80*) failed to find an enhancing effect of CO in sodium chloride and cholesterol-fed cynomolgus monkeys. In experiments (*2*) with White Carneau pigeons (which develop fibro-fatty spontaneous as well as dietary atherosclerosis), no enhancement of spontaneous aortic atherogenesis was found after exposure to CO. Enhancement of coronary atherogenesis was seen in cholesterol-fed birds exposed to CO and killed after one year of exposure, but not in those sacrificed after about a year and a half. Exposure also enhanced hypercholesteremia. It has been reported that spontaneous arteriosclerotic disease in rabbits is aggravated by exposure to CO (*147*).

It has been reported that, in rabbits, hypoxia increases cholesterol atherogenesis and hyperoxia diminishes it (*72, 74*). Hyperoxia has also been reported to enhance the regression of plaques in rabbits (*139*). Hypoxia and CO have been reported to cause subendothelial edema in rabbits (*13,73*) and smoke inhalation (*46*) to lead acutely to desquamation of aortic endothelial cells and adhesion of platelets in rabbits.

Auerbach and associates have reported on the effect of the chronic inhalation of whole smoke through a tracheostomy apparatus in beagle dogs. A hyaline thickening of myocardial arterioles was found in them, the degree of change being related to the duration and amount smoked (*16*).

At the present time, animal experiments on atherogenesis and CO have provided conflicting data and must be regarded as unsatisfactory. Experiments have variously employed continuous and intermittent exposure, have estimated lesions biochemically and morphologically, and have used diverse short- or long-term dietary loads so that comparisons of results are difficult. Animal experiments remain to be done in which CO or nicotine are varied in a setting of whole smoke administered by inhalation without aversive stress and in a suitable atherogenic context.

Research Needs

While current autopsy data on humans leave no reasonable doubt that smoking promotes atherosclerosis of the aorta and coronary arteries in men, equivalent data do not exist for women or for other major arterial beds. Within practical limits of study, it would be informative for pathogenetic concepts to have better information on multiple-risk factors, including oral contraceptives in conjunction with smoking and with smoking cigarettes of different potential hazard, in autopsy studies. In particular, it would be of great interest to know the influence of smoking on the development of the common fatty streaks and occasional fibrous plaques found at autopsy in adolescents and young adults.

The mechanisms by which smoking enhances atherogenesis require elucidation. Such information might assist in the fabrication of a cigarette less hazardous in terms of atherogenesis and its consequences. Conceptual frameworks and biological systems exist within which to study the mechanisms by which smoking enhances atherogenesis. They include effects on the arterial endothelium, which may alter its permeability to macromolecules; effects on endothelial-platelet interactions which influence thrombogenesis or affect the proliferation of intimal cells; effects on the metabolism of the vessel wall; and systemic and local effects on lipoprotein or sterol metabolism. With respect to the monoclonal hypothesis, research to identify mutagens or promoting agents at the level of the vessel wall is feasible.

A necessary step in such research will be the use of animal models and biological systems that have a high level of analogy with man and that are credible both in terms of experimental atherogenesis and in their exposure to cigarette smoke.

Conclusions

Cigarette smoking has been shown to enhance the prevalence and extent of atherosclerosis of the aorta and coronary arteries in men. Experiments on the effects of nicotine or carbon monoxide on experimental atherogenesis in animals have produced conflicting results and are inconclusive. Chronic inhalation of whole smoke is associated with the development of hyaline thickening of myocardial arterioles in dogs. In man, cigarette smoking is associated with fibrotic and hyaline changes in small arteries and arterioles in the myocardium.

Myocardial Infarction

The Nature of Myocardial Infarction

Heart attack as generally understood can comprise nonfatal or fatal myocardial infarction, cardiac arrest or asystole, and cardiac standstill or ventricular fibrillation. Asystole and fibrillation result in sudden cardiac death. These conditions are generally the result of cardiac ischemia which, in turn, is generally attributable to coronary atherosclerosis, although other conditions may uncommonly precipitate heart attack.

Myocardial infarction is that condition in which a volume of heart muscle fibers in a discrete part of the heart dies because of inadequate circulation. It is generally larger than 5mm in diameter and may be several centimeters in major diameter. It may vary from a small subendocardial portion of the heart to the full thickness of the myocardial wall. It may, particularly when subendocardial in location, impinge on the conducting system of the heart and be conducive to disturbances in conduction. The infarction may affect primarily the pumping capacity of the muscle and lead to acute or chronic circulatory failure. The most common location of infarction involves the left ventricle, but involvement of the right ventricle and atria is common. If the myocardial infarction does not prove to be fatal, it may be subject to local extension during the acute episode of illness. Healing is by scar formation. The patient is at high risk of a second attack.

The association between atherosclerosis of the coronary arteries and myocardial infarction is close. Most cases examined at autopsy show an involvement of about 70 percent or more of the surface of the major vessels, and more than 50 percent stenosis of the lumen with or without recent thrombosis. However, a small minority of cases show less extensive lesions and narrowing, and it has been speculated that these infarctions may have arisen because of vascular spasm, or because of transient vascular occlusion by thrombi that have dissolved after obstructing the coronary circulation.

Ischemia of a local mass of heart muscle initiates a complex chain of biochemical, functional, and structural events at the level of the heart muscle cell that continues to be a subject for intensive research. A

reduction in arterial blood flow such that cellular oxygen demand is not met by oxygen supply causes myocardial cells to shift their metabolism to anaerobic glycolysis and to accumulate lactate and other acidic metabolites. Such acidosis depresses cellular contractility. For reasons that remain to be clarified, cell membranes are damaged by ischemia. Moreover, the mitochondria are sensitive to ischemia and rapidly lose their ability to synthesize adenosine triphosphate, and are unable to maintain the energy requirements of the cell to live and function. Cell death ensues (*65*, *137*). The organized contraction of the heart is integrated by the sequential spread of an electrical stimulus. Ischemia, with or without overt infarction, can disrupt this integration and alter rhythmic stimulation, causing bradycardia or asystole or, more commonly, aberrant foci of electrical activity and fibrillation.

Hypoxia is not identical with ischemia since hypoxia can occur while the circulation maintains the local concentrations of other ions and substrates. However, the lack of adequate cellular oxygen is so important a part of the events summarized above that the addition of hypoxia to a marginally tolerated ischemia may initiate critical changes.

Since the major risk factors can be shown to enhance atherogenesis, it is usually implied that their association with heart attack is through the ischemia resulting from coronary atherosclerosis. However, direct effects upon cardiac function may also play a role. Hypertension increases the work and mass of the heart and creates a larger nutritional demand and relative ischemia. Nicotine releases catecholamines and transiently increases cardiac rate and work. Carbon monoxide decreases oxygen availability to the heart.

Animal models of acute myocardial infarction include embolism of the coronary arteries, slow or rapid constriction of arteries, intimal sclerosis and narrowing by various techniques and, by dietary cholesterol, atherosclerosis leading to acute or subacute myocardial ischemia and infarction. These different models can serve different experimental purposes. Each has limited analogy to myocardial infarction in man because infarction in man is itself a pathologically variable phenomenon and because of anatomical differences in size and circulation between animal and human hearts. Perhaps the model creating events most like those in man is the nonhuman primate (particularly M. fascicularis) with advanced dietary atherosclerosis. It is however, a variable one (*58*).

Summary of Epidemiological Data

The epidemiological concept of risk factors for myocardial infarction is based on data gathered prospectively or retrospectively about myocardial infarction rather than about atherosclerosis per se. As noted in the section on atherosclerosis, the data that associate risk factors with human atherosclerosis seen at post mortem are limited. On the other

hand, there is a very large body of data, suitable for treatment by sophisticated analytical methods, that associates risk factors with myocardial infarction. Usually, the data are treated in terms of fatal infarcts including both sudden and nonsudden (acute) death. However, analyses have dealt with sudden death alone, morbidity, and congestive heart failure in individuals free of detectible heart disease on initial study, individuals with some evidence of disease when first seen, and those experiencing second heart attacks.

Prospective studies of risk factor associations with myocardial infarction or coronary heart disease (CHD) have identified a number of clinical descriptors strongly associated with liability to future infarction. These descriptors include age, male sex relative to female sex before age 65, blood cholesterol level, arterial blood pressure, and cigarette smoking. Other associations have also been documented, including the "Type A personality," diabetes mellitus, obesity, blood uric acid, the use of oral contraceptives, hematocrit reading, evidence of coronary heart disease or other atherosclerotic disease, vital capacity, family history, and physical inactivity. Recently high density lipoprotein (HDL) has been shown to be apparently protective against myocardial infarction (*49, 92*).

Reports dealing with risk factors, particularly smoking, but in many studies with other risk factors as well, have been extensively tabulated in the 1976 reference edition of *The Health Consequences of Smoking.* (*138*) (Tables 1-4, pp. 19-31; Tables 9-14, pp. 38-41; Table A6, pp. 89-93; Tables A17-A18, pp. 101-102). The tables of the prospective studies of CHD mortality (Table 2, pp. 22-25) and morbidity (Table 4, pp. 26-31) are reproduced below as Tables 2 and 3. The major risk factors of blood cholesterol level, blood pressure, and cigarette smoking are independent and strong predictors of susceptibility to CHD. Each is dose-related to the liability to CHD, and each of about the same importance when considered independently. Cessation of smoking and reduction of high blood pressure will reduce the risks of cardiovascular disease. As summarized in Tables 15 and 16 on page 42 of the 1976 report (*138*) (and reproduced below as Tables 4 and 5), it has been found that ex-smokers suffer fewer myocaridal infarctions than continuing smokers. With reduced blood pressure it has been shown that less cerebrovascular disease and congestive heart failure occur. The effect of reducing blood cholesterol on liability to CHD remains under study.

Identified risk factors account for a major part but not all of the variance in CHD among a population. Cigarette smoking is an important risk factor, but it is not essential, nor is it, in those parts of the world in which people have levels of cholesterol in the range of about 160 mg percent, as strong a risk factor as in the United States. It has been reported from a follow-up study of about 265,000 adults over 40 years old in Japan (*99*) that smokers compared with nonsmokers have a relative mortality ratio of 1.22 for death from all causes and

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		Cigars, pipes		Age variation				Comments
Hammond and Horn, 1958, U.S.A.	187,783 white males in 9 states 50–69 years of age	Questionnaire and follow-up of death certificate	3 1/2	5,297	NS	1.00 (709)	$^2(p<0.001)$	Cigars		50–54	55–59	60–64	65–69	
					All smokers	1.70 (3361)	NS	1.00	NS	1.00 (90)	1.00 (142)	1.00 (204)	1.00 (273)	
					<10	1.29 (192)	SM	1.28 (420)	All smokers	1.93 (765)	1.85 (962)	1.66 (921)	1.41 (713)	
					10–20	1.89 (864)		Pipes	<10	1.38 (35)	1.38 (50)	1.17 (49)	1.27 (58)	
					20–40	2.20 (604)	NS	1.00	10–20	2.00 (213)	2.04 (258)	1.91 (235)	1.58 (158)	
					>40	2.41 (118)	SM	1.03 (312)	>20	2.51 (203)	2.47 (199)	1.92 (129)	1.56 (73)	
Doyle et al., 1964, U.S.A.	2,282 males, Framingham, 30–62 years of age. 1,913 males, Albany, 39–55 years of age.	Detailed medical examination and follow-up	10	93	NS	1.00 (20)								Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
			8		All smokers	2.40 (73)								
					<20	2.00 (17)								
					20	1.70 (20)								
					>20	3.50 (36)								
Doll and Hill, 1964, Great Britain	Approximately 41,000 male British physicians	Questionnaire and follow-up of death certificate	10	1,376	NS	1.00				35–44	45–64	65–84		
					All smokers	1.35	NS			1.00	1.00	1.00		
					1–14	1.29	1–14			3.73	1.40	1.71		
					15–24	1.27	15–24			4.45	1.73	1.27		
					>25	1.43	>25			1.36	1.92	1.58		

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Strobel and Gsell 1965 Switzerland	3,749 male Swiss physicians	Questionnaire and follow-up of death certificate	9	162	NS ..... 1.00 1-20 ..... 1.48 >20 ..... 1.76	NS ..... 1.00 SM 1.45		
Best, 1966 Canada	Approximately 78,000 male Canadian veterans	Questionnaire and follow-up of death certificate	6	2,000	NS ..... 1.00 All smokers 1.60 (1380) <10 ..... 1.55 (337) 10-20 ..... 1.58 (766) >20 ..... 1.78 (277)	Cigars NS .. 1.00 SM .. 0.98 (16) Pipes NS .. 1.00 SM .. 0.96 (95)	30-49 50-69 70 and over NS ..... 1.00 1.00 1.00 <10 ..... 0.97 (18) 1.56 (220) 1.71 (99) 10-20 ..... 1.45 (115) 1.67 (557) 1.29 (94) >20 ..... 1.85 (65) 1.76 (184) 1.73 (28)	
Kahn 1966 U.S.A.	U.S. male veterans 2,265,674 person years	Questionnaire and follow-up of death certificate	8 1/2	10,890	NS ..... 1.00 (2997) All smokers 1.74 (4150) 1-9 ..... 1.39 (439) 10-20 ..... 1.78 (2102) 21-39 ..... 1.84 (1292) >39 ..... 2.00 (266)	Cigars NS .. 1.00 SM .. 1.04 (623) Pipes NS .. 1.00 SM .. 1.08 (386)		

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Hirayama, 1967, Japan	265,118 Japanese adults over age 40	Trained interviewers and follow-up of death certificate	1	91	NS 1.00 (17) 1-24 1.13 (69) 25 1.00 (5)			Preliminary report
Kannel et al., 1968, U.S.A.	5,127 males and females age 30-59	Medical examination and follow-up	12	52	NS 1.00 (27) SM 20 2.20 (25)	(p= 0.05)		
Hammond and Garfinkel, 1969, U.S.A.	358,384 males 445,855 females age 40-79 at entry	Questionnaire and follow-up of death certificate	6	14,819	Males / Females NS 1.00 / 1.00 1-9 1.27 / 0.84 10-19 1.60 / 1.22 20-30 1.73 / 1.52 >40 1.77 / 0.61		Males 40-49 / 50-59 / 60-69 / 70-79 NS 1.00 / 1.00 / 1.00 / 1.00 1-9 1.60 / 1.59 / 1.48 / 1.14 10-19 2.59 / 2.13 / 1.82 / 1.41 20-30 3.76 / 2.40 / 1.91 / 1.49 >40 5.51 / 2.79 / 1.79 / 1.47 Females NS 1.00 / 1.00 / 1.00 1-9 1.31 / 1.15 / 1.04 / 0.76 10-19 2.08 / 2.37 / 1.79 / 0.98 20-30 3.62 / 2.68 / 2.08 / 1.27 >40 †3.31 / 3.73 / †2.02	†Based on 5-9 deaths.

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Paffenbarger and Wang 1969 U.S.A.	50,000 male former students	Baseline interview and examination and follow-up by death certificate	17.51	1,146 matched with 2,292 controls	NS ..... 1.00 SM ..... 1.50 (385) (p< 0.01)	NS ..... 1.00 (p< 0.01) SM 1.80 (88)	30-44 45-54 55-69 1.00 1.00 1.60 (160) 1.20 (134)	
Paffenbarger et al., 1970, U.S.A.	3,263 male longshoremen 35-64 years of age.	Initial multiphasic screening and follow-up of death certificate.	16	291	NS and ≤20 1.00 (137) SM >20 2.08 (154) (p< 0.01)			
Taylor et al., 1970, U.S.A.	2,371 male railroad employees 40-59 years of age at entry	Interviews and regular follow-up examination.	5	46	NS 1.00 (4) ≤20 ..... 1.97 (20) >20 ..... 3.60 (22)			Data apply only to those free of CHD at entry

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		Cigars, pipes	Age variation				Comments
									35–44	45–54	55–64	65–69	
Weir and Dunn, 1970, U.S.A.	68,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	1,718	NS	1.00		NS	1.00	1.00	1.00	1.00	NS includes pipes and cigars.
					All smokers	1.60		±10	4.22	2.06	1.41	1.17	SM includes ex-smokers.
					±10	1.39		±20	6.14	3.17	1.64	1.26	
					±20	1.67		±30	8.57	3.33	1.66	1.36	
					>30	1.74		>40	7.93	3.15	1.42	1.42	
								All	6.24	2.95	1.56	1.24	
Pooling Project, American Heart Association, 1970, U.S.A.	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	239	NS	1.00 (27)	1.00 (27)						
					<10	1.65 (34)	1.20 (24)						
					20	1.70 (86)							
					>20	3.00 (68)							

[1]Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

[2]"p" values specified only for those provided by authors.

SOURCE: U.S. Public Health Service (*138*).

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day		Pipes, cigars	Age variation	Comments
Doyle et al., 1964, U.S.A.	2,282 males Framingham, 30-62 years of age. 1,913 males Albany, 39-55 years of age.	Detailed medical examination and follow-up.	10	243 myocardial infarctions and CHD deaths.	NS All smokers <20 20 >20	1.00(52) 2.36(191) 1.98(44) 2.05(64) 3.04(83)			Data include CHD deaths, only on males 40-49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
Stamler et al., 1966, U.S.A.	1,329 CHD-free male employees of Peoples Gas Company 40-59 years of age.	Interview and examination with clinic follow-up.	4	46 CHD	NS <10 cigarettes <5 cigars <5 pipes 10-19 cigarettes >20 cigarettes >5 cigars >5 pipes	1.00(2) 2.92(6) 3.67(8) 3.83(29) 			NS includes ex-smokers. Includes all CHD.

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars	Age variation			Comments
Jenkins, et al., 1968, U.S.A.	3,182 males 39-59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4 1/2	104 myocardial infarctions.	NS	1.00(21)				39-49	50-59	†Includes nonsmokers and ex-smokers. NS includes former pipe and cigar smokers.
					EX	2.47(15)	($p<0.001$)		NS	1.00(4)	1.00(6)	
					Current	2.78(68)			Current	4.23(35)	2.26(33)	
					0-15/day	†1.39(45)	($p<0.001$)					
					>16	3.06(59)	(comparing 0-15 and 16+)					
Kannel, et al., 1968, U.S.A.	5,127 males and females 30-59 years of age.	Medical examination and follow-up.	12	228 myocardial infarctions. 380 CHD.	Myocardial Infarction							
					Males		Females					
					NS	1.00(21)	1.00(31)					
					All SM	*1.51(153)*	*1.71(23)*					
					Heavy SM	1.85(59)						
					Risk of CHD (overall)							
						Males	Females					
					NS	1.00(61)	1.00(89)					
					1-10	1.34(25)	0.86(18)					
					11-20	1.80(90)	1.29(18)					
					>20	2.41(76)	0.93(3)					

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars		Age variation	Comments
Epstein, 1967, U.S.A.	6,565 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions.		Males 40-59	60 and over		Males 40-59		Reexamination of patients was spread over 1 1/2 6-year period, but data are reported in terms of 4-year incidence rates. Actual number of CHD incidents derived from data on incidence and total in smoking class.
					NS	1.00(1)	1.00(7)	SM	1.80(2)		
					EX	6.53(10)	1.27(11)		60 and over		
					Cigarettes	5.20(36)	1.96(23)	SM	0.86(6)		
						Females					
					NS	1.00(21)	1.00(47)				
					EX	0.89(3)	1.31(5)				
					Cigarettes	1.02(14)	0.42(2)				

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars		Age variation						Comments
						Males	Females	Males only			Males			Females		
Shapiro et al., 1969, U.S.A.	110,000 male and female enrollees of Health Insurance Plan of Greater New York (HIP) 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	3	Total unspecified.	NS	1.00	1.00	NS	1.00	35-44	45-54	55-64	35-44	45-54	55-64	Total myocardial infarction includes those dead within 48 hours
					All current cigarettes	2.14 (p<0.01)	2.00 (p>0.01)	SM (p<0.01)	1.82	1.00	1.00	1.00	1.00	1.00	1.00	
					<20	1.50				2.47	3.06	1.69	2.25	2.87	1.80	
					>20	2.33	1.77			0.52	2.15	1.32	1.25	2.31	1.65	
					>40	6.36	5.92			3.04	3.29	1.81				
										10.09	7.69	5.30	20.25	11.79	4.07	NS include ex-smokers.
Keys 1970 Yugoslavia Finland Italy Netherlands Greece	9,186 males in 5 countries 40-59 years of age at entry.	Interviews and regular follow-up examination by local physicians.	5	65 deaths. 80 *myocardial* infarctions. 128 angina pectoris. 155 other †428 total.	NS, EX (SM <20)	1.00(305)										Includes all CHD incidence including EKG diagnoses. Covers all countries investigated except U.S.A. †Difference between total CHD and the sum of smoking groups is due to difference in figures presented by authors.
					All current (>20)	1.31(103)										

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day		Pipes, cigars	Age variation	Comments
Taylor, et al. 1970 U.S.A.	2,571 male railroad employees 40-59 years of age at entry.	Interviews and regular follow-up examination.	5	46 deaths. 33 myocardial-infarctions. 78 angina pectoris. 55 other CHD. 212 total.	NS and EX ..... All current	1.00(62) 1.77(150)			All CHD including EKG diagnoses.
Dayton et al., 1970, U.S.A.	422 male U.S. veterans participating as controls in a clinical trial of a diet high in unsaturated fat.	Interviews and routine follow-up examinations.	up to 8	27 sudden deaths. 44 definite myocardial infarctions.	<10 ..... 10-20 ..... >20	1.00(25) 1.04(22) 1.17(13)			No data on NS as a separate group.

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Pipes, cigars	Age variation	Comments
Dunn et al., 1970 U.S.A.	13,148 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 14	Total unspecified.			30-39 40-49 50-59 †Low SM 1.00(25) 1.00(125) 1.00(157) ‡High SM 2.17(10) 0.90(31) 1.41(53)	†Includes NS, EX, and <20 cigarettes/day. ‡ >20 cigarettes/day. Includes all CHD but excludes death. No data available comparing smokers and nonsmokers.
Pooling Project, American Heart Association 1970, U.S.A.	7,427 white males 30-59 years of age at entry.	Medical examination and follow-up.	10	538 Includes fatal and nonfatal myocardial infarction and sudden death.	Never smoked ..... <10 ..... 20 ..... >20	1.00(53) 1.65(72) 2.08(206) 3.28(154)	1.00(53) 1.25(54)	

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES									
Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars	Age variation	Comments
						Coronary cases (87)	Noncoronary controls (1,786)			
Paul et al., 1963, U.S.A.	1,989 Western Electric Co. male workers participating in a prospective study for 4 1/2 years.	Screening examination and history.			NS	23	33			88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.
					1-7	2	7			
					8-12	9	11			
					13-17	6	12			
					18-22	47	30			
					23-27	3	2			
					>28	9	6			
							($p<0.005$)			

[1]Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

Source: U.S. Public Health Service (*158*).

TABLE 4.—The effect of the cessation of cigarette smoking on the incidence of CHD. (Incidence ratios—actual number of cases or events are shown in parentheses)

Author, year, country	Results			Comments
		All CHD events	All myocardial infarction	
Jenkins, et al., 1968 U.S.A.	Never smoked	1.00(30)	1.00(21)	
	Current cigarette smokers	2.36(84)	2.78(68)	
	Former cigarette smokers	2.15(19)	2.47(15)	
		Death from CHD		
		Smoked 1–19 cigarettes/day	Smoked >20 cigarettes/day	
Hammond and Garfinkel, 1969, U.S.A.	Never smoked regularly	1.00(1,841)	1.00(1,841)	Male data only
	Current cigarette smokers	1.90(1,063)	2.55(2,822)	
	Stopped <1 year	1.62(29)	1.61(62)	
	1–4	1.22(57)	1.51(154)	
	5–9	1.26(55)	1.16(135)	
	10–19	0.96(52)	1.25(133)	
	>20	1.08(70)	1.05(80)	
	All ex-cigarette smokers	1.16(253)	1.28(564)	
		Total definite myocardial infarction		
Shapiro, et al., 1969, U.S.A.	Never smoked	1.00		
	Current cigarette smokers	1.87		
	Stopped ≤5 years	0.76		
		All CHD deaths	First major coronary event	
Pooling Project, American Heart Association 1970, U.S.A.	Never smoked	1.00(27)	1.00(53)	
	>½ pack/day	1.65(34)	1.65(72)	
	1 pack/day	1.70(86)	2.08(205)	
	>1 pack/day	3.00(68)	3.28(154)	
	Ex-smokers	0.80(19)	1.25(51)	

SOURCE: U. S. Public Health Service (*158*).

1.16 for all cardiovascular diseases in males. The reported ratios were 1.64 among men and 1.57 among women for ischemic heart disease. This effect on ischemic heart disease was related directly to the

TABLE 5.—Annual probability of death from coronary heart disease, in current and discontinued smokers, by age, maximum amount smoked, and age started smoking

Age	Maximum daily number of cigarettes smoked	Age started smoking 15–19		Age started smoking 20–24	
		Current smokers	Discontinued for five or more years	Current smokers	Discontinued for five or more years
		(Probability x 10^5)			
55–64	0	501	—	501	—
	10–20	798	568	811	551
	21–39	969	766	872	698
65–74[1]	0	1,015	—	1,015	—
	10–20	1,501	1,169	1,478	1,213
	21–39	1,710	1,334	1,573	1,098

[1]For age group 65–74, probabilities for discontinued smokers are for 10 or more years of discontinuance since data for the 5–9 year discontinuance group are not given.

SOURCE: U. S. Public Health Service (*138*).

amount smoked and to the age at which smoking began, in a study of a small subset of the population.

In industrial societies which share about the same general nutritional and metabolic circumstances as the United States, it has been shown repeatedly that cigarette smoking is associated with a considerable increase in risk of myocardial infarction and death following infarction when compared to the risk among nonsmokers. The effect is dose-related in terms of years of smoking, number of cigarettes smoked per day, and the habit of inhaling. The association is generally consistent, reproducible, and predictive. It is independent in the sense that its effect is found when other risk factors for heart disease are controlled in statistical analysis. The effect is seen chiefly in cigarette smokers. Pipe and cigar smokers are apparently at only minor increased risk. The effect is greatest in young middle life and decreases with age to become a minor risk beyond age 65. Cessation of smoking reduces, over time, the increased risk attributable to smoking toward the risk of nonsmokers. While most of the data have been gathered on men, there are sufficient data to provide similar general conclusions that cigarette smoking is also a risk factor for myocardial infarction in women. The studies of Hammond and Garfinkle, listed in Table 2, and of Shapiro and colleagues, in Table 3, record positive associations between smoking and mortality and morbidity from CHD in large populations of women. It has been observed that women who use oral contraceptive pills are at higher risk of infarction if they also smoke (*102*). Recently, a case-control study has reported that, among 55 women who had suffered myocardial infarction below the age of 50 years, the proportion of smokers was 89 percent compared to 55 percent among

the case controls ($p < 0.001$). A dose relationship was present. Compared to nonsmokers, heavy smokers using 35 or more cigarettes a day had an infarction rate estimated to be increased 20 times. The women did not use oral contraceptives (*124*).

The final report of the Pooling Project considers data from the Albany civil servant study, the Chicago Peoples Gas Co. study, the Chicago Western Electric Co. study, the Framingham community heart study, and the Tecumseh community study. It presents typical findings from prospective studies and ones that are particularly important for the United States because the data are derived from several locations in the country. In this report (*107*), fatal and nonfatal myocardial infarction and sudden coronary heart disease death have been designated as major coronary events.

Cholesterol values, blood pressure readings, and smoking history observed just once in men at the beginning of a 10-year follow-up period showed a high predictibility of risk of CHD. Multiple logistic analysis showed these three characteristics to be independent. Combinations of these risks were not additive but compounded. The highest combined quintile of risk characteristics compared to the lowest quintile had a relative risk of CHD events of about 6 to 1. About 40 percent of cases emerged from the 20 percent at highest risk, while 86 percent emerged from the upper 60 percent of risk traits, and 96 percent derived from the upper 80 percent. Not only is risk of CHD events associated with the more deviant levels of these traits, but appreciable risk may attach to combinations of mild deviations of risk factors.

Smoking habit was classified as more than a pack of cigarettes a day, about a pack a day, about half a pack a day, less than half a pack, cigar and pipe only, never smoked, and past smokers. For most analyses, the report groups past smokers, never smoked, and smokers of less than half a pack a day into a single group labeled nonsmokers, noting that the majority of the less than a half pack per day smokers were only occasional users. This group of nonsmokers was then compared with those who smoked more. It was found that men who smoked a pack or more a day had a standardized incidence or risk ratio[1] of a first major coronary event 2.5 times that of the nonsmoker (confidence interval 2.1 to 3.1). Those who reported smoking more than a pack a day were found to have 3.2 times the risk of nonsmokers in terms of standardized incidence ratio (confidence limits 2.6 to 4.2). The risk of pipe and cigar smokers was intermediate between that of the nonsmokers and the half a pack a day smokers, but was not statistically different from either group in this study. Risk was found

[1]This calculation removes that portion of any difference attributable to age differentials. The average rate for the total group is assigned the value of 100. The rates for subgroups are proportional to the average for the entire group after removing the effects of age.

to rise rapidly above half a pack a day and to be almost twice as high in the pack a day group of cigarette smokers.

Among additional recent papers, the Framingham Heart Study reports that smoking 20 cigarettes a day is associated with an annual incidence of coronary events per 1,000 in the fifth, sixth, and seventh decades of life of 11.9, 19.3, and 19 per 1000 of population. The corresponding rates for nonsmokers were 3.6, 5.7, and 15.3 (*69*). The Western Collaborative Group Study (*116*) in California has detailed a dose relationship of relative risk analysed for the fifth and sixth decades of life among men smoking either less than a pack per day, a pack, and more than a pack in comparison with nonsmokers. The reported relative risks were 1.05, 1.53, and 1.93 in the fifth decade, and 0.098, 1.63, and 2.32 in the sixth. Reid and colleagues (*110*) have reported on more than 18,000 male civil servants in Great Britain between the ages of 40 and 64 who were followed over 5 years of prospective study. The risk of death from coronary heart disease was lowest among nonsmokers or ex-smokers. Current smokers had a significantly higher risk of death from CHD. Moreover, when classified by inhalation habit, inhalers were found to have higher risk of CHD death than those who do not inhale. In yet another study from Great Britain, more than 34,000 physicians have been followed for 20 years. It is reported that annual death rates (per 100,000, standardized for age) among light, medium, and heavy smokers for ischemic heart disease are 501, 598, and 677 respectively (*35*).

There have been inconsistent reports on the effect of smoking on the occurrence of a second or subsequent heart attack. Studies in New York (*150*) failed to find a relationship between smoking and second heart attacks, while the Newcastle and Scottish studies (*43, 111*) did find an adverse trend. A recent contribution to this issue has been the findings of the Coronary Drug Project Research Group (*29*) who reported on 2,789 male survivors of myocardial infarction in the New York Heart Association cardiac functional classes I or II. These men had been randomized to placebo treatment and usual care. They were followed for 5 years and provide a natural history study under usual current therapy conditions. Smokers at the time of entry into the study were at somewhat higher risk than nonsmokers. The relative risk of smoking after myocardial infarction was appreciable, but less than for men with no prior history of heart attack as, for example, those documented in the Pooling Project (*107*). The absolute risk of death is much higher for men who have already experienced a myocardial infarction, however, so that the difference in mortality rates for them between smokers and nonsmokers becomes correspondingly important. In this study, the hospitalization rate was 36 percent higher for cardiovascular events among smokers than nonsmokers.

Other recent papers include the Western Collaborative Group Study (*64*), which has reported that the number of cigarettes smoked daily

correlates significantly with the occurrence of new myocardial infarction among men who have had a prior attack. Mulcahy and colleagues (*97*) have reported that over a 5-year period, subsequent smoking after an infarction did not affect morbidity, but there was an increased mortality among those who continued to smoke. In the British civil servant study (*115*), it was found that among those with existing evidence of ischemic heart disease, the mortality rates over 5 years were 4.7 and 4.0 percent among those who smoked relative to nonsmokers. Again, in a Swedish study (*154*), those who ceased to smoke after a heart attack had only half the rate of nonfatal recurrences, and half the rate of cardiovascular mortality of those who continued to smoke over a 2-year follow-up period.

There is persuasive evidence from population studies in the United States and in the United Kingdom (*35*) that ex-smokers adopt a lesser risk after ceasing to smoke, which in time is little different from the nonsmoker who never smoked. The 1976 reference report on *The Health Consequences of Smoking* (*138*) tabulated several important studies in Tables 15 and 16 on page 42 (reproduced above as Tables 4 and 5). The Framingham Heart Study (*50*) also reports a beneficial effect below the age of 65. Men who stopped smoking had coronary attack rates only one-half those who continue to smoke 10 or more cigarettes per day. In a paper that may be germane, although it relates to differences in exposure rather than cessation, Hammond and associates (*53*) find that smokers of low tar and nicotine delivery cigarettes had lower death rates from coronary heart disease than those who smoked the same number of high tar-nicotine cigarettes. Both groups of smokers, however, had higher rates than nonsmokers.

It is of interest in discussing other risk factors that physical activity markedly shortens the half life of carboxyhemoglobin in the blood and that active people attain lower equilibrium levels than sedentary ones when smoking (*27, 56, 145*). Physical activity, particularly when heavy, has been shown in several studies to reduce the incidence of heart attack, and it can be speculated that at least some of this effect may arise from a reduced burden of COHb among physically active smokers (*145*). Morris and colleagues obtained evidence in a study of British civil servants that, among men who did not exercise vigorously during their leisure time, smokers had 2.5 times the risk of nonsmokers. Among the physically active group, however, the relative risk of smokers was 1.5. The amount of tobacco used daily was the same in the two groups (*95*).

The Effect of Smoking on Myocardial Infarction in Man

The epidemiological data that associate cigarette smoking and myocardial infarction are summarized in the preceeding section. The effect is major and adverse for the incidence of first events; it is

apparently also adverse for second attacks, but this is not yet well defined.

The mechanism of effect is usually attributed to an enhancement of coronary atherosclerosis in smokers and the consequent occurrence of cardiac ischemia and ischemic necrosis of heart muscle. Other phenomena have been offered as supplementary mechanisms. Aronow has recently discussed these in the context of relative ischemia and cardiac effects (*5*, *6*). In patients with exercise-inducible angina, smoking various nicotine or non-nicotine-containing cigarettes was found to aggravate angina and in a manner related to the nicotine content. Nicotine-containing cigarettes increase heart rate and blood pressure transiently, non-nicotine cigarettes do not. The nicotine effect is mediated through catecholamine discharge. Both nicotine and non-nicotine cigarettes increase blood CO. There is a decreased availability of oxygen for the heart. Aronow reports a rise in left ventricular end-diastolic pressure and a decrease in stroke volume due to a negative inotropic effect of CO on the myocardium. Jain and associates (*60*) have found that, in normal subjects, smoking decreases the preejection/left ventricular ejection time ratio and external isovolumetric contraction time, whereas in patients with coronary heart disease these measurements increased on smoking. They concluded that left-ventricular performance is diminished after cigarette smoking in the presence of significant coronary artery disease.

In the individual with ischemic heart disease, it is hypothesized that nicotine may aggravate ischemia: by increasing cardiac oxygen demand but not supply; by increasing platelet adhesiveness (*78*) and causing circulatory obstruction at the microvascular or macrovascular level; by lowering the cardiac threshold to ventricular fibrillation (*20*); and by depressing conduction and enhancing automaticity (*52*) favoring the development of arrhythmias. CO might aggravate ischemia by exaggerating hypoxia, producing a negative inotropic effect, reducing the fibrillation threshold (*6*), or increasing platelet adhesiveness (*25*). Regardless of which of these several mechanisms might operate in individual cases, it can be hypothesized that patients on the border of myocardial ischemia may be pushed into impending or actual infarction by the effects of nicotine and CO. Moreover, it may be speculated that, in the presence of coronary atherosclerosis of a degree insufficient to cause ischemia, the actions of smoking on platelet pathophysiology may precipitate occlusive thrombosis and infarction.

These possible mechanisms for the conversion of marginal ischemia into overt infarction may be thought to require that the attack follow immediately in time or coincide with the act of smoking. In fact, experience with myocardial infarction or sudden death does not seem to support the idea that the majority of habitual smokers suffer myocardial infarction or sudden death in such close temporal relationship to the act of smoking. However, the exact timing of the onset of

heart attack by clinical criteria is not possible. A considerable number of infarcts are clinically unrecognized. It is also possible that the initiation of ischemia or of platelet aggregation begun at one time might culminate in heart attack only hours later. At present, it is not possible to clarify these temporal uncertainties.

The Effect of Smoking on Myocardial Infarction in Animals

There are limited data on the effect of smoke constituents on experimental myocardial infarction in animals. Table A20 (pp. 103-108) of the 1976 reference edition of *The Health Consequences of Smoking* (*137*) lists 18 separate publications involving the effect of smoke and nicotine on cardiovascular function. Three studies used animals with coronary artery narrowing or ligation. In one there was an increase in the frequency of nicotine-induced arrhythmias. This was less evident as the time interval (up to 45 days) increased between artery ligation and nicotine challenge. In another study, nicotine increased coronary blood flow less in the presence of coronary narrowing than in normal animals. One paper reported that animals with damaged myocardium due to isoproterenol lesions or ligation of the coronary artery responded to a nicotine challenge with an increased expression of arrhythmias. It was found that it required more nicotine to increase coronary flow and heart rate in rabbits with dietary-induced atherosclerosis than in normal animals. It was also reported that in dogs with acute coronary occlusion that nicotine caused coronary vasodilation in the normal heart, but in ischemic myocardium, flow increased only proportional to aortic pressure. Dogs with coronary occlusion manifest excessive left atrial pressure and ventricular arrhythmias on exposure to nicotine (*36*).

The effect of CO inhalation on monkeys with experimental myocardial infarction produced electrocardiographic evidence of greater myocardial ischemia and increased liability to induced-ventricular fibrillation (*34*).

Research Needs

The epidemiological data relating smoking to myocardial infarction leave no doubt that smoking is a major risk factor for both fatal and nonfatal CHD. Data in certain situations need strengthening or verification. There is much less information concerning women than men. Data are few on the effect of smoking on myocardial infarction in old age. The published reports on the adverse effect of smoking on the incidence of second heart attacks are probably adequate, but are inconsistent and not well-defined. Studies to investigate the separate relationships of nicotine and CO in whole smoke to the incidence of myocardial infarction would be particularly useful. Detailed data on the effect of "less hazardous" cigarettes compared with ordinary cigarettes in relation to myocardial infarction are not available,

although, as noted above, it has been shown that there is a rising gradient of risk of cardiovascular death for smokers of the same number of low, medium, and high tar and nicotine cigarettes (*53*). If such studies are feasible, they could provide for the public and for cigarette production important information about the risks to be attributed to different smoke deliveries of tar, nicotine, CO, and perhaps other substances.

A major need is to understand better the mechanisms by which smoking can induce or affect the evolution of myocardical infarction. Animal experiments using several different models of myocardial ischemia or infarction in conjunction with exposure to smoke constituents alone, and in combination, should provide some clarification. They could be conducted under precise if somewhat artificial circumstances. Nonhuman primates susceptible to experimental atherosclerosis have been trained to smoke in a humanlike manner without overt stress or aversion (*86*), and studies of whole smoke of different characteristics in a more natural setting of acute and chronic inhalation exposure can be done.

Conclusions

Cigarette smoking is a major independent risk factor for the development of fatal and nonfatal myocardial infarction in men and women in the United States. It also appears to be a risk factor for second heart attacks among those who have experienced one, and diminishes survival after a heart attack among those who continue to smoke. It acts synergistically with high blood pressure and elevated blood cholesterol. The effect is directly related to the amount smoked. Ceasing to smoke reduces the risk towards that of nonsmokers. Smokers of low tar and nicotine cigarettes have a higher risk than nonsmokers, but they have a lesser risk than those who smoke high tar and nicotine cigarettes.

Sudden Cardiac Death

The Nature of Sudden Cardiac Death in Man

A recent symposium (*28*) on sudden cardiac death has delineated the nature of the problem and the many definitions that are used to classify it. The data gained from hospital practice and from coroner's experience differ quantitatively from the findings of prospective epidemiological studies, but the nature of the disorder is probably the same in all the samples. Coronary heart disease (CHD) accounts for 90 percent of examples of sudden cardiac death, but there are other cardiac causes for sudden death (*28*).

In a prospective epidemiological study, Kannel and associates (*71*) reported that individuals with overt CHD are four times as liable to sudden death as those without CHD. They report that about 55 percent

of cases occur in individuals with no prior clinical evidence of CHD. The standard CHD risk factors have been confirmed also to be predictors of sudden cardiac death in both a case control study (*44*) and in a prospective cohort investigation (*38*). Whether death from CHD is sudden does not appear to depend upon the mix of risk factors, and no combination of standard risk factors (including smoking) appears to designate those destined to die suddenly in contrast with those who will experience a more protracted death. The proportion of sudden cardiac deaths to more protracted deaths is about the same whether or not prior overt CHD has been recognized (*38, 71*). Evidence has been accumulated in several studies that, in the presence of recognizable heart disease, ventricular premature beats are associated with an excess liability to sudden cardiac death (*142*). A recent study by Ruberman and associates (*118*) followed 1,739 men in the New York City area who had a myocardial infarction at least 3 months before entering the study. They were examined for ventricular premature beats by means of a continuous 1-hour record of the electrocardiogram. The follow-up period was from 6 months to 4 years, averaging 24.4 months. During this period there were 208 deaths, of which 85 were classified as sudden cardiac deaths (defined here as occurring within minutes and in the absence of signs or symptoms suggesting acute myocardial infarction). Much higher mortality was experienced in those subjects manifesting complex beats (runs, early beats, bigeminal, and multiform beats) than in those without. The authors report that by the 3-year observation point the risk of sudden cardiac death, adjusted for age, was four times above the comparison experience, and the risk of death from any cause was 2.6 times greater than expected. Moreover, although such complex beats were often associated in this study with other findings that relate to severe heart damage, they were shown to be independent risk factors.

Autopsy studies on persons dying sudden cardiac deaths have produced somewhat variable findings. In general there is a close association with extensive and severe coronary atherosclerosis, and an appreciable number of patients show evidence of old or recent myocardial infarction. Reichenbach and coauthors (*109*) have tabulated data from several studies. Their own experience in the Seattle, Washington area was that 97 percent of decedents had a prior history of heart disease (much higher than other studies); 55 percent had pathological evidence of old myocardial infarction; 8 percent had less than 75 percent luminal stenosis in any major coronary artery with the remainder showing 75 percent or greater stenosis in one or more vessels; and 57 percent had occlusion of one or more vessels. Recently formed thrombi were found in 10 percent of hearts, which was, generally, appreciably less than other studies; acute myocardial infarction was found in only 5 percent of hearts, which also was, generally, appreciably less than in other studies. Other reports that

consider a history of smoking in relation to autopsy examinations and sudden death are those of Spain and coworkers (*127, 128*) and Friedman and associates (*44*).

Two major mechanisms for sudden cardiac death may be postulated. One is asystole or arrest, generally arising in response to severe ischemia and impending or spreading acute myocardial infarction. The other is ventricular fibrillation arising from regional myocardial ischemia and ventricular ectopy and modulated by a number of circumstances that may contribute to electrical instability of the heart.

Sudden Cardiac Death in Animals

Sudden death has been reported in nonhuman primates that were fed cholesterol to induce atherosclerosis (*58*), and it has been induced in many experiments by acute coronary ligation or obstruction. The latter experiments have produced a large body of data on the ability of regional ischemia to initiate ventricular fibrillation and sudden cardiac death, and have helped to elucidate local tissue metabolism, electrical behavior, and the relation of neural and pharmacologic agents to the precipitation or control of arrythmias and fibrillation.

Summary of Epidemiological Data

Sudden cardiac death is the first manifestation of coronary heart disease (CHD) in about 20 percent of CHD deaths. Of all CHD deaths about 50 to 60 percent are sudden (*71*).

The 1976 reference report on smoking and health (*138*) noted in Table 3 (p. 26) data on sudden cardiac death from the Pooling Project that found an increased mortality ratio of 1.9 for men who smoked either 10-or-less or 20 cigarettes a day, and a ratio of 3.36 for those smoking more than 20 a day, in comparison with nonsmokers (1.00). A more recent report combines data from Framingham and the Albany Civil Servant Study (*38, 71*). These data relate to men only, and are derived from 1,838 subjects from Albany, New York, and 2,282 from Framingham, Massachusetts, aged 45 to 74, and were collected prospectively over 16 years. Sudden death was defined as demise within one hour of onset. Deaths within 30 days of a known heart attack were excluded as were those of subjects found dead in bed. Data are presented on the associations between sudden cardiac death and a number of factors such as age, a prior history of CHD, blood pressure, serum cholesterol, and other items. Smoking was found to be a risk factor, with smokers having a threefold higher rate than nonsmokers. In a multivariate analysis of systolic blood pressure, electrocardiographic evidence of left ventricular cardiac hypertrophy, relative body weight, cigarettes smoked per day, and serum cholesterol as contributors to risk among men ages 45 to 54 and 55 to 64 at their biennial examination antecedent to death, it was judged that, of these factors, the use of cigarettes was the most potent contributor to sudden death.

A case control study based on the Kaiser-Permanente health insurance system in California (*44*) has reported on 197 sudden cardiac deaths among men. The case to control findings with reference to percentage of smokers among 40- to 54-year-old decedents were 67.9 and 39.3. It was found that smoking had a somewhat stronger relationship to deaths occurring 1 hour after onset of symptoms than to instantaneous deaths or those within 1 hour. Talbott, et al. (*134*) have reported on sudden death among white women and find an excess use of tobacco and alcohol among those dying suddenly.

The relationship of smoking to sudden death among those with existing recognized CHD has had little attention. In a prospective study, Graham and associates (*51*) found no association between smoking and mode of death in patients known to have had a prior infarction. Oberman and co-workers found no relationship between the major risk factors including smoking and sudden death in patients evaluated earlier for ischemic heart disease (*100*). It was found that the best five variable models to predict sudden death in this group of patients included the number of coronary arteries obstructed 70 percent or more, the use of digitalis or diuretics, premature beats and ventricular conduction defects. The Coronary Drug Project (*29*), which was also a prospective study, reported a 5-year age and race adjusted sudden death-rate ratio of smokers to nonsmokers of 1.28 (t value 1.98) in the placebo or customary therapy group.

The Effect of Smoking on Sudden Cardiac Death in Man

The epidemiological associations have been noted above. The act of cigarette smoking does not appear to be immediately related in time to sudden death. In relation to second heart attacks, Moss and colleagues (*96*) report a prospective follow-up study of patients discharged from hospital after myocardial infarction. They reported on 42 deaths (sudden and nonsudden) of cardiac nature in the following 6 months. Information on smoking prior to death was available on 28 patients; of these, only 5 were said to have smoked in the week before death.

The mechanisms postulated to explain the association of sudden cardiac death with smoking have been described under atherogenesis and under myocardial infarction as possible mechanisms for effects of smoke, nicotine, and CO. They include accelerated atherogenesis, enhancement of ischemia through inotropic effects, increased platelet adhesiveness obstructing coronary flow, or, through increased cardiac work caused by nicotine, and simultaneously reduced oxygen delivery to the heart due to CO. Any of these mechanisms can be evoked as possible initiators of critical ischemia and of sudden death due to asystole or to ventricular fibrillation. The smoking and health report of 1976 (*138*) tabulates in Table A21 (pp. 109-114) the effects of smoking and nicotine on the cardiovascular system in man. While these data

suggest hypotheses for mechanisms of sudden death in man, they do not, of course, deal directly with cases of sudden death.

The Effect of Smoking on Sudden Cardiac Death in Animals

The smoking and health report of 1976 (*138*) has tabulated in Table A20 (pp. 103-108) papers concerned with the effect of smoke or nicotine on the cardiovascular system of animals. In the presence of myocardial ischemia, exposure to tobacco smoke or nicotine may precipitate conditions of increased cardiac demand, relative ischemia, and, in one experiment, arrhythmias. Bellet and colleagues (*20*) found that the ventricular fibrillation threshold was reduced in dogs exposed by intubation to cigarette smoke both in the presence and in the absence of acute myocardial infarction.

Malinow and colleagues failed to induce infarction or sudden death in cholesterol-fed cynomolgus monkeys by chronic exposure to CO (*80*). There are, however, no animal experiments in which animals have been brought chronically to a state of incipient myocardial ischemia by atherogenesis and then exposed to whole smoke by inhalation in a nonstressful setting.

Research Needs

There are fewer data on sudden cardiac death than on myocardial infarction in general. Smoking is clearly a strong risk factor for sudden death, but present indications are that it is not unique among the mix of risk factors for coronary heart disease and that it is not highly predictive. However, there are theoretical reasons to speculate that smoking might have a relationship to sudden death, not only through its effects on the circulation, but also through a myocardial one. It should be considered whether present epidemiological and clinical research data are adequate to exclude in smokers a myocardial element in sudden cardiac death, in relation to either first or multiple heart attacks, or whether additional research is warranted.

The mechanisms of sudden cardiac death, its precursor states, and preventive therapy require further elucidation. These should be clarified where possible in man and in experimental animal models with close analogy to man. The study of smoking or of smoke constituents as variables in such studies may be informative both about sudden death and the role of smoking in its occurrence.

Conclusions

Smoking is a powerful risk factor for sudden cardiac death. It is, however, only one of the general group of risk factors that contribute to coronary heart disease and sudden death. The mechanisms by which smoking might induce sudden death, in addition to an exacerbation of coronary artery arteriosclerosis, can be hypothesized from experiments

that indicate that an exacerbation of regional ischemia may promote electrical instability of the heart, fibrillation, or asystole. Further research will be required if these mechanisms are to be well understood and if they are to be shown to be actual mechanisms in man in relation to smoking and sudden death.

Angina Pectoris

The Nature of Angina Pectoris in Humans

Pain in the thorax may have several different origins and can create a difficult problem of differential diagnosis. Angina pectoris arises typically in the face of exercise and increased demand for work and oxygen on the part of the heart which cannot be met immediately in the presence of ischemia imposed by coronary atheroscleosis. The origin of the pain is thought to be the ischemic myocardium. It can occur in individuals with or free from preexisting myocardial infarction. Since the common use of angiographic diagnostic methods, it has become apparent that angina also occurs occasionally in persons with little or no evidence of coronary arteriosclerosis.

Angina pectoris is associated with an increased death rate from heart attack. Women survive better than men. Among the risk factors associated with a poorer prognosis are hypertension, cardiac hypertrophy, congestive heart failure, and electrocardiographic abnormalities (*149*). Recent studies employing angiography have shown a close relationship between the extent of coronary arteriosclerosis and prognosis in angina pectoris. Reeves and associates (*108*) have summarized these reports to indicate that if only one of the three major coronary artery branches is significantly stenosed, an annual mortality rate of about 2 percent results; if two major branches are stenosed, the resulting annual mortality rate is about 7 percent a year; with three-vessel disease, it is about 11 percent a year.

Summary of Epidemiological Data

The major studies on smoking in relation to the incidence of angina pectoris in the United States are not consistent in their conclusions. The 1976 report on smoking and health (*138*) has tabulated four major reports in Table 5 on page 33. (Table 5 is reproduced below as Table 6.) Doyle and colleagues (*38*) report no association in a 10-year follow-up of men from the Albany civil servant study, together with men from the Framingham Heart Study. Jenkins, et al. (*63*) reported a slight positive association, but not a statistically significant one. Similarly, Kannel and Castelli (*70*) reported on both men and women from the Framingham Heart Study and found a positive risk association among men and a negative one among women. In a large study of 110,000 men and women enrolled in a health insurance medical care plan in New York City and followed for 3 years, Shapiro, et al. (*122*) reported a

TABLE 6. — Coronary heart disease morbidity as related to smoking — angina pectoris — prospective studies (Risk ratios—actual number of CHD manifestations shown in parentheses).[1] [SM = Smokers NS = Nonsmokers]

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments
Doyle, et al., 1964, U.S.A.	2,999 males, Framingham, 30–62 years of age.	Detailed medical examination and follow-up	10	81	NS ..... 1.00(30) All ..... 1.08(51) <20 ..... 1.17(15)			NS include ex-smokers and pipe and cigar smokers
	1,913 males, Albany, 20–55 years of age.		8		20 ..... 0.98(18) >20 ..... 1.15(18)			
Jenkins, et al., 1968, U.S.A.	3,182 males aged 30–59 at entry.	Initial medical examination and follow-up by repeat examination.	4½	29	NS ..... 1.00(9) All current cigarettes ..... 1.44(16) >16 ..... 1.69(14)			NS include former pipe and cigar smokers.
Kannel, et al., U.S.A.	5,127 males and females years of age 30–59	Medical examination and follow-up.	12	107	Males NS ..... 1.00(16) Heavy SM, >20 cigarettes ..... 2.04(17) Females NS ..... 1.00(58) Cigarette SM ..... 0.65(16)			
Shapiro, et al., 1969, U.S.A.	110,000 male and female enrollees of New York City HIP 35–64 years of age.	Baseline medical interview and examination and regular follow-up.	3	Total 1, Unspecified	Males Females NS ..... 1.00 1.00 Current cigarettes ..... †1.91 1.20 <40 ..... 1.51 1.20 >40 ..... 4.95	Males NS ..... 1.00 SM ..... ‡1.71	35–44 45–54 55–64 NS ..... 1.00 1.00 1.00 Current cigarettes ..... 2.40 1.57 2.06 <40 ..... 2.25 1.40 1.54 >40 ..... 10.15 2.58 6.15 Females NS ..... 1.00 1.00 1.00 Current cigarettes ..... 1.56 1.07 0.97 <40 ..... 1.67 1.53 1.04 >40 ..... 4.12	†($p<0.01$) ‡($p<0.05$) NS include ex-smokers

[1] Unless otherwise specified, disparities between the total number of manufestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

SOURCE: U. S. Public Health Service (*158*).

significantly increased incidence rate for smokers among men who were current users of cigarettes. Among females, the trend was positive but not significant. A study of the incidence over 5 years of angina among 10,000 Israeli men found that there was a higher incidence rate among men who smoked over 20 cigarettes a day than in those who smoked less, but the difference did not reach the 0.01 level of significance (*91*). In addition, a questionnaire survey (*45*) of about 70,000 persons has found that more smokers than nonsmokers admitted to chest pain. Some nine different kinds of angina-like and nonanginal pains were included as chest pain. Reid and associates have reported a significant association between angina and current cigarette smoking among British civil servants (*110*).

The Effect of Smoking on Angina Pectoris

As noted above, the predictive risk factor association of smoking with the incidence of angina pectoris is not clear. However, there is evidence among persons with angina that smoking lessens the threshold of exercise for the onset of pain. Aronow (*7, 8, 9, 10, 12*) has reported clinical studies in which smoking cigarettes with high, low, or no nicotine content aggravated angina. In these studies, high nicotine cigarettes aggravated exercise-induced angina more than low nicotine cigarettes, and low nicotine cigarettes more than cigarettes without nicotine. He has also reported in patients with angina pectoris and coronary artery stenosis documented by angiography that when 50 parts per million of CO were inhaled until the mean COHb level of venous blood was raised to 2.68 percent, it was accompanied by a significant decrease in exercise time before anginal pain. There was also a decrease in the amount of cardiac work represented by the product of systolic blood pressure and heart rate needed before the onset of angina compared to when air was breathed. S-T segment depression of 1.0 mm or greater in the electrocardiogram occurred earlier, after less exercise and at lower cardiac work levels among these patients when they breathed CO rather than air. Although it is uncommon, there are patients in whom the act of smoking a cigarette will itself precipitate an attack of angina (*26, 143*).

An interpretation of such data is that, in the patient with a compromised regional myocardial blood supply who can provide little or no compensatory increase in circulation to meet an increased cardiac demand, smoking enhances both hypoxia and cardiac demand, resulting in a more severe ischemia and an earlier onset of angina.

Research Needs

Epidemiological data with respect to the predictive or risk factor association of smoking and angina pectoris tend to show an inconsistent positive association. Despite this unsatisfactory state of affairs,

there would seem relatively little reason to attempt to study the issue further at this time.

Conclusions

Studies of the possible role of smoking as a risk factor for the incidence of angina pectoris suggest a positive association, but the findings are inconsistent.

In patients with angina pectoris, smoking lowers the threshold for the onset of angina. Both nicotine and CO aggravate exercise-induced angina.

Cerebrovascular Disease

The Nature of Cerebrovascular Disease in Man

The underlying circumstances of stroke are varied. They include tumors and bleeding dyscrasias leading to intracerebral hemorrhage or infarction, unusual diseases of blood vessels in the brain, aneurysms of intracranial vessels, embolism, thrombosis, vascular rupture, and atherosclerosis of the vessels of the neck and their distributing vessels in the brain.

The great majority of strokes, perhaps more than 90 percent, may be classified either as intracerebral hemorrhage associated primarily with hypertension, or ischemic cerebral infarction associated with atherothrombotic disease of the vessels of the neck and their main distributing branches in the brain. Infarction is more common than hemorrhage. The clinical diagnostic subclassification or separation of hemorrhagic stroke and ischemic stroke contains an appreciable margin for misclassification. It is these conditions that are under consideration here, rather than the rare disorders.

The risk factor data for stroke have been considered recently by two panels (*31*, *40*). They are less clearly defined than those for coronary heart disease. The strongest gradients of risk are associated with age, blood pressure, preexisting cardiovascular disease, and diabetes mellitus. Prospective studies have not found a clear and direct relationship with serum cholesterol concentration. It has been of interest that a Japanese study has recently reported that among a population with a high incidence of stroke but low levels of blood cholesterol by Western standards, there was no evidence that hypercholesterolemia defined as levels above 200 mgm/100 ml increased the incidence of stroke. Cerebral infarct developed in 11 percent of those with hypertension and hypercholesterolemia and 21 percent of those with hypertension alone (*101*).

Models of cerebrovascular disease in animals have largely been limited to acute occlusive manipulations. Only recently have experimental dietary and hypertensive sclerosis of cerebral vessels with cerebral hemorrhage (*58*) been reported in nonhuman primates. A

genetic strain of stroke-prone, spontaneously-hypertensive rats has been developed.

Summary of Epidemiological Data

The epidemiological data on cerebrovascular disease (stroke) and smoking were summarized in the 1976 reference edition of the report on *The Health Consequences of Smoking* (*138*), Table 137 (pp. 64-66). Kannel reviewed the subject for the Third World Conference on Smoking and Health (*68*).

The results of various studies have not been congruent and no conclusion can be stated with confidence. Kannel has noted that the prospectively collected data have been difficult to interpret because of deficiencies, such as small sample numbers, failure to consider separately cerebral hemorrhage and ischemic infarction, failure to consider separately men and women, and inadequate classification by age.

The 1976 report on *The Health Consequences of Smoking* (*138*) comments (on page 152 and in light of its data in Table 7 on page 153, reproduced below as Table 7) on the possible role of age dependency in the various studies, noting that cigarette smoking may be a risk factor for stroke at all ages, but that other causes of stroke may be proportionately so important in older ages that the smoking risk is masked by strokes due to other causes in studies that do not involve very large populations. Although two very large studies, involving about 250,000 and 1,000,000 respondents, found relative risks of about 1.52 and 1.41 for cigarette smokers (*41*), no certain conclusion can be offered at the present time because of apparently conflicting data. A recent study of a large cohort of women has reported that the risk of subarachnoid hemorrhage is significantly associated both with cigarette smoking and with the use of oral contraceptives. The risk to cigarette smokers was 5.7 times that of nonsmokers while it was increased 6.5 times for users of oral contraceptives. The risk was increased 22 times among women who both smoked and used oral contraceptives compared to nonsmokers and nonusers (*106*).

The Effect of Smoking on Cerebrovascular Disease

It has been noted that risk factor data are inconclusive on the relation of smoking to the incidence of stroke. Carbon dioxide causes cerebrovascular dilatation. Both nicotine and CO increase cerebral blood flow (*123*). Unlike the case of cardiac metabolism, there is no evidence that nicotine affects cerebral oxidative metabolism in a dose equivalent to smoking. It is uncertain that these effects relate in any way to stroke. It may be speculated that pathogenetic mechanisms could operate through effects on blood platelets, oxygen transfer, emboli from the heart, or through vessel wall toxicity and enhanced atherogenesis of large and small vessels to the brain. There are no data

TABLE 7.—Age-standardized death rates and mortality ratios for cerebral vascular lesions for men and women, by type of smoking (lifetime history) and age at start of study

Type of smoking	Age groups			
	45–54	55–64	65–74	75–84
	CVL death rates per 100,000 person-years			
Men				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,168
Total	35	116	391	1,272
Women				
Never smoker regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
	CVL mortality ratios			
Men				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	0.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	0.73
Cigarette only	1.50	1.41	1.37	0.86
Women				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

NOTE. - CVL = Cerebral vascular lesions.
SOURCE: U. S. Public Health Service (*158*).

dealing directly with experimental cerebrovascular disease in animals and smoking that examine such pathogenetic hypotheses.

Research Needs

Clarification of the existing conflicting epidemiological data may be sought. It has been suggested by Kannel (*68*) that a retrospective study of brain infarctions under the age of 55 years might help to resolve some uncertainties.

Chronic experimental cerebrovascular disease of hypertensive or atherosclerotic types in animals has received little attention. Such disease has recently been produced in nonhuman primates (*58*). While its characterization is incomplete, it may possibly offer an opportunity to study the effects of smoking or of smoke constituents. The effect of smoke constituents on the stroke-prone rat is also an area for study.

Conclusions

The relationship of smoking to the incidence of stroke is not established. An association with subarachnoid hemorrhage has been reported in women.

Peripheral Vascular Disease

The Nature of Peripheral Vascular Disease in Man

Atherosclerotic peripheral vascular disease (PVD) is primarily a stenosing or occlusive disorder of the arteries of the legs. Other branches of the aorta such as the subclavian, celiac, or renal arteries may be diseased similarly, but use applies the term to the arteries that supply the leg unless noted otherwise. Atherosclerotic involvement resembles that of the coronary arteries or aorta, but the plaques are more fibrous and cellular and contain less fat. Involvement includes not only the large iliac and femoral arteries, but extends to branches in the anastomotic connections around the knee and to the lesser branches of the lower leg and foot. Thrombosis is common, and embolism from ulcerated plaques in the aorta or iliac arteries occurs. The effect is to create distal circulatory ischemia of a chronic nature that can be complicated by acute occlusive events. The circulation to the leg may become inadequate to the needs of the muscles during exercise. Pain in the calf or thigh is precipitated by exercise, relieved by rest, and is designated intermittent claudication. It resembles angina pectoris in these respects and it is often a changeable and unstable symptom. Severe ischemia will result over time, in some individuals, in tissue atrophy and necrosis or ischemic gangrene.

The risk factors for atherosclerotic peripheral vascular disease are generally similar to those for coronary heart disease, but an elevated blood pressure may be only a minor contributor to risk of PVD (*68*).

Peripheral vascular disease has been reported in experimental dietary atherosclerosis in the nonhuman primate, but the subject has only recently received systematic study (*144*).

Summary of Epidemiological Data

Kannel has recently reviewed the data pertaining to occlusive peripheral vascular disease (*68*). Several clinical reports find that about 90 percent of individuals with arteriosclerotic obstructive peripheral vascular disease (PVD) are cigarette smokers. This is a marked excess of smokers compared to the general or age- and sex-matched population. Moreover, clinical experience finds that continuation of smoking worsens prognosis after surgical therapy (*157*). In one clinical study of 187 consecutive patients who underwent surgical vascular grafting with synthetic grafts for arterial occlusive disease of the lower abdominal aorta and iliac arteries, the patients who continued to smoke more than a pack a day had three times the graft occlusion rate of nonsmokers, both in absolute terms and in month-patency time (*113*). Koch (*75*) has reported that cessation of smoking will lead to a reversion of risk to that of nonsmokers over 5 years. Diabetes is a strong risk factor for PVD; it acts synergistically with smoking. A diabetic who smokes is reported to have a 50 percent greater risk of PVD than one who does not (*151*). Lawton has reported from a small series examined by angiography that smoking is associated with atherosclerotic distortion of the distal aorta and common iliac arteries in a dose-dependent manner, but not with lesions in the external iliac or femoral arteries (*77*).

Epidemiological studies have also demonstrated an association of PVD with smoking. In one, it was concluded that cigarette smoking was more common than expected for both sexes among those with PVD, that it was an independent risk factor, and that 70 percent of nondiabetic PVD was related to smoking (*152*). The prospective Framingham Heart Study reports a strong association between smoking and obstructive peripheral vascular disease including intermittent claudication (*68*). At all ages and in both sexes a higher incidence of claudication was found in smokers. Heavy smokers had a three times greater incidence and the risk tended to relate directly to the number of cigarettes smoked. The effect was independent by multivariate analysis. At any level of other risk factors the smoker is at greater risk than the nonsmoker. Smoking was found to contribute as strongly to PVD in women as in men. Data for pipe and cigar smoking do not appear to be available.

The Effect of Smoking on Peripheral Vascular Disease

The epidemiological and clinical evidence for smoking as a risk factor has been noted above. The Framingham data on multiple risk factors allow the identification of a top decile of risk from which 40 percent of

cases will emerge (*68*). Wald, et al. (*146*) have reported a closer association between blood COHb in smokers and myocardial infarction, angina, or intermittent claudication (considered together) than with smoking history in a survey of Copenhagen workers.

An acute effect of CO on intermittent claudication has been noted by Aronow, et al. (*11*). They have reported that patients manifesting intermittent claudication of the calf or thigh muscles, and angiographic evidence of iliofemoral arteriosclerosis, who breathed CO to increase mean venous COHb levels from 1.08 to 2.77 percent, experienced a decreased exercise threshold to produce leg pain.

Table A30 (pp. 129-130) of the 1976 report on *The Health Consequences of Smoking* (*138*) lists a number of experiments in man in which the effect of smoking or of nicotine was assessed on some aspect of the peripheral circulation of the arm or leg. The data are not consistent, although the tabulated data in normal individuals tend to show a decrease in skin temperature and a decrease in blood flow. In another study, calf-blood flow was measured plethysmographically in 51 men, aged 59, who were heavy smokers, but who ceased to smoke for about 2 months. They showed an increase in blood flow during reactive hyperemia (*62*) after the cessation period. No experiments on animal models of chronic peripheral vascular disease and smoking have been found.

Research Needs

In general, epidemiological data are adequate. It is likely that current epidemiological research will provide additional data to furnish more exact figures than are currently available. New studies appear to be unnecessary except to establish levels of risk for different "less hazardous" cigarettes. The possible association of postmenopausal estrogen treatment, smoking, and PVD in older women may warrant attention.

However, it is not clear what roles atherogenesis, nicotine, CO, and perhaps tobacco allergy may play in the development and expression of PVD in smokers or in its responsiveness to smoking withdrawal. Studies of the mechanisms responsible for these aspects of smoking and PVD are warranted and may also have interest for the study of the pathogenesis of atherosclerosis in general.

Animal studies involving chronic or acute smoking, hypertension, atherogenesis, and PVD are possible, particularly in nonhuman primates conditioned to smoke. These may offer a direct, if difficult, experimental approach to understanding the circulatory effects of smoking and smoke components on PVD.

Conclusions

Cigarette smoking is a major risk factor for ischemic peripheral vascular disease of arteriosclerotic type. It increases appreciably the

risk of peripheral vascular disease in diabetes mellitus. Clinical experience and case series studies find that cessation of smoking benefits the prognosis in peripheral vascular disease and is advantageous to its surgical treatment.

Aortic Aneurysm of Atherosclerotic Type

The Nature of Atherosclerotic Aortic Aneurysm

Atherosclerosis involves the abdominal aorta early in life about equally in males and females. Progression of the disease in some individuals is such that large plaques rich in lipid and pultaceous with necrosis become confluent and encroach upon the media of the vessel, causing necrosis of its cells and attenuation of the wall. Dilatation of the vessel and aneurysm formation follows. Thrombosis on the lumenal surface is common. Eventually the wall may become so thin that leakage and rupture occur.

Fatal outcome is more common in men than women. The condition usually becomes clinically apparent after the age of 50 and its incidence increases with age. It is not known why some individuals develop this form of progressive disease in the abdominal aorta. An association with smoking is noted below. The morphological features of the process are exaggerated but similar to those of atheroma in other arteries, and it is generally considered that aortic aneurysms of this type are variants of the general process of atherogenesis. There is a high concordance with coronary heart disease.

Equivalent atheromatous lesions have not been produced in experimental animals.

Summary of Epidemiological Data

Atherosclerotic aneurysm of the aorta (nonsyphilitic aneurysm) may cause death by rupture or, occasionally, by thrombotic occlusion. It is an uncommon cause of death, less than 1 percent of cardiovascular deaths being attributed to it. Table 29 (p. 67) of the 1976 report on *The Health Consequences of Smoking* (*138*) lists four population studies in which a total of 947 such deaths are recorded. The two largest studies—that of Kahn involving more than 248,000 U.S. male veterans, and that of Hammond and Garfinkel involving approximately 358,000 males—find a dose-dependent mortality ratio such that pack-a-day male smokers have a ratio of about 4 or 5, while smokers of more than 39 (Kahn) or 40 (Hammond and Garfinkel) cigarettes per day have a mortality ratio between 7 and 8 when compared with nonsmokers. These are unusually large ratios relative to other atherosclerotic disease. Data permitting multivariate analysis in terms of other conventional risk factors are unavailable.

The Effect of Smoking on Aortic Aneurysm

Aside from the strong risk factor association noted above, nothing more is known about smoking and aneurysm formation in man. It may be speculated that CO exposure enhances the circumstances that promote plaque growth and medial hypoxia, which leads to attenuation and necrosis of the aorta. It may also be speculated that smoking may lead to excessive thrombosis, which leads to excessive plaque development and aneurysm formation. However, there are no data in men with aneurysm formation that allow comment on these speculations.

Spontaneous medial calcific arteriosIcerosis occurs in the rabbit, particularly along the thoracic aorta, leading to mild localized aneurysmal dilatations (*55*). It has generally not been specifically reported in relation to smoking or smoke products, although it may possibly have been observed incidentally in various experiments. Wanstrup and associates (*147*) reported the enhancement of such change with CO exposure. Schievelbein (*120*) studied the chronic effect of nicotine in animals (rabbits) liable to develop spontaneous arteriosclerosis in the absence of an atherogenic diet. There was no enhancement of morphological arteriosclerosis by nicotine, but the aortas of the experimentally treated group contained more calcium, more free fatty acids, and more lipoprotein lipase. Aneurysmal differences were not noted.

Research Needs

Atherosclerotic aneurysms of the aorta are uncommon. Study of their pathogenesis is not likely to be promising in the absence of convenient animal model analogues. A study of experimental poststenotic dilatation might illuminate atherogenic processes in relation to smoking. Research initiatives in this area show little promise at present.

Conclusions

Cigarette smoking is a strong risk factor for atherosclerotic aortic aneurysm. The association provides a mortality ratio of about eight among males who smoke more than about 40 cigarettes a day and a dose relationship is evident.

High Blood Pressure

The Nature of Hypertension

Many factors are known to be involved in and affect the control of arterial blood pressure. It is directly dependent on cardiac output and total peripheral resistance. Some of the factors influencing pressure include the renin-angiotensin system, aldosterone, catecholamines, central and peripheral nervous activity, plasma volume, changes in

vessel elasticity, red cell mass and blood viscosity, sodium metabolism, obesity, and genetic predisposition. The manner or means by which most cases of hypertension—essential hypertension—develop is not understood. The effect, however, is to enhance atherogenesis and atherosclerotic diseases, particularly heart disease and stroke, and to shorten life.

Experimental models of hypertension in animals are available for research. There are both genetic models and those induced by hormonal and surgical procedures. However, smoke or smoke constituents have not been assessed in such models.

Summary of Epidemiological Data

Arterial hypertension is a very common disorder constituting a risk factor for atherogenesis, stroke, heart attack, heart failure, renal failure, and retinal damage. Hypertension is a continuous variable and an independent risk factor.

Although smoking can raise blood pressure acutely, there is no evidence that smoking induces hypertension. On the contrary, smokers appear to have, on the average, a slightly lower blood pressure than nonsmokers. Table A8 (pp. 99-100) of the 1976 report on smoking and health (*138*) tabulates several studies; recent reports repeat such data trends or show little relationship (*23, 129*).

An exception to these data is the finding of Kahn and associates (*67*) in their study of 10,000 Israeli male civil servants. In a period of 5 years, they found that the incidence of hypertension adjusted for age was about two times greater in smokers than nonsmokers. However, the conclusion can be considered in additional ways. Since weight gain is associated with an increase in blood pressure and weight loss is associated with a decrease in blood pressure and, moreover, since smokers tend not to gain as much weight as nonsmokers, this complex relationship has attracted attention. Seltzer (*121*) has offered data in which men who stopped smoking gained about 8 pounds and showed an increase of about 4 mm Hg in systolic blood pressure. In examining the data for weight change, it was found that continuing smokers who lost weight had a decrease in systolic blood pressure of about 3 mm Hg, while quitters who also lost weight had an increase in blood pressure of about 2 mm Hg. The gradient between these two groups was about 5 mm Hg in systolic blood pressure. The reference report of 1976 on *The Health Consequences of Smoking* (*138*) comments critically on this report (p. 138ff.), and notes a marginal sample size.

Available data indicate that smoking is not a major risk factor for hypertension, and in practice, the association is slightly negative. In this sense, it should be balanced against the other strong positive risk factor associations of smoking for various expressions of heart attack, for PVD, aortic aneurysm, lung disease, and cancers.

Data from several epidemiological studies indicate that, when hypertension is present, its combination with another risk factor, such as elevated blood lipids or smoking, is synergistic.

The Effect of Smoking on Blood Pressure

The chronic epidemiological effects of cigarette smoke on the incidence and level of hypertension and in conjunction with hypertension as an additional risk factor for cardiovascular disease have been noted above.

The acute and transient effect of smoking in man is to increase heart rate and blood pressure to a minor degree. These effects are thought to be due primarily to the action of nicotine releasing cathecholamines. In the 1976 report on *The Health Consequences of Smoking* (*138*), Table A20 (pp. 103-108) and Table A21 (pp. 109-114) summarize a series of acute effects of smoking and nicotine on the blood pressure of animals and humans. Table A22 (p. 115), notes the effects on catecholamines in humans and animals. Beaumont and colleagues (*17*) have recently reported on a paroxysmal arterial hypertension as a reaction to cigarette smoking in which, under clinical diagnostic testing, a single high nicotine cigarette induced a rise in blood pressure of about 50 mm Hg systolic and 20 mm Hg diastolic over about 20 minutes. The reaction was accompanied by headache, palpatations, and sweating. The reaction was elicited in 13 of 178 persons tested, all of whom were moderate to heavy smokers.

Research Needs

It would be of some interest for an understanding of chronic hypertension to elucidate the pathogenesis of what appears to be a very mild hypotensive chronic effect of smoking. Since genetic and induced animal models of hypertension and hypertensive vasculopathy exist, including stroke-prone spontaneously hypertensive rats, it may be informative to assess the acute and chronic effects of smoke and smoke constituents in them.

Conclusions

Cigarette smoking does not induce chronic hypertension. Indeed, present evidence indicates that it is associated with a mild chronic hypotensive effect. However, in the presence of hypertension as a risk factor for coronary heart disease, smoking acts synergistically to increase the effective risk by joining the risks attributable to hypertension and to smoking alone.

Other Conditions

Among other conditions of interest are arterial and venous thrombosis, the synergism of smoking with oral contraceptives in relation to

myocardial infarction, thromboangiitis obliterans, the effect of smoking on blood lipids and lipoproteins, and tobacco constituents other than CO and nicotine.

Venous Thrombosis

Pathological studies in human autopsies that address the question of a difference in the presence of venous thrombi in relation to smoking habits have not been reported. On the other hand, epidemiological studies have clearly shown that conditions such as myocardial infarction or peripheral vascular disease that are commonly induced or accompanied pathogenetically by arterial thrombosis are more common in smokers than nonsmokers. Vessey and Doll (*140*) reported in a case control study among 84 women with venous thromboembolism (deep vein thrombosis or pulmonary embolism) that there were no appreciable differences in smoking habits of subjects with or without venous thromboembolism. In the same paper, the authors mention a mortality study conducted among British doctors and report that among 31 male deaths from venous thromboembolism over 15 years of observation, the age-standardized mortality rates per 100,000 were 96 among nonsmokers, 57 among cigarette smokers, and 71 among pipe and cigar smokers. Lawson and coworkers (*76*) report the absence of an effect of smoking on venous thromboembolism among premenopausal women who were users of oral contraceptives. It has been reported that smokers suffer less thrombosis of the deep veins of the leg after myocardial infarction (*39, 83*). The failure to confirm such a finding has also been published (*57*). There have been a number of studies of various aspects of blood coagulation and platelet pathophysiology in relation to smoking. In general, these have been acute experimental investigations. Table A27 (pp. 126-1138) of the 1976 report on smoking and health (*138*) recorded a number of such studies, including a review by Murphy. The data tend in the direction of phenomena that might be expected to promote thrombosis. However, confounding variables are uncertain and the meaning of *in vitro* tests for *in vivo* phenomena of thrombosis is not established.

From the limited data available, smoking does not appear to enhance venous thrombotic disease.

The interest in venous thrombosis and smoking lies not only in the question of the presence or absence of an association but in its possible meaning for arterial thrombosis. Arterial thrombosis is involved to an important degree in atherogenesis, and in the precipitation and complication of heart attack, ischemic stroke, and peripheral vascular disease. There are research opportunities to learn more about thrombosis in general and, in particular, in relation to possible pathogenetic associations with smoking.

Thromboangiitis Obliterans (Buerger's Disease)

Buerger's disease is a relatively rare vascular disease that severely affects the legs and sometimes affects the arms and other vessels. It is usually present as a painful ischemic disease of progressive and subacute type in young male adults. Pathologically, there is a focal subacute inflammatory phase involving the artery, nerve, and vein coursing in the limb. The vascular inflammation is accompanied by arterial and venous thrombosis and local obstruction to the circulation. A migrating thrombophlebitis is often prominent. Lesions may heal with vascular sclerosis and new lesions may appear at other sites. The ultimate outcome is ischemic loss of the limb(s) and when the lesion extends to other vessels, loss of life. While the disease has been regarded as a fulminant form of atherosclerosis (*153*), the more common view with stronger evidence is that it is a separate disease (*87*) and a vasculitis. An infectious etiology (*24*) has been proposed, as has a hypersensitivity cause (*54*). Risk factors such as hypercholesterolemia or diabetes are not present and coronary heart disease occurs only very late in the course of the disease.

Smoking has been noted clinically to be strongly associated with Buerger's disease (*68*). Retrospective studies indicate that its occurrence among nonsmokers must be very rare. The lesions are compatible with an angiitis of hypersensitive or immunologic pathogenesis. Therefore, it has been speculated that hypersensitivity to tobacco components may be the basis of thromboangiitis obliterans (*54*). The evidence for this theory is suggestive but inadequate at present. Adequate investigations will probably require the use of much purer tobacco antigens than have been available in the past (*19*). There is conceptual interest for the pathogenesis of atherosclerosis in such investigations that extends beyond thromboangiitis itself since atherosclerotic lesions commonly show evidence of a slight inflammatory component and since a form of coronary atherosclerosis bearing a remarkable resemblance to advanced plaques in man has been produced in fat-fed rabbits by immunologic means (*93*), and also because a glycoprotein isolated from tobacco leaves has been shown to activate Factor XII in samples of human plasma, resulting in the generation of clotting activity, fibrinolytic activity, and kinin activity (*18*).

Oral Contraceptives, Smoking, Myocardial Infarction, and Subarachnoid Hemorrhage Among Women

Extensive population studies have determined that the risk of nonfatal myocardial infarction among women during child bearing ages is increased by a factor of about two times by the use of estrogen-containing oral contraceptives, and that it is increased to about 10 times the expected value when users also smoke (*61, 81, 82, 102*). A recent study reports that oral contraceptive use increases the risk of

subarachnoid hemorrhage about six times and that the additional use of cigarettes increases the risk to about 20 times (*106*).

The mechanisms that may underlie these phenomena in women are considered elsewhere, but estrogen and estrogen analogue administration to men with cancer of the prostate or with preexisting myocardial infarction have been shown to increase the risk of heart attack (*30, 141*). These reports did not contain information on smoking, however. While the associations between smoking, oral contraceptive use, and enhanced risk of cardiovascular disease are not in doubt, research opportunities exist in seeking explanations for the effect.

The Effect of Smoking on Blood Lipids

The report, *The Health Consequences of Smoking* of 1976 (*138*), dealt with the question of a possible effect of smoking on blood or serum cholesterol. Acute effects in man and animals were tabulated in Tables A25 and A25a (pp. 119-124). Case control and population studies are listed in Table A7 (pp. 94-98). The data are not very uniform, but there is a preponderance of results in man in which smokers have a somewhat higher blood cholesterol level than nonsmokers. Paul (*103*) has recently presented additional data with this same finding. Dawber has analyzed the Framingham Heart Study data in terms of pipe, cigar, and cigarette smoking (*33*). Since these forms of smoking deliver different amounts of tar, nicotine, and CO to the smoker, such an analysis might reflect specific responses on the part of the serum lipids. No major differences were found. Pipesmokers had average cholesterol levels of about 216.25 mg, cigar smokers of 220.95 mg, and cigarette smokers of 224.34 mg (nonsmokers 223.83 mg). These differences are too small to account for the observed differences in risk associated with type of smoking habit. There may indeed be a minor tendency for cigarette smokers to have slightly elevated blood cholesterol levels for whatever reason, but smoking and cholesterol are clearly established independent risk factors.

Experimental data based on acute manipulation of smoke exposure or nicotine appear to show a consistent elevation of free fatty acids in the blood. Animals exposed to CO and high cholesterol diets have been reported to develop more hypercholesterolemia than expected, but confirmation has not been established with whole smoke (*14, 136*).

Other recent reports have found HDL levels to be a strong and independent risk factor for coronary heart disease that has an inverse relationship (*49, 92, 94*); high levels are protective and low levels are associated with increased risk. Both in a subset of the Tromso study (*94*) and in the Framingham study (*49*), almost identical HDL cholesterol levels among smokers and nonsmokers were found; there was no significant association between them.

Observations on 10,000 males in Israel show that alpha cholesterol is depressed among smokers of cigarettes compared to nonsmokers and

ex-smokers, with the trend persisting in different age groups. The concentration of alpha cholesterol decreased according to increased amounts smoked daily when the smokers were grouped as never having smoked, and having smoked 0 to 10, 11 to 20, and more than 20 cigarettes smoked per day. Total serum cholesterol, and hence beta cholesterol, were increased in direct relationship to the amount smoked (*48*). HDL cholesterol has also been measured among approximately 4,000 men and women who are the adult offspring of the original Framingham Heart Study cohort. After control for reported alcohol consumption, subscapular skinfold thickness, and age in multiple regression analysis, cigarette smoking was found to be associated with significantly lower HDL levels in both men and women. There was no evidence of lower HDL cholesterol among former cigarette smokers (*47*). In an examination of 447 women and 471 men aged 40 or 41 in Holland, it has been found that HDL cholesterol is (as expected) higher in women than in men. Cigarette smoking was associated with a reduced serum HDL-cholesterol in both men and women. Among the women there was also a strong negative association with the use of oral contraceptives that was independent of smoking (*4*).

Hulley and colleagues (*59*) have recently reported in a multiple-risk-factor intervention trial group that over a period of a year the change in serum thiocyanate (an indirect measure of smoking activity) showed a univariate regression coefficient, with an HDL cholesterol of –.12 that was significant at less than the 0.05 level. The multivariate regression coefficient was –.15 and significant at less than 0.01. While more data should be gathered to ascertain the effect of smoking on HDL levels, present indications are that, when other factors that also affect HDL levels are controlled in statistical analysis, cigarette smoking displays an independent inverse relationship with HDL levels. Moreover, since total cholesterol levels appear to be slightly elevated among smokers, lipoprotein cholesterol that is positively atherogenic will also be increased. Consequently, it can be hypothesized that the effect of smoking on CHD morbidity and mortality may be to some degree a reflection of altered lipoprotein metabolism.

Other Constituents of Smoke

Smoke is a remarkably complex mixture of chemical substances and physical chemical states. Our understanding of the relationships of nicotine and CO and of whole smoke to cardiovascular disease have been noted above. Other substances have attracted some investigation also. Those of possible cardiovascular interest include cadmium, zinc, chromium, carbon disulphide, carbon dioxide, hydrogen cyanide, oxides of nitrogen, and polonium-210. McMillan (*90*) concluded that, while these substances provide interesting grounds for speculation as to their possible role in cardiovascular disease, only nicotine and CO offer both data and rational concepts for a role in smoking and cardiovascular

disease that command serious attention at the present time. As noted very briefly above in the section on thromboangiitis and considered in a separate chapter, hypersensitivity to tobacco protein does offer reasonable concepts in relation to the pathogenesis of arteriosclerosis, thrombosis, and angiitis. Its investigation will require more systematic study and the use of immunologic methods superior to those employed in the past.

Discussion and Conclusions

The present report on cardiovascular disease and smoking is able to summarize and to comment on far more extensive and detailed data than were available 15 years ago. It draws heavily on the 1976 reference report on smoking and health (*138*) and adds recent references.

Systematic observations on the associations between smoking and cardiovascular diseases have been made on considerably more than a million individuals in the United States alone and have involved many millions of person-years of experience. The majority of these have been gathered on men.

Sample sizes are now extensive in both retrospective and prospective studies. The variables observed in retrospective studies have been relatively limited; in some prospective studies, they have been more numerous and have allowed for complex analyses in which the independence of smoking as a risk factor among other risk factors has been defined.

The data collected from western countries, particularly the United States, but also the United Kingdom, Canada, and others, show that smoking is one of three major independent risk factors for heart attack manifest as fatal and nonfatal myocardial infarction and sudden cardiac death in adult men and women. Moreover, the effect is dose related, synergistic with other risk factors for heart attack, and of stronger association at younger ages. Based on smaller but still extensive samples, smoking cigarettes is strongly associated with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta.

There is no reasonable doubt that cigarette smoking as a risk factor for these cardiovascular diseases has been proven. Its dimensions as a risk factor for them have been established for the American public.

Atherosclerosis, the basic lesion of ischemic disease studied at autopsy, has been observed in restricted samples and limited numbers of cases. Nevertheless, the data establish adequately that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries than is found among nonsmokers. The effect is related to the amount smoked. Existing autopsy data have not allowed adequate multivariate analysis, but several prospec-

tive studies have now collected sufficient standard risk factor data, including smoking information and autopsy findings, to report preliminary multivariate analyses. While more data might be desirable in order to establish better the dimensions of effect as seen at autopsy, and more data are needed to extend multivariate analyses, there is no reasonable doubt that cigarette smoking enhances atherogenesis. This knowledge establishes a fundamental rationale for the findings on the incidence of heart attack, including sudden cardiac death, aortic aneurysm, and peripheral vascular disease in relation to smoking. It is somewhat uncertain, but likely, that smoking has an adverse effect on the recurrence of heart attack among survivors of a prior myocardial infarction.

On the other hand, epidemiologic data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive. There are major and unresolved inconsistencies between existing reports. While certain reports on these diseases may have more technical strength than others and thus provide more credible conclusions, a basis for drawing final conclusions is not established in these two conditions. It is of interest that, in acute experiments on atherosclerotic patients with angina pectoris or with the intermittent claudication of peripheral vascular disease, smoking or exposure to carbon monoxide reduces the patients' established threshold for the precipitation of angina or claudication.

There is no apparent relationship between smoking and the incidence of hypertension. Available evidence indicates a neutral or slight hypotensive effect. Nevertheless, in the presence of hypertension, smoking joins with hypertension to affect the patient with the cardiovascular burden of both risk factors.

There are opportunities for further epidemiological research into smoking as a risk factor for cardiovascular disease; these have been detailed in each of the foregoing sections. The need and priority of such research should be debated in specific cases. It can be argued that little public health or medical therapeutic advantage would arise from a clarification of the relationship of smoking to angina or cerebrovascular disease in the face of the existing conclusive evidence of its adverse effect on the incidence of heart attack and lung diseases and the benefits of smoking avoidance or cessation. On the other hand, it could be of some medical value to learn more accurately what the association may be for second heart attacks. It would be of great interest for preventive medicine to know whether smoking affects the severity of atherosclerosis of the aorta and coronary arteries in childhood and adolescence and the premature development of adult forms of lesions in youth. It would also be of great interest to learn whether present-day cigarettes modified to deliver less tar and nicotine are less hazardous for cardiovascular health. Earlier data, which no longer represent current products, found that low tar and nicotine cigarettes

carried less risk than high tar and nicotine ones but that they also bore a considerably greater risk than not smoking.

Relatively little is known about the mechanisms by which smoking enhances atherogenesis or increases the risk of heart attack. This ignorance in no way weakens the force of the information noted above; nevertheless, better insight into the pathogenesis of these effects would be of potential value in designing less hazardous cigarettes or in attempting otherwise to limit the hazard of smoking. Moreover, it is likely that there would be an appreciable gain of information about basic processes of atherogenesis, thrombosis, cardiac metabolism and ischemia, and cardiac rhythmicity and ectopic electrical activity. Some experiments can be done acutely in man; many can be done in animal models with smoke constituents. Chronic or acute experiments in nonhuman primates with natural or modified whole smoke taken by inhalation in a humanlike nonaversive manner of smoking now appear possible. It should be emphasized that a number of strong concepts exist in atherogenesis, thrombosis, and cardiac structure and function within which to mount appropriate experiments.

Data on the epidemiological relationships between smoking and heart attack, peripheral vascular disease, aortic aneurysm, and arteriosclerosis noted above have been assembled in a manner to allow a statistical statement of the nature of the correlations between cigarette smoking and cardiovascular disease. Correlation is not synonymous with causation. It is important for the public to understand the nature or character of the associations that have been found. The characteristics are fully established for heart attack and include the fact that the correlations are strong ones, generally having a relative risk of two or more. They are consistent, reappearing in different population samples over and over, and they are independent of other major risk factors. There is also a graded relationship; smoking is an antecedent event in time and the cessation of smoking is followed by a reduction in risk over time; the association has strong predictive capacity in the same population sample and also when applied to other samples. Within the limits of the research that has been done, the findings of epidemiology, clinical investigation, and pathology are generally congruent. The results from the various disciplines and techniques of study tend to support each other. Although there are reports which do not confirm the statements made above, they constitute a minor part of the data and fail to cast reasonable doubt. Animal experimentation is not yet well developed in smoking research in relation to cardiovascular disease.

Smoking is not a necessary condition for atherosclerosis and heart attack since these occur in nonsmokers. Repeated and very extensive experience has found, however, that it is a sufficient condition to increase the mortality from heart attack among the category of people who smoke and that it does so in a predictable way.

Given the characteristics of its associations with heart attack (such as strength, graded relationship, independence, consistency, antecedence, loss of relationship on withdrawal, predictive capability, and a degree of coherence), it can be concluded that smoking is causally related to coronary heart disease in the common sense of that idea and for the purposes of preventive medicine. It may be argued that the characteristics of the associations noted above would occur if people who were constitutionally liable to heart attack were also constitutionally liable to smoke; that is, that smoking activity and susceptibility to atherosclerotic heart disease were both due to some underlying constitutional condition of the individual. An attempt has been made to study this point by observing large numbers of monozygotic and dizygotic twins. The result has been inconclusive. A discussion of references will be found in the 1976 report on *The Health Consequences of Smoking* (p. 44ff.) (*138*). It should be noted, however, that the fact that risk in smokers reverts to normal or nonsmokers' levels after they cease to smoke is contrary to the constitutional concept as expressed above, unless further complex assumptions are made and it is assumed that large numbers of individuals underwent a change in their underlying constitutional factor in midlife, acquired low risk, and ceased to smoke because of that new constitution. This is not to say that genetic susceptibility or resistance may not also be a risk factor that plays a role in the individual expression of or resistance to disease along with other risk factors, or that people who stop smoking may not also adopt additional health-oriented behaviors when they stop; but the constitutional hypothesis as expressed above does not provide a credible basis to doubt that cigarette smoking is a cause of coronary heart disease.

From the point of view of cardiovascular disease, research on the mechanisms whereby smoking causes its adverse effects and a more precise quantification of certain risk factors through epidemiological studies are significant topics of medical science. The major goal in smoking and cardiovascular disease research is, however, the development of long-term effective methods of smoking avoidance and cessation.

Cardiovascular Diseases: References

(1) ALBERT, R.E., VANDERLAAN, M., BURNS, F.J., NISHIZUMI, M. Effect of carcinogens on chicken atherosclerosis. Cancer Research 37(7): 2232-2235, July 1977.

(2) ARMITAGE, A.K., DAVIES R.F., TURNER D.M. The effects of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon. Atherosclerosis 23(2): 333-344, March/April 1976.

(3) ARMSTRONG, M.L. Regression of Atherosclerosis. In: Paoletti, R., Gotto, A.M. Jr. (Editors). Atherosclerosis Reviews, Volume 1, New York, Raven Press, 1976, pp. 137-182.

(4) ARNTZENIUS, A.C., VAN GENT, C.M., VAN DER VOORT, H., STEGERHOEK, C.I., STYBLO, K. Reduced high-density lipoprotein in women aged 40-41 using oral contraceptives. Consultation Bureau Heart Project. Lancet: 1221-1223, June 10, 1978.

(5) ARONOW, W.S. Carbon monoxide and cardiovascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 321-328.

(6) ARONOW, W.S. Introduction to smoking and cardiovascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 231-236.

(7) ARONOW, W.S., CASSIDY, J., VANGROW, J.S. MARCH, H., KERN, J.C., GOLDSMITH, J.R., KHEMKA, M., PAGANO, J., VAWTER, M. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. Circulation 50(2): 340-347, August 1974.

(8) ARONOW, W.S., ISBELL, M.W. Carbon monoxide effect on exercise-induced angina pectoris. Annals of Internal Medicine 79(3): 392-395, September 1973.

(9) ARONOW, W.S., KAPLAN, M.A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3): 529-536, September 1968.

(10) ARONOW, W.S., ROKAW, S.N. Carboxyhemoglobin caused by smoking non-nicotine cigarettes. Effects in angina pectoris. Circulation 44: 782-788, November 1971.

(11) ARONOW, W.S., STEMMER, E.A., ISBELL, M.W. Effect of carbon monoxide exposure on intermittent claudication. Circulation 49: 415-417, March 1974.

(12) ARONOW, W.S., SWANSON, A.J. The effect of low-nicotine cigarettes on angina pectoris. Annals of Internal Medicine 71(3): 599-601, September 1969.

(13) ASTRUP, P. Some physiological and pathological effects of moderate carbon monoxide exposure. British Medical Journal 4(5838): 447-452, November 25, 1972.

(14) ASTRUP, P., KJELDSEN, K., WANSTRUP, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7: 343-354, 1967.

(15) AUERBACH, O., CARTER, H.W., GARFINKEL, L., HAMMOND, E.C. Cigarette smoking and coronary artery disease: A macroscopic and microscopic study. Chest 70(6): 697-705, December, 1976.

(16) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L., KIRMAN, D. Thickness of walls of myocardial arterioles in relation to smoking and age: Findings in men and dogs. Archives of Environmental Health 22: 20-27, January 1971.

(17) BEAUMONT, J.-L., BUXTORF, J.-C., JACOTOT, B., JAN, F. Les accidents hypertensifs paroxystiques observes chez les fumeurs (Incidence of paroxysmal hypertension in smokers). Concours Medical 98(17): 2611-2612, 2615-2617, April 24, 1976.

(18) BECKER, C.G., DUBIN, T. Activation of factor XII by tobacco glycoprotein. Journal of Experimental Medicine 146: 457-467, 1977.

(19) BECKER, C.G., DUBIN, T., WIEDEMANN, H.P. Hypersensitivity to tobacco antigen. Proceedings of the National Academy of Sciences of the U.S.A. 73(5): 1712-1716, May 1976.

(20) BELLET, S., DEGUZMAN, N.T., KOSTIS, J.B., ROMAN, L., FLEISCHMANN, D. The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. American Heart Journal 83(1): 67-76, January 1972.

(21) BENDITT, E.P. The monoclonal hypothesis, which holds that the proliferating cells of an atherosclerotic plaque all stem from one mutated cell, suggests new lines of research on the causes of coronary disease. Scientific American: 74-85, February 1977.

(22) BENDITT, E.P., BENDITT, J.M. Evidence for a monoclonal origin of human atherosclerotic plaques. Proceedings of the National Academy of Sciences of the U.S.A 70(6): 1753-1756, June 1973.

(23) BERGLUND, G., WILHELMSEN, L. Factors related to blood pressure in a general population sample of Swedish men. Acta Medica Scandinavica 198(4): 291-298, October 1975.

(24) BERNARD, J.G., MOREL, E. Peripheral arteritis—infectious aetiology. In: Shimamoto, T., Numano, F., Addison, G.M. (Editors). Atherogenesis, Volume II. Proceedings of the Second International Symposium on Atherogenesis, Thrombogenesis and Pyridinolcarbamate Treatment, Tokyo, May 18-20, 1972. Amsterdam, Excerpta Medica, 1973, pp. 325-329.

(25) BIRNSTINGL, M.A., BRINSON, K., CHAKRABARTI, B.K. The effect of short-term exposure to carbon monoxide on platelet stickiness. British Journal of Surgery 58(11): 837-839, November 1971.

(26) BRITISH MEDICAL JOURNAL. Cigarette smoking and chest pain. British Medical Journal 4(5993): 368, November 15, 1975.

(27) CASTLEDEN, C.M., COLE, P.V. Carboxyhaemoglobin levels of smokers and nonsmokers working in the City of London. British Journal of Industrial Medicine 32: 115-118, 1975.

(28) CORDAY, E., DODGE, H.T., (Guest Editors). Symposium on Identification and Management of the Candidate for Sudden Cardiac Death. The American Journal of Cardiology 39(6): 813-815, May 26, 1977.

(29) THE CORONARY DRUG PROJECT RESEARCH GROUP. Cigarette smoking as a risk factor in men with a prior history of myocardial infarction. Journal of Chronic Diseases, 15 pp. (to be published)

(30) THE CORONARY DRUG PROJECT RESEARCH GROUP. The Coronary Drug Project: Initial findings leading to modifications of its research protocol. Journal of the American Medical Assocation 214(7): 1303-1313, November 16, 1970.

(31) COUNCIL ON CEREBROVASCULAR DISEASE. Risk factors in stroke due to cerebral infarction. A statement for physicians prepared by a subcommittee and approved by the executive committee of the Council on Cerebrovascular Diseases of the American Heart Association. Stroke 2(5): 423-428, September-October 1971.

(32) DAVIES, R.F., TOPPING, D.L., TURNER, D.M. The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. Atherosclerosis 24: 527-536, September 1976.

(33) DAWBER, T.R. The interrelationship of tobacco smoke components to hyperlipidemia and other risk factors. In: Wynder, E.L., Hoffmann, D., Gori, G.B., (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 285-292.

(34) DEBIAS, D.A., BANERJEE, C.M., BIRKHEAD, N.C., GREENE, C.H., SCOTT, S.D., HARRER, W.V. Effects of carbon monoxide inhalation on ventricular fibrillation. Archives of Environmental Health 31(1): 42-46, January-February 1976.

(35) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2(6051): 1525-1536, December 25, 1976.

(36) DOWNEY, H.F., BASHOUR, C.A., BOUTROS, I.S., BASHOUR, F.A., PARKER, P.E. Regional myocardial blood flow during nicotine infusion: Effects of beta adrenergic blockade and acute coronary artery occlusion. Journal of Pharmacology and Experimental Therapeutics 202(1): 55-68, July 1977.

(37) DOYLE, J.T., DAWBER, T.R., KANNEL, W.B., KINCH, S.H., KAHN, H.A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, New York, and Framingham, Massachusetts, studies. Journal of the American Medical Association 190(10): 886-890, December 7, 1964.

(38) DOYLE, J.T., KANNEL, W.B., MCNAMARA, P.M., QUICKENTON, P., GORDON, T. Factors related to suddenness of death from coronary disease: combined Albany-Framingham studies. American Journal of Cardiology 37(6): 1073-1078, June 1976.

(39) EMERSON, P.A., MARKS, P. Preventing thromboembolism after myocardial infarction: Effect of low-dose heparin or smoking. British Medical Journal 1(6052): 18-20, January 1, 1977.

(40) THE EPIDEMIOLOGY STUDY GROUP. Epidemiology for stroke facilities planning. Report of the Joint Committee for Stroke Facilities. Stroke 3: 360-371, May-June 1972.

(41) FEINLEIB, M., WILLIAMS, R.R. Relative risks of myocardial infarction, cardiovascular disease and peripheral vascular disease by type of smoking. In: Wynder, E.C., Hoffmann, D., Gori, G.B., (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 243-256.

(42) FISHER, E.R., ROTHSTEIN, R., WHOLEY, M.H., NELSON, R. Influence of nicotine on experimental atherosclerosis and its determinants. Archives of Pathology 96: 298-304, November 1973.

(43) FIVE-YEAR STUDY BY A GROUP OF PHYSICIANS OF THE NEWCASTLE UPON TYNE REGION. Trial of clofibrate in the treatment of ischaemic heart disease. British Medical Journal 4: 767-776, December 25, 1971.

(44) FRIEDMAN, G.D., KLATSKY, A.L., SIEGELAUB, A.B. Predictors of sudden cardiac death. Circulation (Supplement III to Volumes 51 and 52): III-164—III-169, December 1975.

(45) FRIEDMAN, G.D., SIEGELAUB, A.B., DALES, L.G. Cigarette smoking and chest pain. Annals of Internal Medicine 83(1): 1-7, July 1975.

(46) FROST, H. Investigations into the pathogenesis of arteriosclerosis: drug prophylaxis. In: Shimamoto, T., Numano, F., Addison, G.M., (Editors). Atherogenesis, Volume II. Proceedings of the Second International Symposium on Atherogenesis, Thrombogenesis and Pyridinolcarbamate Treatment, Tokyo, May 18-20, 1972. Amsterdam, Excerpta Medica, 1973, pp. 32-50.

(47) GARRISON, R.J., KANNEL, W.B., FEINLEIB, M., CASTELLI, W.P., MCNAMARA, P.M., PADGETT, S.J. Cigarette smoking and HDL cholesterol. The Framingham Offspring Study. Atherosclerosis 30: 17-25, 1978.

(48) GOLDBOURT, U., MEDALIE, J.H. Characteristics of smokers, nonsmokers and ex-smokers among 10,000 adult males in Israel. II. Physiologic, biochemical and genetic characteristics. American Journal of Epidemiology 105(1): 75-86, 1977.

(49) GORDON, T., CASTELLI, W.P., HJORTLAND, M.C., KANNEL, W.B., DAWBER, T.R. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. American Journal of Medicine 62: 707-714, May 1977.

(50) GORDON, T., KANNEL, W.B., MCGEE, D., DAWBER, T.R. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham study. Lancet 2: 1345-1348, December 7, 1974.

(51) GRAHAM, I., MULCAHY, R., HICKEY, N., SYNNOTT, M. Mode of death related to smoking in patients with coronary heart disease. Journal of the Irish Medical Association 70(7): 234-235, May 14, 1977.

(52) GREENSPAN, K., EDMANDS, R.E., KNOEBEL, S.B., FISCH, C. Some effects of nicotine on cardiac automaticity, conduction, and inotrophy. Archives of Internal Medicine 123(6): 707-712, June 1969.

(53) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. Environmental Research 12(3): 263-274, December 1976.

(54) HARKAVY, J. Tobacco allergy in cardiovascular disease: A review. Annals of Allergy 26(8): 447-459, August 1968.

(55) HAUST, M.D., MORE, R.H. Spontaneous lesions of the aorta in the rabbit. In Roberts, J.C., Jr., Straus, R. (Editors). Comparative Atherosclerosis. The Morphology of Spontaneous and Induced Atherosclerotic Lesions in Animals and Its Relation to Human Disease. New York, Harper and Row, 1965, pp. 255-275.

(56) HAWKINS, L.H. Blood carbon monoxide levels as a function of daily cigarette consumption and physical activity. British Journal of Industrial Medicine 33(2): 123-125, May 1976.

(57) HAYES, M.J., MORRIS, G.K., HAMPTON, J.R. Lack of effect of bed rest and cigarette smoking on development of deep venous thrombosis after myocardial infarction. British Heart Journal 38(9): 981-983, September 1976.

(58) HOLLANDER, W., PRUSTY, S., KIRKPATRICK, B., PADDOCK, J. NAGRAJ S. Role of hypertension in ischemic heart disease and cerebral vascular disease in the cynomolgus monkey with coarctation of the aorta. Circulation Research 40(5, Supplement 1): I-70—I-83, May 1977.

(59) HULLEY, S.B., COHEN, R., WIDDOWSON, G. Plasma high-density lipoprotein cholesterol level. Influence of risk factor intervention. Journal of the American Medical Association 238(21): 2269-2271, November 21, 1977.

(60) JAIN, A.C., BOWYER, A.F., MARSHALL, R.J., ASATO, H. Left ventricular function after cigarette smoking by chronic smokers: Comparison of normal subjects and patients with coronary artery disease. Americal Journal of Cardiology 39(1): 27-31, January 1977.

(61) JAIN, A.K. Cigarette smoking, use of oral contraceptives, and myocardial infarction. American Journal of Obstetrics and Gynecology 126(3): 301-307, October 1, 1976.

(62) JANZON, L. Smoking cessation and peripheral circulation. A population study in 59-year-old men with plethysmography and segmental measurements of systolic blood pressure. VASA 4(3): 282-287, 1975.

(63) JENKINS, C.D., ROSENMAN, R.H., ZYZANSKI, S.J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1140-1155, December 1968.

(64) JENKINS, C.D., ZYZANSKI, S.J., ROSENMAN, R.H. Risk of new myocardial infarction in middle-aged men with manifest coronary heart disease. Circulation 53(2): 342-347, February 1976.

(65) JENNINGS, R.B. Relationship of acute ischemia to functional defects and irreversibility. Circulation 53(3, Supplement 1): I-26—I-29, March 1976.

(66) KAGAN, A.R., STERNBY, N.H., UEMURA, K., VANECEK, R., VIHERT, A.M., LIFSIC, A.M., MATOVA, E.E., ZAHOR, Z., ZDANOV, V.S. Atherosclerosis of the aorta and coronary arteries in five towns. Bulletin of the World Health Organization 53(5-6): 485-645, 1976.

(67) KAHN, H.A., MEDALIE, J.H., NEUFELD, H.N., RISS, E., GOLDBOURT, U. The incidence of hypertension and associated factors: The Israel ischemic heart disease study. Americal Heart Journal 84(2): 171-182, August 1972.

(68) KANNEL, W.B. Epidemiologic studies on smoking in cerebral and peripheral vascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B., (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 257-274.

(69) KANNEL, W.B. Some lessons in cardiovascular epidemiology from Framingham. American Journal of Cardiology 37: 269-282, February 1976.

(70) KANNEL, W.B., CASTELLI, W.P. Significance of nicotine, carbon monoxide and other smoke components in the development of cardiovascular disease. U.S. Public Health Service, DHEW Publication No. (NIH) 76-1221, 1976, pp. 369-381.

(71) KANNEL, W.B. DOYLE, J.T., MCNAMARA, P.M. QUICKENTON, P., GORDON, T. Precursors of sudden coronary death. Factors related to the incidence of sudden death. Circulation 51: 606-613, April 1975.

(72) KJELDSEN, K., ASTRUP, P., WANSTRUP, J. Reversal of rabbit atheromatosis by hyperoxia. Journal of Atherosclerosis Research 10: 173-178, 1969.

(73) KJELDSEN, K., THOMSEN, H.K. The effect of hypoxia on the fine structure of the aortic intima in rabbits. Laboratory Investigation 33(5): 533-543, 1975.

(74) KJELDSEN, K., WANSTRUP, J., ASTRUP, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 8: 835-845, 1968.

(75) KOCH, A. Smoking and peripheral arterial disease. In: Wynder, E.L. Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 281-283.

(76) LAWSON, D.H., DAVIDSON, J.F., JICK, H. Oral contraceptive use and venous thromboembolism: Absence of an effect of smoking. British Medical Journal 2: 729-730, September 17, 1977.

(77) LAWTON, G. Cigarette consumption and atherosclerosis. Their relationship in the aortic and iliac and femoral arteries. British Journal of Surgery 60(11): 873-876, November 1973.

(78) LEVINE, P.H. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. Circulation 48: 619-623, September 1973.

(79) LIFSIC, A.M. Atherosclerosis in smokers. Bulletin of the World Health Organization 53(5-6): 631-638, 1976.

(80) MALINOW, M.R., MCLAUGHLIN, P., DHINDSA, D.S., METCALFE, J., OCHSNER, A.J., III, HILL, J., MCNULTY, W.P. Failure of carbon monoxide to induce myocardial infarction in cholesterol-fed cynomolgus monkeys (Macaca fascicularis). Cardiovascular Reasearch 10: 101-108, 1976.

(81) MANN, J.I., INMAN, W.H.W., THOROGOOD, M. Oral contraceptive use in older women and fatal myocardial infarction. British Medical Journal 2: 445-447, August 21, 1976.

(82) MANN, J.I., VESSEY, M.P., THOROGOOD, M., DOLL, R. Myocardial infarction in young women with special reference to oral contraceptive practice. British Medical Journal 2: 241-245, May 3, 1975.

(83) MARKS, P., EMERSON, P.A. Increased incidence of deep vein thrombosis after myocardial infarction in nonsmokers. British Medical Journal 3(5925): 232-234, July 27, 1974.

(84) MCGILL, H.C., JR. Atherosclerosis: Problems in pathogenesis. In: Paoletti, R., Gotto, A.M., Jr. (Editors). Atherosclerosis Reviews, Volume 2. New York, Raven Press, 1977, pp. 27-65.

(85) MCGILL, H.C., JR., (Editor). General findings of the International Atherosclerosis Project. Laboratory Investigation 18(5): 498-502, May 1968.

(86) MCGILL, H.C., JR., ROGERS, W.R., WILBUR, R.L., JOHNSON, D.E. Cigarette smoking baboon model: Demonstration of feasibility (40119). Proceedings of the Society for Experimental Biology and Medicine 157: 672-676, 1978.

(87) MCKUSICK, J.A., HARRIS, W.S., OTTESEN, O.E., GOODMAN, R.M., SHELLEY, W.M., BLOODWELL, R.D. Buerger's disease: A distinct clinical and pathologic entity. Journal of the American Medical Association 181(1): 5-12, July 7, 1962.

(88) MCMAHAN, C.A., RICHARDS, M.L., STRONG, J.P. Individual cigarette usage: Self-reported data as a function of respondent-reported data. Atherosclerosis 23(3): 477-488, May/June 1976.

(89) MCMILLAN, G.C. Development of Arteriosclerosis.The American Journal of Cardiology 31: 542-546, May 1973.

(90) MCMILLAN, G.C. Evidence for components other than carbon monoxide and nicotine as etiological factors in cardiovascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 363-367.

(91) MEDALIE, J.H., SNYDER, M., GROEN, J.J., NEUFELD, H.N., GOLDBOURT, U., RISS, E. Angina pectoris among 10,000 men. 5 year incidence and univariate analysis. American Journal of Medicine 55: 583-594, November 1973.

(92) MILLER, N.E., FORDE, O.H., THELLE, D.S., MJOS, O.D. The Tromso Heart Study. High-density lipoprotein and coronary heart disease: A prospective case-control study. Lancet 1 (8019): 965-968, May 7, 1977.

(93) MINICK, C.R., MURPHY, G.E. Experimental induction of atheroarteriosclerosis by the synergy of allergic injury to arteries and lipid-rich diet. II. Effect of a repeatedly injected foreign protein in rabbits fed a lipid-rich, cholesterol-poor diet. American Journal of Pathology 73(2): 265-300, November 1973.

(94) MJOS, O.D., THELLE, D.S., FORDE, O.H., VIK-MO, H. Family study of high density lipoprotein cholesterol and the relation to age and sex. Acta Medica Scandinavica 201(4): 323-329, 1977.

(95) MORRIS, J.N., CHAVE, S.P.W., ADAM, C., SIREY, C., EPSTEIN, L., SHEEHAN, D.J. Vigorous exercise in leisure-time and the incidence of coronary heart-disease. Lancet 1: 333-339, February 17, 1973.

(96) MOSS, A.J., DECAMILLA, J., DAVIS, H. Cardiac Death in the first 6 months after myocardial infarction: Potential for mortality reduction in the early posthospital period. American Journal of Cardiology 39(6): 816-820, May 26, 1977.

(97) MULCAHY, R., HICKEY, N., GRAHAM, I.M., MACAIRT, J. Factors affecting the 5-year survival rate of men following acute coronary heart disease. American Heart Journal 93(5): 556-559, May 1977.

(98) NAEYE, R.L., TRUONG, L.D. Effects of cigarette smoking on intramyocardial arteries and arterioles in man. American Journal of Clinical Pathology 68(4): 493-498, October 1977.

(99) NAKAYAMA, Y. Epidemiological research in Japan on smoking and cardiovascular diseases. In: Schettler, G., Goto, Y., Hata, Y., Klose, G. (Editors). Atherosclerosis IV. Proceedings of the Fourth International Symposium, Tokyo, 1976. Berlin, Springer-Verlag, 1977, pp. 149-153.

(100) OBERMAN, A., RAY, M., TURNER, M.E., BARNES, G., GROOMS, C. Sudden death in patients evaluated for ischemic heart disease. Circulation 51/52 (Supplement III): 170-172, December 1975.

(101) OMAE, T., TAKESHITA, M., HIROTA, Y. The Hisayama study and joint study on cerebrovascular diseases in Japan. In: Scheinberg, P. (Editor). Cerebrovascular Diseases. Proceedings of the Tenth Princeton Conference, New Jersey, 1976. New York, Raven Press, 1976, pp. 255-265.

(102) ORY, H.W. Association between oral contraceptives and myocardial infarction. A review. Journal of the American Medical Association 237(24): 2619-2622, June 13, 1977.

(103) PAUL, O. Discussion on Dr. Dawber's Paper (The interrelationship of tobacco smoke components to hyperlipidemia and other risk factors). In: Wynder, E.L., Hoffmann, D., Gori, G.B., (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 293-295.

(104) PEARSON, T.A., DILLMAN, J.M., SOLEZ, K., HEPTINSTALL, R.H. Clonal markers in the study of the origin and growth of human atherosclerotic lesions. Circulation Research 43(1): 10-18, July 1978.

(105) PEARSON, T.A., WANG, A., SOLEZ, K., HEPTINSTALL, R.H. Clonal characteristics of fibrous plaques and fatty streaks from human aortas. American Journal of Pathology 81(2): 379-387, November 1975.

(106) PETITTI, D.B., WINGERD, J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. Lancet 2: 234-236, July 29, 1978.

(107) THE POOLING PROJECT RESEARCH GROUP. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. Journal of Chronic Diseases 31(4): 201-306, April 1978.

(108) REEVES, T.J., OBERMAN, A., JONES, W.B., SHEFFIELD, L.T. Natural history of angina pectoris. American Journal of Cardiology 33: 423-430, March 1974.

(109) REICHENBACH, D.D., MOSS, N.S., MEYER, E. Pathology of the heart in sudden cardiac death. The American Journal of Cardiology 39(6): 865-872, May 26, 1977.

(*110*) REID, D.D., HAMILTON, P.J.S., MCCARTNEY, P., ROSE, G., JARRETT, R.J., KEEN, H. Smoking and other risk factors for coronary heart-disease in British civil servants. Lancet 2(7993): 979-984, November 6, 1976.

(*111*) RESEARCH COMMITTEE OF THE SCOTTISH SOCIETY OF PHYSICIANS. Ischaemic heart disease. A secondary prevention trial using clofibrate. Report by a Research Committee of the Scottish Society of Physicians. British Medical Journal 4: 775-784, December 25, 1971.

(*112*) RHOADS, G.G., BLACKWELDER, W.C., STEMMERMAN, G.N., HAYASHI, T., KAGAN, A. Coronary risk factors and autopsy findings in Japanese-American men. Laboratory Investigation 38(3): 304-311, 1978.

(*113*) ROBICSEK, F., DAUGHERTY, H.K., MULLEN, D.C. MASTERS, T.N., NARBAY, D., SANGER, P.W., COOK, J.W. The effect of continued cigarette smoking on the patency of synthetic vascular grafts in Leriche syndrome. Collected Works on Cardio-Pulmonary Disease 20: 62-70, December 1975.

(*114*) ROCK, W., OALMANN, M., STRONG, J. Community pathology of myocardial lesions in men 25 to 44 years of age. Laboratory Investigation 32(3): 433, March 1975. (Abstract)

(*115*) ROSE, G., REID, D.D., HAMILTON, P.J.S., MCCARTNEY, P., KEEN, H., JARRETT, R.J. Myocardial ischaemia, risk factors and death from coronary heart-disease. Lancet 1(8003): 105-109, January 15, 1977.

(*116*) ROSENMAN, R.H., BRAND, R.J., SHOLTZ, R.I., FRIEDMAN, M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. American Journal of Cardiology 37(5): 903-910, May 1976.

(*117*) ROSS, R., GLOMSET, J.A. The pathogenesis of atherosclerosis (Parts One and Two). New England Journal of Medicine 295(7): 369-377, August 12, 1976 and 295(8): 420-425, August 19, 1976.

(*118*) RUBERMAN, W., WEINBLATT, E., GOLDBERG, J.D., FRANK, C.W., SHAPIRO, S. Ventricular premature beats and mortality after myocardial infarction. The New England Journal of Medicine 297(14): 750-757, October 6, 1977.

(*119*) ST. CLAIR, R.W. Metabolism of the arterial wall and atherosclerosis. In: Paoletti, R., Gotto, A.M. Jr. (Editors). Atherosclerosis Reviews, Volume 1. New York, Raven Press, 1976, pp. 61-117.

(*120*) SCHIEVELBEIN, H. The evidence for nicotine as an etiological factor in cardiovascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No.(NIH) 76-1221, 1976, pp. 297-307.

(*121*) SELTZER, C.C. Effect of smoking on blood pressure. American Heart Journal 87(5): 558-564, May 1974.

(*122*) SHAPIRO, S., WEINBLATT, E., FRANK, C.W., SAGER, R.V. Incidence of coronary heart disease in a population insured for medical care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. American Journal of Public Health 59 (Supplement 6): 1-101, June 1969.

(*123*) SKINHOJ, E., OLESEN, J., PAULSON, O.B. Influence of smoking and nicotine on cerebral blood flow and metabolic rate of oxygen in man. Journal of Applied Physiology 35(6): 820-822, 1973.

(*124*) SLONE, D., SHAPIRO, S., ROSENBERG, L., KAUFMAN, D.W., HARTZ, S.C., ROSSI, A.C., STOLLEY, P.D., MIETTINEN, O.S. Relation of cigarette smoking to myocardial infarction in young women. New England Journal of Medicine 298(23): 1273-1276, June 8, 1978.

(125) SMALL, D.M. Cellular mechanisms for lipid deposition in atherosclerosis (Parts One and Two). The New England Journal of Medicine 297(16): 873-877, October 20, 1977 and 297(17): 924-929, October 27, 1977.

(126) SMITH, E.B., SMITH, R.H. Early changes in aortic intima. In: Paoletti, R., Gotto, A.M., Jr. (Editors). Atherosclerosis Reviews, Volume 1. New York, Raven Press, 1976, pp. 119-136.

(127) SPAIN, D.M., BRADESS, V.A. Sudden death from coronary heart disease: Survival time, frequency of thrombi, and cigarette smoking. Chest 58(2): 107-110, August 1970.

(128) SPAIN, D.M., SIEGEL, H., BRADESS, V.A. Women smokers and sudden death. The relationship of cigarette smoking to coronary disease. Journal of the American Medical Association 224(7): 1005-1007, May 14, 1973.

(129) STAMLER, J., RHOMBERG, P., SCHOENBERGER, J.A., SHEKELLE, R.B., DYER, A., SHEKELLE, S., STAMLER, R., WANNAMAKER, J. Multivariate analysis of the relationship of seven variables to blood pressure: Findings of the Chicago Heart Association Detection Project in Industry, 1967-1972. Journal of Chronic Diseases 28(10): 527-548, November 1975.

(130) STENDER, S., ASTRUP. P., KJELDSEN, K. The effect of carbon monoxide on cholesterol in the aortic wall of rabbits. Atherosclerosis 28(4): 357-367, December 1977.

(131) STRONG, J.P., OMAE, P. (CHAIRMEN). Workshop 3. Epidemiology of atherosclerosis and geographic differences in risk factors. In: Schettler, G., Goto, Y., Hata, Y., Klose, G. (Editors). Atherosclerosis IV. Proceedings of the Fourth International Symposium, Tokyo, 1976. Berlin, Springer-Verlag, 1977, pp. 92-120.

(132) STRONG, J.P., RICHARDS, M.L. Cigarette smoking and atherosclerosis in autopsied men. Atherosclerosis 23(3): 451-476, May/June 1976.

(133) STRONG, J.P., SOLBERG, L.A., RESTREPO, C. Atherosclerosis in persons with coronary heart disease. Laboratory Investigation 18(5): 527-537, May 1968.

(134) TALBOTT, E., KULLER, L.H., DETRE, K., PERPER, J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. The American Journal of Cardiology 39(6): 858-864, May 26, 1977.

(135) THOMAS, W.A., FLORENTIN, R.A., REINER, J.M., LEE, W.M., LEE, K.T. Alterations in population dynamics of arterial smooth muscle cells during atherogenesis. IV. Evidence for a polyclonal origin of hypercholesterolemic diet-induced atherosclerotic lesions in young swine. Experimental and Molecular Pathology 24: 244-260, 1976.

(136) TOPPING, D.L. Metabolic effects of carbon monoxide in relation to atherogenesis. Atherosclerosis 26(2): 129-137, February 1977.

(137) TRUMP, B.F., MERGNER, W.J., KAHNG, M.W., SALADINO, A.J. Studies on the subcellular pathophysiology of ischemia. Circulation 53(3) Supplement 1: I-17—I-26, March 1976.

(138) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition: 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.

(139) VESSELINOVITCH, D., WISSLER, R.W., FISHER-DZOGA, K., HUGHES, R., DUBIEN, L. Regression of atherosclerosis in rabbits. Part 1. Treatment with low-fat diet, hyperoxia, and hypolipidemic agents. Atherosclerosis 19: 259-275, 1974.

(140) VESSEY, M.P., DOLL, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. British Medical Journal 2(5658): 651-657, June 14, 1969.

(141) VETERANS' ADMINISTRATION COOPERATIVE UROLOGICAL RESEARCH GROUP. Treatment and survival of patients with cancer of the prostate. Surgery, Gynecology and Obstetrics 124(5): 1011-1017, May 1967.

(142) VISMARA, L.A., VERA, Z., FOERSTER, J.M., AMSTERDAM, E.A., MASON, D.T. Identification of sudden death risk factors in acute and chronic coronary artery disease. American Journal of Cardiology 39(6): 821-828, May 26, 1977.

(143) VON AHN, B. Tobacco smoking, the electrocardiogram, and angina pectoris. Annals of the New York Academy of Sciences 90(1): 190-198, September, 1960.

(144) WAGNER, W.D., ST. CLAIR, R.W., CLARKSON, T.B. Angiochemical and tissue cholesterol changes of Macaca fascicularis fed an atherogenic diet for 3 years. Experimental and Molecular Pathology 28(2): 140-153, April 1978.

(145) WALD, N.J. Carbon monoxide as an aetiological agent in arterial disease—Some human evidence. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No.(NIH) 76-1221, 1976, pp. 349-361.

(146) WALD, N., HOWARD, S., SMITH, P.G., KJELDSEN, K. Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. British Medical Journal 1: 761-765, March 31, 1973.

(147) WANSTRUP, J., KJELDSEN, K., ASTRUP, P. Acceleration of spontaneous intimal-subintimal changes in rabbit aorta by a prolonged, moderate carbon monoxide exposure. Acta Pathologica et Microbiologica Scandinavica 75(3): 353-362, 1969.

(148) WEBSTER, W.S., CLARKSON, T.B., LOFLAND, H.B. Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. Experimental and Molecular Pathology 13: 36-50, 1970.

(149) WEINBLATT, E., FRANK, C.W., SHAPIRO, S., SAGER, R.V. Prognostic factors in angina pectoris—A prospective study. Journal of Chronic Diseases 21: 231-245, July 1968.

(150) WEINBLATT, E., SHAPIRO, S., FRANK, C.W., SAGER, R.V. Prognosis of men after first myocardial infarction: Mortality and first recurrence in relation to selected parameters. American Journal of Public Health 58(8): 1329-1347, August 1968.

(151) WEINROTH, L.A., HERZSTEIN, J. Relation of tobacco smoking to arteriosclerosis obliterans in diabetes mellitus. Journal of the American Medical Association 131(3): 205-209, May 1946.

(152) WEISS, N.S. Cigarette smoking and arteriosclerosis obliterans: An epidemiologic approach. American Journal of Epidemiology 95(1): 17-25, 1972.

(153) WESSLER, S., MING, S.-C., GUREWICH, V., FREIMAN, D.G. A critical evaluation of thromboangiitis obliterans. The case against Buerger's disease. New England Journal of Medicine 262(23): 1150-1160, June 9, 1960.

(154) WILHELMSEN, L. Recent studies on smoking and CVD epidemiology: Scandinavia and some other Western European countries. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 171-177.

(155) WISSLER, R.W., VESSELINOVITCH, D., GETZ, G.S. Abnormalities of the arterial wall and its metabolism in atherogenesis. Progress in Cardiovascular Diseases 18(5): 341-369, March/April 1976.

(*156*) WOLINSKY, H. A new look at atherosclerosis. Cardiovascular Medicine: 41-54, September 1976.

(*157*) WRAY, R., DEPALMA, R.G., HUBAY, C.H. Late occlusion of aortofemoral bypass grafts: Influence of cigarette smoking. Surgery 70(6): 969-973, December 1971.

5. CANCER.

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Introduction

Cancer has been the second leading cause of death in the United States since 1937. There were an estimated 390,000 deaths from cancer in 1978 (*4*). The association between tobacco smoking and the development of lung cancer was first suggested in the 1920's and early 1930's (*159, 206*). In the early 1950's, more than a dozen retrospective studies were published which first generally alerted the medical and scientific community to the health hazards associated with cigarette smoking. The public was informed of the results of these studies, and as a consequence there was a significant, but brief, dip in the per capita consumption of cigarettes. The next decade brought an intensive worldwide investigation into the various diseases associated with cigarette smoking. The first official statement on smoking and health by the U.S. Government was contained in the Report of the Advisory Committee to the Surgeon General of the U.S. Public Health Service, which was released 15 years ago. The evidence available at that time warranted the conclusion that "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction. The risk of developing lung cancer increases with the duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking" (*217*). In the 15 years since the 1964 Surgeon General's Report was published, these conclusions have been confirmed by numerous investigations in many countries. Cigarette smoking has also been implicated as a significant cause of cancer of the larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas. As data concerning the relationship of smoking to the development of cancer at various sites became available, they were summarized and published in the annual issues of the Health Consequences of Smoking (*209, 210, 211, 212, 212a, 213, 214, 215, 216*).

This chapter reviews the epidemiological and experimental data for each of the cancer sites associated with cigarette smoking. Discussions of the specific cancers are presented sequentially, based on the strength of the association with cigarette smoking: cancer of the lung, larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas.

Lung Cancer

This year more people in the United States will die from lung cancer than from any other malignant disease. In 1950, when the nation first became generally aware that there was an association between smoking and lung cancer, there were 18,313 lung cancer deaths. In 1964, there were 45,838 deaths from lung cancer. The National Center for Health Statistics reported that in 1976 there were 86,267 deaths from lung cancer in the United States (*150*). It is estimated that there

were 92,400 deaths from lung cancer in 1978 (*4*). For every preventable death from highway accidents, there were approximately two deaths from lung cancer which could have been prevented if the individual had not smoked cigarettes. There are about 280 deaths from lung cancer each day in the United States.

This epidemic increase in lung cancer is reflected in rapidly changing mortality rates in both men and women. The mortality rate for men in 1950 was 19.9/100,000/year. This rose to 41.4 in 1964, and to 63.0 in 1976. The comparable figures for white females were 4.7 in 1950 and 8.0 in 1965, and climbing rapidly to 19.5 in 1976 (Table 7).

According to results from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the mortality rates for black males and females are higher than for whites. In 1976, the lung cancer mortality rate for black males was 93.0, for black females it was 17.4 (*154*). Due to recent increases in death rates among females, the ratio of male to female mortality for lung cancer has dropped from 7:1 to less than 4:1.

While recent years have seen dramatic increases in relative survival rates for acute leukemias in children, Hodgkin's disease, multiple myeloma, and certain other malignancies, there has been little increase in survival rates for lung cancer. The 5-year survival rate for lung cancer in all states is 8 percent for males and 12 percent for females (*151*). The difference in survival rates between males and females can be explained by sex-specific differences in histology or stage of the disease.

Trends in Lung Cancer Mortality

In the United States there has been in the past few years a significant reduction in the percent of males and females who smoke cigarettes. As yet, there has not been a decline in the age-adjusted *total* mortality rates for lung cancer. When the lung cancer mortality rates by age are examined from 1950 through 1975, there is a continuining increase in older age groups for both males and females. This is probably due to the elevated risk experienced by older persons who use nonfiltered, high tar and nicotine cigarettes and who have done so for the majority of their lives. However, for female cohorts born in 1950–54 and male cohorts born in 1935–39 and 1940–44, the *age-specific* lung cancer mortality rates are below those of previous cohorts. This probably results from the reductions in cigarette consumption which have occurred in these groups.

There has been a change in the epidemic of lung cancer in England and Wales, as summarized by the International Union Against Cancer (UICC) workshop on the biology of cancer (*243*):

> In England and Wales, lung cancer mortality stopped increasing in men under the age of 50 years during the 1950's and more recently has fallen in men under the age of 60 years. The death rate from

lung cancer in women ages 40 years and over has continued to rise, but has leveled, or fallen in younger women since the 1960's...The fall in lung cancer mortality among men under the age of 60 years is likely to be due to their reduced consumption since the end of the Second World War, and to the reduction in the tar yield of cigarettes since 1955; particularly with the change to filter cigarettes.

Although lung cancer mortality in women over 40 years has continued to increase along with their cigarette consumption, it is unlikely that the incidence of lung cancer will ever reach the high levels recorded in men, because the increasing cigarette consumption by women has been, and is continuing to be compensated for by a decrease in tar yield.

Epidemiological Studies

The first comprehensive reviews of the effects of smoking on lung cancer were published in 1962 and 1964 by the Royal College of Surgeons of London and the Surgeon General of the United States, respectively (*171, 217*). They included data from studies on epidemiology, profiles of the consumption of tobacco, the composition and carcinogenicity of components of tobacco smoke, the effects of smoke on experimental animals, and the pathological changes observed in humans and animals. The conclusions reached in these assessments and by all of the periodic reviews that have followed at regular intervals (*209, 210, 211, 212, 212a, 213, 214, 215, 216*) are impressively uniform and consistent. So much so that it has been observed that the results of any one of the major studies might be taken to represent all of them.

There have been at least nine major prospective epidemiological studies which have examined the relationship between cigarette smoking and mortality from various causes. The results of eight of these studies are related to cigarette smoking and lung cancer and are presented in Table 1. The lowest mortality ratios are experienced by female smokers. The mortality ratios for male cigarette smokers are as low as 3.85 for Japanese males and as high as 14.0 for British doctors and Canadian veterans. Combining the data from the largest studies allows the conclusion that cigarette smokers on the average are 10 times as likely to develop lung cancer as nonsmokers. The mortality ratios are much higher for heavy cigarette smokers. This will be detailed in the section on dose-response relationships.

In the past 30 years, more than 50 retrospective studies on the relationship between cigarette smoking and lung cancer have been published. These data are too extensive for convenient summarization; they have been reviewed in recent issues of the Health Consequences of Smoking (*212, 212a, 213, 214, 215*).

TABLE 1.—Lung cancer mortality ratios—prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British doctors(*47a*)	34,000 males	441	1.00	14.0
Swedish study(*32*)	27,000 males	55	1.00	8.2
	28,000 females	8	1.00	4.5
Japanese study(*77a,78*)	122,000 males	590	1.00	3.76
	143,000 females	148	1.00	2.08
A.C.S. 25-State Study(*65*)	440,000 males	1,159	1.00	9.20
	562,000 females	183	1.00	2.20
U.S. veterans(*90*)	239,000 males	1,256	1.00	12.14
Canadian veterans(*20*)	78,000 males	331	1.00	14.2
A.C.S. 9-State Study(*68*)	188,000 males	448	1.00	10.73
California males in 9 occupations(*228*)	68,000 males	368	1.00	7.61

Dose-Response Relationships

An important factor in the causal relationship between smoking and lung cancer is the demonstration of dose-response relationships. In most epidemiological studies, dosage has been measured by the number of cigarettes smoked per day at the time of entry into the study. Other dose variables which have been examined include the maximum number of cigarettes smoked per day, the age an individual began smoking, the degree of inhalation of tobacco smoke, the total number of years an individual has smoked, the total lifetime number of cigarettes smoked, tar and nicotine levels of the brand of cigarettes used, the number of puffs per cigarette, the length of the unburned portion of the cigarette, and combinations of these variables into "dosage" scores. All of these variables have been shown in one study or another to contribute to the risk of developing lung cancer. Only a few representative samples of dosage variables as related to lung cancer mortality are examined in this section.

Number of Cigarettes Smoked Per Day

The risk of developing lung cancer increases with the number of cigarettes smoked per day. In the U.S. and British populations, the risk of developing lung cancer for individuals smoking more than two packs

TABLE 2.—Lung cancer mortality ratios for males, by current number of cigarettes smoked per day, from selected prospective studies

	Cigarettes smoked per day	Mortality ratio
A.C.S. 25-state study(*65*)	Nonsmoker	1.00
	1-9	4.62
	10-19	8.62
	20-39	14.69
	40+	18.77
British doctors(*47a*)	Nonsmoker	1.00
	1-14	7.80
	15-24	12.70
	25+	25.10
Swedish males(*32*)	Nonsmoker	1.00
	1-7	2.30
	8-15	8.80
	16+	13.90
Japanese males(*78*)	Nonsmoker	1.00
	1-9	1.90
	10-14	3.52
	15-24	4.11
	25-49	4.57
	50+	5.78

a day is approximately 20 times that of nonsmokers (*47a*, *65*, *68*, *80*, *228*). Data for Swedish males are of the same magnitude (*32*). Japanese males who smoke 50 or more cigarettes a day experience a risk which is 5.8 times greater than for nonsmokers. Hirayama noted that the slope of the dose-response curve for lung cancer was less in Japan than in the United States and that this was probably due to the lower percentage of regular deep inhalers, a lower level of environmental promoting conditions, and also a higher percentage of adenocarcinoma in Japan than in the United States (*78*). Table 2 presents lung cancer mortality ratios from selected prospective studies for males by the current number of cigarettes smoked per day.

Age at which Smoking Began

Lung cancer mortality ratios exhibit an inverse relationship with the age of initiation of the smoking habit. Lung cancer mortality ratios for males by age at which they began smoking are presented in Table 3. Most cigarette smokers began the habit while in high school and are at the greatest risk of developing lung cancer. Those who began smoking

TABLE 3.—Lung cancer mortality ratios for males, by age began smoking, from selected prospective studies

	Age began smoking in years	Mortality ratio
A.C.S. 25-State Study(*65*)	Nonsmoker	1.00
	25+	4.08
	20–24	10.08
	15–19	19.69
	under 15	16.77
Japanese study(*78*)	Nonsmoker	1.00
	25+	2.87
	20–24	3.85
	under 20	4.44
U.S. veterans(*90*)	Nonsmoker	1.00
	25+	5.20
	20–24	9.50
	15–19	14.40
	under 15	18.70

after the age of 25 have mortality ratios which are only 4 to 5 times greater than those of nonsmokers.

Inhalation of Cigarette Smoke

Inhalation of tobacco smoke is an important dosage variable. Inhalation of smoke well into the lungs is the major mechanism whereby lung tissue is exposed to the carcinogens which ultimately produce lung cancer. Techniques for quantitating the degree of tobacco smoke inhalation have been developed using carboxyhemoglobin levels or end expiratory carbon monoxide levels as an index of smoke inhalation. These objective methods of measuring inhalation have not been applied to studies of lung cancer mortality. In most investigations, the smoker was asked to report subjectively on his own inhalation practices. This is subject to considerable variation but is not as inaccurate as might be presumed. Available data show a strong dose-response relationship between self-reported inhalation of cigarette smoke and lung cancer mortality. Representative figures from selected prospective studies are presented in Table 4. These data suggest that cigarette smokers may underestimate the degree to which they inhale cigarette smoke. Those who report that they do not inhale cigarette smoke experience lung cancer mortality ratios which are 4 to 8 times greater than for nonsmokers. Deep inhalation results in mortality ratios which are as high as 17 times greater than for nonsmokers.

TABLE 4.—Lung cancer mortality ratios for males, by degree of inhalation, from selected prospective studies

	Degree of inhalation	Mortality ratio
A.C.S. 25-State Study(*65*)	Nonsmoker	1.00
	None	8.00
	Slight	8.92
	Moderate	13.08
	Deep	17.00
Swedish males(*32*)	Nonsmoker	1.00
	None	3.70
	Light inhalation	7.80
	Deep inhalation	9.20

Tar and Nicotine Content of Cigarettes

The major constituents of cigarette smoke that cause lung cancer are among the more than 2,000 different compounds found in cigarette smoke. Cigarette filters, first introduced during the mid-1950's, have the effect of trapping tar. Data presented by Maxwell (*136*) show that, in 1976, more than 600 billion cigarettes were smoked and that 88.4 percent of these were filtered. It has been known that the risk of developing lung cancer increased with the tar and nicotine content of cigarettes. Until recently, however, there has not been a great deal of evidence that individuals who switch to lower tar and nicotine cigarettes experience less lung cancer mortality (*27*). It has been argued that, if the tar and nicotine content of tobacco were reduced, individuals might increase the number of cigarettes smoked per day and thereby abolish any benefit that might be gained. Alternatively, those who switch to low tar and nicotine cigarettes might inhale the smoke more deeply than smokers of high tar and nicotine cigarettes, and thereby exposure to tar and nicotine might not be reduced. In a large prospective study by Hammond, et al. (*67*), these tar and nicotine relationships were examined with respect to lung cancer. The 897,825 men and women in 23 States were divided into 3 tar and nicotine categories. The high tar and nicotine (T/N) category was defined as 2.0 to 2.7 mg of nicotine and 25.8 to 35.7 mg of tar. The medium T/N category was defined as 1.2 to 1.9 mg of nicotine and 17.6 to 25.7 mg of tar. The low T/N category included cigarettes containing less than 1.2 mg of nicotine and less than 17.6 mg of tar. A matched-group analysis, similar to age standardization, was utilized. Individuals in each group were alike with respect to age, race, number of cigarettes smoked per day, age when they began to smoke cigarettes, place of residence,

TABLE 5.—Age-adjusted lung cancer mortality ratios* for males and females, by tar and nicotine in cigarettes smoked

	Males	Females
High T/N	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

*The mortality ratio for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.
SOURCE: Hammond, E.C. (*67*)

occupational exposure to dust fumes, chemicals, etc., education, prior history of lung cancer, and prior history of heart disease. Results of this analysis are presented in Table 5. The mortality ratio for the category with the highest risk was made 1.0 so that the relative reduction in risk with the use of lower T/N cigarettes could be visualized. For males smoking the same number of cigarettes per day, there appears to be a 20 percent reduction in risk of developing lung cancer with the use of low T/N cigarettes. For females, there was a 40 percent reduction in the risk of developing lung cancer with the use of low T/N cigarettes, keeping the number of cigarettes smoked per day constant. The amount of tar and nicotine taken into the body per day depends on the number of cigarettes smoked, as well as on the tar and nicotine content of each cigarette. Hammond conducted a second matched-group analysis comparing subjects who smoked 1 to 19 high T/N cigarettes per day and those who smoked 20 to 39 low T/N cigarettes per day. These results are presented in Table 6. The number of cigarettes smoked per day was a relatively more important variable than the tar and nicotine content of cigarettes. The mortality ratio was 1.6 for males and 2.1 for females who smoked 20 to 39 low T/N cigarettes a day, compared to individuals who smoked only 1 to 19 high T/N cigarettes per day.

Wynder and Stellman (*253*) conducted a large retrospective study of 1,034 white males and females with histologically proved cancer of the lung and larynx. Relative risks were consistently lower among long-term smokers of filter cigarettes, compared to smokers of nonfilter cigarettes. These groups were standardized for number of cigarettes smoked, duration of smoking, inhalation, and cigarette butt length. These dose-response relationships are presented in Figures 1 and 2.

Lung Cancer in Women

Trends in Cigarette Consumption Among Females

In 1964, the Advisory Committee to the Surgeon General concluded that cigarette smoking was causally related to cancer in men, and that

TABLE 6.—Age-adjusted lung cancer mortality ratios* for males and females, comparing those who smoked a few high T/N cigarettes with those who smoked many low T/N cigarettes

	1-19 high T/N cigarettes/day	20-39 low T/N cigarettes/day
Males	1.00	1.6
Females	1.00	2.1

*The mortality ratio for the category with lowest risk was made 1.00 so the increase in risk with smoking more cigarettes/day could be illustrated.
SOURCE: Hammond, E. C. (*67*)

"the data for women though less extensive, point in the same direction" (*217*). Today, 15 years later, the lung cancer epidemic among women is well established. Several investigators had predicted sharp increases in lung cancer mortality among women. In 1966, Linden (*118*) examined lung cancer mortality in California women and predicted: "One can expect to see further increase in the number of lung cancer deaths and the death rates as the increasing proportions of women who smoke cigarettes reach the age when lung cancer is most likely to occur."

In 1964, lung cancer was the fifth leading cause of death from cancer in women. It became the fourth leading cause in 1967 and moved to the third leading cause of death from cancer in 1969, passing cancer of the uterus. Projections for 1979 indicate that lung cancer is approaching cancer of the colon and rectum as the second leading cause of death from cancer in women. If present trends are not reversed, during the next decade lung cancer will become the leading cause of death from cancer in women, exceeding deaths from cancer of the breast.

In 1955, there were only 4,100 deaths from lung cancer in women. In 1976, the National Center for Health Statistics reported there were 20,455 deaths from lung cancer among females in the United States (*150*); the American Cancer Society estimated that in 1978 this increased to 21,900 deaths (*4*).

These increases are not due to increases in the population. Death rates for lung cancer have been steadily rising in women, especially in the past decade. The lung cancer mortality rate for white females in 1950 was 4.7 per 100,000; by 1976 this had risen to 19.5 per 100,000. This is more than a fourfold increase (Table 7).

The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute recently reported that the lung cancer death rate for black females exceeded that of white females (16.8 blacks, 15.0 whites)(*154*). Data from this survey are collected from 10 geographic areas in the United States and therefore do not represent

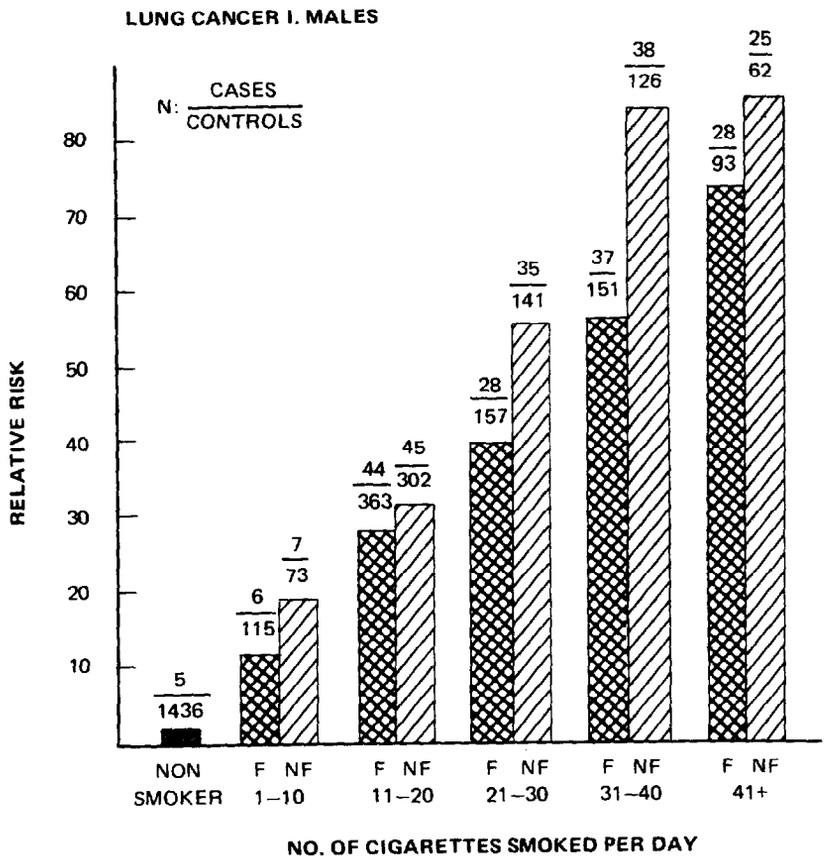


FIGURE 1.—Relative risk of lung cancer for males, by number of cigarettes smoked per day and long-term use of filter (F) or nonfilter (NF) cigarettes
SOURCE: Wynder, E.L. (*253*)

national trends per se. The lung cancer mortality rate (15.0 per 100,000) among black females in the general U.S. population is equal to that of whites.

Increases in lung cancer mortality among females cannot be explained by exposure to occupational carcinogens. Increases in cigarette consumption are responsible for these trends.

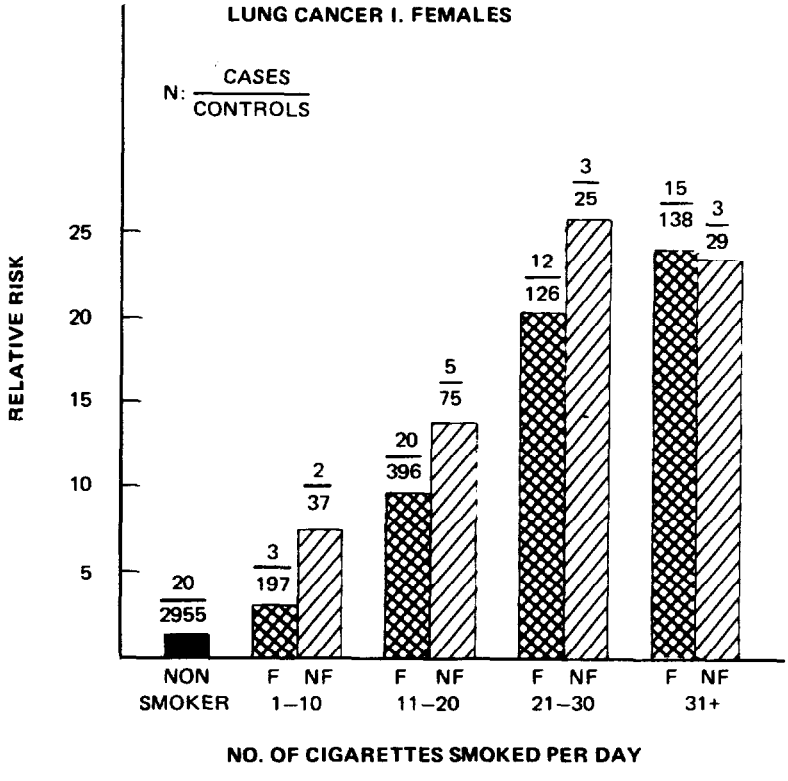


FIGURE 2.—Relative risk of lung cancer for females, by number of cigarettes smoked per day and long-term use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder, E.L. (*253*)

The epidemic of lung cancer in women has lagged behind that in men, primarily because of differences in patterns of cigarette smoking. There are fewer women smoking than men, but the gap is narrowing. Among teenagers in several age categories, girls are smoking more than boys (*155*). Table 8 shows the percentage of the U.S. adult population who are currently smoking cigarettes for selected years. In 1975, approximately 29 percent of adult females were smoking, whereas 39 percent of adult males were smoking (*155*). It should also be noted that, over the past decade, there has been a 2.6 percent

TABLE 7.—Mortality rates for lung cancer and cancer of the respiratory tract for white females in the United States per 100,000 population for selected years, 1940 to 1976

Year	Lung and Bronchus	Respiratory System
1940	—	3.6
1945	—	4.6
1950	4.7	5.4
1955	5.1	5.7
1960	5.9	6.4
1965	8.0	8.6
1970	12.3	13.1
1975	17.8	18.8
1976	19.5	20.5

SOURCE: National Center for Health Statistics (*150*)

TABLE 8.—Percent of adult population who were current cigarette smokers in selected years in the United States

Year	Percent smokers	
	Females	Males
1964	31.5	52.9
1966	33.7	51.9
1970	30.5	42.2
1975	28.9	39.3
Percent reduction since 1964	2.6	13.6

SOURCE: National Clearinghouse for Smoking and Health (*155*)

reduction in the number of adult females who smoke cigarettes, whereas there has been a 13.6 percent reduction in the number of adult males smoking. Trends in the percentage of teenagers who are regular cigarette smokers are presented in Table 9. Cigarette smoking among girls has increased steadily, so that at the present time equal numbers of boys and girls are smoking cigarettes and many of the differences which existed in the past between male and female smokers have disappeared.

Epidemiological Studies

Three of the large prospective epidemiological studies contain information on lung cancer in women. Data from these studies are summarized in Table 10. A number of retrospective studies have examined the

TABLE 9.—Percent of teenagers who were current cigarette smokers in selected years in the United States

Year	Percent smokers Ages 12–18	
	Girls	Boys
1968	8.4	14.7
1970	11.9	18.5
1972	13.3	15.7
1974	15.3	15.8

SOURCE: National Clearinghouse for Smoking and Health (*155a*)

TABLE 10.—Lung cancer mortality ratios for women—prospective studies

Study	Population	Number of deaths	Mortality ratio	
			Female nonsmokers	Female smokers
A.C.S. 25-State Study(*65*)	562,671 Females	183	1.00	2.20
Swedish study(*32*)	27,732 Females	8	1.00	4.50
Japanese study(*78*)	142,857 Females	148	1.00	2.03

relationship of lung cancer to smoking habits in women (*46, 63, 64, 80a, 122, 128, 139, 160, 164, 167, 198, 222, 227, 232, 236, 242, 247*).

Dose-Response Relationships

Dose-response relationships between lung cancer and cigarette smoking have been described for females by the number of cigarettes smoked per day, the degree of inhalation, and the duration of smoking. These relationships from selected studies are presented in Tables 11 through 14. The mortality ratios are as high as 10.0 for females who have smoked more than 20 cigarettes per day and for females who have smoked for more than 30 years.

Patterns of Cigarette Use

Although death rates from lung cancer are increasing at an accelerated rate in females, it may be that the peak will be somewhat less than in males; this may be due to substantial differences in the way males

TABLE 11.—Lung cancer mortality ratios for females, by number of cigarettes smoked per day: A.C.S. 25-State Study

Cigarettes smoked per day	Mortality ratios
Nonsmoker	1.00
1-19	1.06
20+	4.76

SOURCE: Hammond, E.C. (*65*)

TABLE 12.—Lung cancer mortality ratios for females, by number of cigarettes smoked per day: Haenszel and Taeuber

Cigarettes smoked per day	Mortality ratios
Nonsmoker	1.00
Occasional	1.33
1-19	2.49
20+	10.80

SOURCE: Haenszel W. (*64*)

TABLE 13.—Lung cancer mortality ratios for females, by duration of smoking: Swedish Study

Duration of smoking in years	Mortality ratios
Nonsmokers	1.0
1-29 years	1.6
30+ years	9.6

SOURCE: Cederlof, R. (*32*)

TABLE 14.—Lung cancer mortality ratios for females, by degree of inhalation: A.C.S. 25-State Study

Degree of inhalation	Mortality ratios
Nonsmokers	1.00
None to slight	1.78
Moderate to deep	3.70

SOURCE: Hammond, E.C. (*65*)

and females smoke cigarettes. A recent survey (*155*) of cigarette smoking behavior shows that women do not smoke as far down on the cigarette where proportionally more nicotine and tar are inhaled. More than 91 percent of females use filter cigarettes, compared with 80 percent of males. Females report that they do not inhale cigarette smoke as deeply into their lungs as males do. Women also smoke fewer cigarettes per day and select brands of cigarettes with lower tar and nicotine yields, compared to men. In 1975, 76.7 percent of current female smokers smoked a pack or less per day, whereas this was true for only 63.6 percent of males (*155*). In the past, women began smoking later than men, but at the present time this is no longer true. The available evidence suggests that women who smoke cigarettes in the same amount and with equal depth of inhalation as men are likely to experience death rates similar to those found in men.

Twins

The best way to control genetic factors as a potentially complicating variable in studies of lung cancer and cigarette smoking is to conduct the investigation in a population of twins who are discordant as to smoking habits (one smokes, the other does not). Cederlof, et al. (*33*) published new data on smoking and lung cancer from the Swedish Twin Registries in 1977. Although the number of deaths from lung cancer among the monozygotic twins is quite low, the trend is clear. The authors state, "The well-documented evidence of a causal association between smoking and lung cancer found in other studies has been further supported."

Lung Cancer and the Use of Other Forms of Tobacco

Pipe and cigar smokers in the United States have experienced lung cancer mortality rates that are somewhat higher than those of nonsmokers but substantially lower than those of cigarette smokers (*1*). Most pipe and cigar smokers report that they do not inhale the smoke, and as a consequence the total exposure is relatively low. There is little evidence that lung cancer is associated with the use of chewing tobacco or snuff. These relationships are explored in detail in the Chapter on Other Forms of Tobacco Use (specifically in Tables 15, 16, 17 and 22 of that chapter).

Histology of Lung Cancer

There are several different histologic types of lung malignancies in humans. These include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, bronchiolo-alveolar, and mixed and undifferentiated carcinomas of the lung. The predominent type of carcinoma in males is squamous cell carcinoma, whereas the most common lung cancer in females is adenocarcinoma. Over the past

15 years there has been little change in the incidence of large-cell, bronchiolo-alveolar, and mixed and undifferentiated carcinomas. There has been an increase in adenocarcinoma and a decrease in squamous cell carcinomas.

In 1962, Kreyberg (*111a*) categorized epidermoid, small-cell, and large-cell carcinoma of the lung as Group I and adenocarcinoma and bronchiolo-alveolar carcinoma as Group II. He noted that the risk for smokers was substantially greater for Group I than for Group II tumors. This view has been supported by some investigators (*40, 47, 221*). Other investigators have disputed this classification (*9, 14, 15, 100, 230, 254*).

Weiss, et al. (*230*) followed the experience of 6,136 men over a 10-year period. They found that well-differentiated squamous cell carcinoma, small-cell carcinoma, and adenocarcinoma displayed a dose-response relationship to smoking, but poor-differentiated squamous cell carcinoma did not.

More recentiy, Auerbach, et al. (*10*) examined histologic types of lung cancer associated with smoking habits from autopsy data on 662 men who had had lung cancer. In this study all cell types seemed to be related to smoking to about the same degree.

Most recently, Vincent, et al. (*221*) reviewed the histopathology of lung cancer in patients seen over a 13-year period at the Roswell Park Memorial Institute. Their data indicated that adenocarcinoma is becoming progressively more prevalent, compared to other forms of lung cancer. They were unable to disassociate smoking as a causative factor in any of the presently defined pathological categories of lung cancer.

Cessation of Smoking

There is a decrease in the risk of developing lung cancer after cessation of smoking. This decrease in risk occurs over a period of several years. After 10 to 15 years, the risk of dying of lung cancer for ex-smokers has decreased to point where it is only slightly above the risk for nonsmokers. All of the major studies show this reduction in risk. The most recent data from the British Doctor's Study are presented here for illustration (Table 15). The mortality ratios for ex-smokers were higher in the first year after quitting than they were for continuing smokers. The explanation for this is that both healthy and sick individuals quit smoking. Higher mortality is experienced by those who quit because of illness. Lower mortality is experienced by those who quit while experiencing apparently good health. In the U.S. Veterans Study, a differentiation is made between ex-smokers who stopped smoking on the recommendation of a doctor and those who quit for other reasons. About 10 percent of the smokers quit because of doctors' orders and were presumably ill. This group had much higher death rates from lung cancer than those who stopped for other reasons.

TABLE 15.—Lung cancer mortality ratios in ex-cigarette smokers, by number of years stopped smoking

Years stopped smoking	Mortality ratio
Still Smoking	15.8
1–4	16.0
5–9	5.9
10–14	5.3
15+	2.0
Nonsmokers	1.0

SOURCE: Doll, R. (*47a*)

The magnitude of the residual risk which ex-smokers experience is determined by the cumulative exposure to cigarette smoke which the individual experienced before he quit smoking. The risk at any point in time would be determined by the maximum amount the individual smoked, the years since stopping smoking, the age when smoking began, degree of inhalation, and reasons for quitting smoking. The lung cancer mortality experience of ex-smokers is graphically presented in Figure 3. The risk of developing lung cancer increases with age, for both smokers and nonsmokers. The incidence in cigarette smokers is much higher than in nonsmokers. It can be seen that the lung cancer mortality of ex-smokers is initially similar to that of smokers, but, with the passage of time, the mortality risk moves progressively closer to that of nonsmokers. It is interesting to note that, except for the first 2 years after stopping smoking, there is a continued increase in the risk of developing lung cancer among ex-smokers, although it is less than that of those who continue to smoke. The slope of this line is less than that for nonsmokers, and so there is a convergence of these two curves.

Lung Cancer and Air Pollution

A number of studies have been conducted in which the relative influence of cigarette smoking, urban residence, and air pollution in the etiology of lung cancer is examined. Eight of the earlier studies were reviewed in the 1971 Report of the Surgeon General (*212*). More recent publications include: "Epidemiological review of lung cancer in man" by Higginson and Jensen (*75*) and a report of a task group, "Air Pollution and Cancer," edited by Cederlof, et al. (*31*). There have also been studies by Doll (*43*), Weiss (*229*), Carnow (*30*), and Kotin and Falk (*109*).

Lung cancer is consistently more common in urban than in rural areas. There is only a small urban-rural lung cancer gradient for nonsmokers. There is a much larger urban-rural gradient for smokers. Cigarette consumption is generally greater in urban areas, but it is

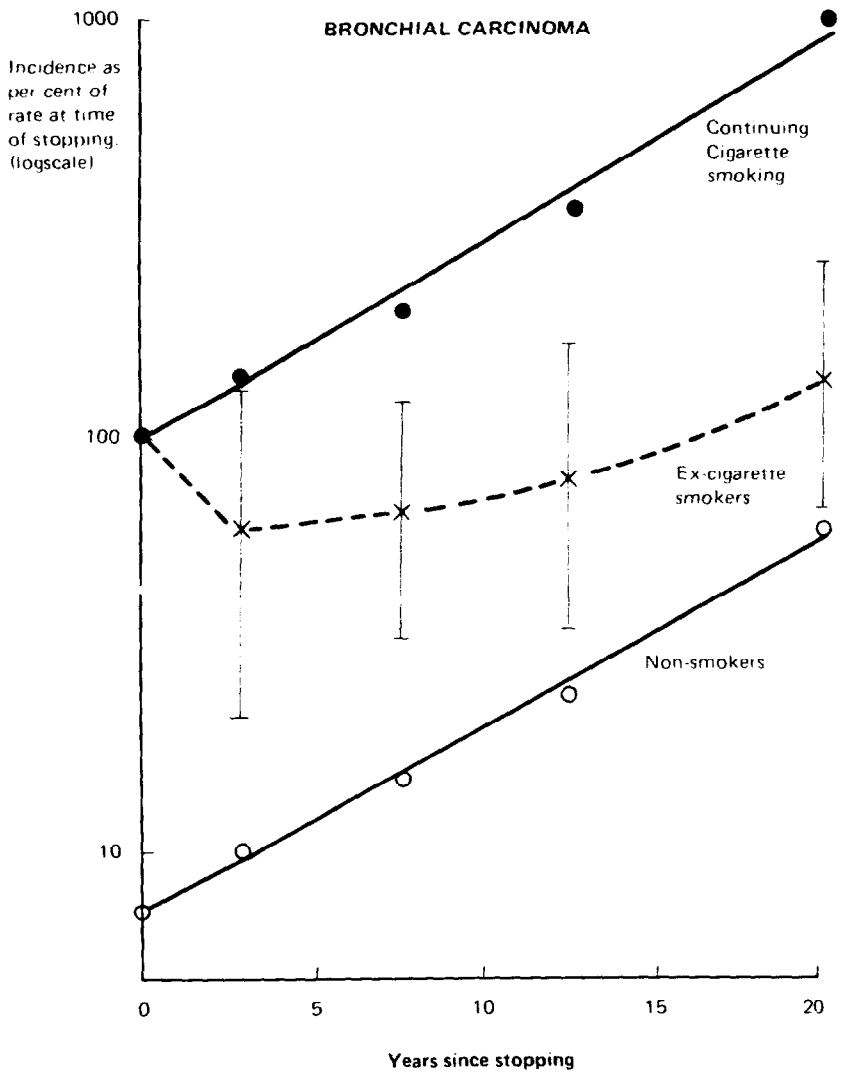


FIGURE 3.—Lung cancer mortality in continuing cigarette smokers and nonsmokers as a percentage of the rate among ex-cigarette smokers at the time they stopped smoking
SOURCE: UICC Technical Reports (*243*)

difficult to estimate how much of the excess urban mortality can be

accounted for by cigarette smoking alone. It is possible that there is an interaction between the carcinogens in cigarette smoke and other compounds in the ambient atmosphere.

Epidemiologic investigations thus far indicate that the most important cause of lung cancer is cigarette smoking and that urban factors such as air pollution have very little independent effect on the development of lung cancer. In the absence of cigarette smoking, the combined effects of all atmospheric agents do not increase the death rates for lung cancer more than a very few cases per 100,000 persons per year.

Lung Cancer and Occupational Factors

There are several occupations (described in Chapter 7) which are associated with the development of lung cancer and cancer at other sites (*84*). Estimates of the fraction of cancer deaths in the United States that can be attributed to occupational exposure have been made by several investigators. These estimates have been as low as 1 to 5 percent (*45, 73, 74, 153, 241*). Cole (*37*) has placed these estimates as high as 10 to 15 percent.

There are difficulties in estimating the proportion of cancers attributable to certain occupational exposures, tobacco, alcohol, or diet. Most of these estimates are based on the assumption that specific cancers are caused by specific agents. It is more likely that cancer is a disease of interactions. The precipitating cause and subsequent development of cancer is likely to be a process with multiple phases and multiple agents. Both internal and external factors interact at each of several stages before cancer becomes clinically apparent. The development of cancer, then, is influenced by two or more different external factors acting simultaneously or sequentially. This principle is illustrated by the synergistic effects of tobacco and alcohol. Cigarette smoking by itself is an important cause of oral cancer, whereas alcohol by itself is a relatively minor cause of oral cancer. Combined exposure to cigarette smoking and alcohol results in an increased risk of developing cancer of the oral cavity which is considerably higher than the risk experienced by cigarette smokers alone or drinkers alone.

The synergistic relationship between cigarette smoking and occupational exposure as it relates to the development of cancer is complicated. Most hazardous occupational exposures are to single agents or to a few at most. Cigarette smoking results in exposure to more than 2,000 chemical compounds, among which are carcinogens, tumor initiators, and promoters (see Chapter 14). It might be expected that cigarette smoking would have an adverse interaction with several occupational exposures, which it is important to try to identify. Insofar as possible, workers should be provided with a safe working environment, free from potentially harmful agents. It is equally true that workers can substantially reduce or eliminate the potential for

harmful occupational interactions by eliminating cigarette smoking from their lifestyle. This would probably eliminate the vast majority of the lung cancers which are occupationally related.

Short of giving up smoking entirely, it might be impossible for the worker to avoid many of the risks of developing cancer which may be related to his employment. Smoking at home but not on the job will not avoid this interaction, because the tars which are trapped in the airways will still be there when the individual goes to work.

Asbestos

In 1935, Lynch and Smith (*127*) in the United States and Gloyne (*61*) in in the United Kingdom reported an association between asbestos and lung cancer. In 1968, Selikoff, et al. (*188, 189*) first took into account the interaction between cigarette smoking and asbestos exposure in the development of lung cancer. They estimated that asbestos workers who smoked cigarettes had eight times the lung cancer risk of smokers without this occupational exposure. This was estimated to be 92 times the risk of nonsmokers who did not work with asbestos. This study has been continued and is supported by other investigations which consistently show a potent synergism between the carcinogens of tobacco smoke and asbestos (*19, 69*). There is evidence that exposure to asbestos carries some real risk to nonsmokers; however, this is of a low order of magnitude compared to the risks experienced by cigarette smokers (*135, 157*).

Uranium Mining

Lung cancer is an occupational risk associated with uranium mining. The causative agents in the atmosphere of mines are alpha particles resulting from the decay of short-lived radon daughters (*12, 48*). Several investigators (*7, 126, 173, 224, 225, 226*) have extensively studied underground uranium miners in the United States. The combined effect of tobacco smoke and radon daughter exposure results in high death rates from lung cancer among uranium miners. The risk for cigarette-smoking uranium miners is at least four times greater than for cigarette smokers who do not work in the mines.

Nickel

Epidemiological studies by Morgan (*146*) and Doll (*44*) and experimental studies by Hueper (*89*) and Sunderman, et al. (*200, 201, 202*) suggest that exposure to nickel or nickel carbonyl is a potent carcinogen for the respiratory tract in humans and animals. The interaction of cigarette smoking on the risk of respiratory cancer in nickel workers will probably never be adequately studied, since the Mond process for refining nickel is rarely used and conditions in nickel refining factories have improved.

Chloromethyl Ethers

Epidemiological and experimental studies (*59, 114*) have identified chloromethyl ethers as potent carcinogens for the human and animal respiratory tract. Investigations are in progress to more fully characterize these relationships, but the closing of the plants producing these substances makes it unlikely that the relative contribution of cigarette smoking to this type of occupational lung cancer will ever be known.

Animal Studies

Experimental animal models have been developed in which to study tobacco-induced carcinogenesis. Over the past 30 years, this field has acquired considerable sophistication and has enhanced our understanding of carcinogenesis in humans.

Experimental carcinogenesis has advanced to the point where it is now possible to reproduce in animals the major categories of respiratory tumors observed in humans and to link the induction of certain types of respiratory tumors to definite categories of exposure (*176*). By intratracheal administration of polynuclear hydrocarbons in rats and hamsters, bronchogenic squamous cell carcinoma is induced. Certain systemic carcinogens, particularly diethylnitrosamine in hamsters, give rise to adenomatous tumors of bronchial and bronchiolar-alveolar origin, as well as to papillary tumors in the trachea. Of the main types of respiratory tumors seen in human pathology, only one, the oat cell carcinoma, has not yet been found to be reproducible in experimental animals (*176*).

Skin Painting and Subcutaneous Injections

The earliest animal models for studying tobacco carcinogenesis involved the single or repeated painting of shaved or unshaved animal skin with solutions containing whole tobacco tar, various tobacco condensate subfractions, or single chemical compounds known to be present in tobacco smoke (*161*). Subcutaneous injections of various substances or fractions found in tobacco were also used as experimental models. Considerable criticism was directed towards these early studies, but they effectively demonstrated that a variety of carcinogenic compounds were found in tobacco smoke and that tobacco tar was a potent carcinogenic substance. Early experiments of these types have been reviewed by Wynder and Hoffmann (*245*).

Tracheobronchial Implantation and Instillation

More complex experiments have been performed using direct implantation, instillation, or fixation of suspected materials in the tracheobronchial tree of animals. Several authors have reviewed these studies (*115, 143, 175, 176, 245*).

Lung tumors which closely resemble lesions found in human cigarette smokers can be induced in hamsters by intratracheal instillation of benzo(*a*)pyrene (B*a*P). B*a*P induces a low incidence of bronchogenic tumors in hamsters when administered in saline; but when it is adsorbed into <1 μ ferric oxide carrier particles, its carcinogenicity is increased. When administered in the absence of B*a*P, ferric oxide particles alone do not induce tumors (*176*). The rate of elimination of B*a*P from the lung influences its tumorigenicity (*71, 72*). When B*a*P is administered alone or in simple mixtures with particles, 95 percent is eliminated within 24 hours. However, B*a*P adsorbed to particles is retained within the lung for several days (*71, 72*). Thus, the duration of the exposure to the carcinogen may be important to tumor induction by polycyclic aromatic hydrocarbons (PAH). These studies suggest that the particulate carrier increases the retention of PAH in the lung with a consequent increase in the exposure of respiratory tissue to the carcinogen.

In the hamster system, intratracheally-instilled B*a*P ferric oxide particles and subcutaneously-administered diethylnitrosamine (*142, 143*) were synergistic. Inhaled ferric oxide particles have also been found to enhance carcinogenicity of subcutaneously administered diethylnitrosamine (*158*) in the peripheral lung.

Inhalation Carcinogenesis

Various species, including mice, rats, hamsters, and dogs, have been exposed to cigarette smoke or to aerosols of its chemical constituents. Most of these substances have been administered to the experimental animal in a passive fashion. Active inhalation experiments more closely simulating human smoking behavior have been conducted by Rockey and Speer (*169*) and Auerbach, et al. (*11, 66*). In these experiments, animals were trained to inhale voluntarily through openings in the trachea.

Nitrosamines

A number of nitrosamines present in tobacco products or smoke have been found to produce respiratory tract tumors in animals. Various N-nitroso compounds of a nicotine metabolite, which are present in cured tobacco and chewing tobacco, can induce respiratory tract tumors in mice and hamsters (*70, 77*). Diethylnitrosamine, a volatile component of cigarette smoke, is a potent inducer of lung tumors in hamsters (*141*). Other nitrosamines present in tobacco products or smoke which have been shown to produce lung or tracheal tumors in animals include nitrosopiperidine (*99*) and N-nitrosodiethanolamine (*81*). This last compound is thought to be derived during curing from the maleic hydrazide triethanolamine salt which is sprayed on growing tobacco plants to reduce sucker formation.

Phagocytosis

Another factor which may be important is phagocytosis by macrophages. Some macrophages with engulfed particles remain in the lung for an extended period of time. A recent study by Palmer, et al. (*162*) showed that macrophages metabolized the potent carcinogen 7,12-dimethylbenz(*a*)anthracene (DMBA) and released the majority of the resultant derivatives into the surrounding medium. Unlike macrophages, cells from lung and tracheal tissues tended to retain the DMBA metabolites that they produced. This and related work by Harris, et al. (*69a*) showed that the human pulmonary macrophages under some conditions *in vitro* may permit the accumulation of metabolic products of carcinogens.

Conclusions

1. Cigarette smoking is the major cause of lung cancer in both men and women. This fact has been supported by prospective and retrospective epidemiological studies, clinical studies, autopsy studies, and experimental studies in animals. This conclusion is based on a weight of evidence which exceeds by several times the evidence available when this same conclusion was first reached in 1964.

2. The past 15 years have brought little significant progress in the earlier diagnosis or treatment of lung cancer. Taken as a whole, 30 percent of lung cancer patients live 1 year, and only 10 percent live 5 years after diagnosis. Fortunately, lung cancer is largely a preventable disease. Significant reductions in the number of deaths from lung cancer can be achieved if a significant portion of the smoking population can be persuaded to stop smoking and if a reduction can be brought about in the number of young people who take up smoking.

3. Lung cancer mortality is increasing in women and is increasing more rapidly than any other cause of death. If present trends continue, lung cancer will be the leading cause of cancer death among women in the next decade.

4. There are dose-response relationships for developing lung cancer with the number of cigarettes smoked per day, the duration of smoking, the age of starting to smoke, degree of inhalation, tar and nicotine content of cigarettes, and several other measures of dosage.

5. The long-term use (10 years or more) of filter cigarettes is associated with lower death rates from lung cancer than those experienced by persons who smoke an equal number of nonfilter cigarettes.

6. Ex-cigarette smokers experience decreasing lung cancer mortality rates, relative to continuing cigarette smokers. The risk of developing lung cancer for ex-smokers depends on the type of smoker he or she used to be. The risk is proportional to the number of cigarettes previously smoked per day, degree of inhalation, the age when smoking

was started, and duration of smoking. Whether the risk based on the previous smoking profile is high or low, there is a fairly rapid initial decline in risk following cessation of smoking which occurs over a 2- to 3- year period. It takes from 10 to 15 years, however, until the risk of developing lung cancer approaches the risk of nonsmokers.

7. Pipe and cigar smokers have lung cancer mortality rates which are higher than those of nonsmokers but which are considerable lower than those of cigarette smokers (see conclusions in the Chapter on Other Forms of Tobacco Use for further refinements and qualifications concerning pipe and cigar smoking).

8. Air pollution may be associated with the development of lung cancer; however, detailed epidemiological surveys indicate that the influence of air pollution on the development of lung cancer is small compared to the overriding effect of cigarette smoking. It is probable that there is a synergistic effect between cigarette smoking and air pollution in causing lung cancer. Air pollution does not appreciably influence lung cancer mortality rates in nonsmokers.

9. Certain occupational exposures, particularly uranium mining and working with asbestos, act synergistically with cigarette smoking, resulting in lung cancer mortality rates which exceed by several times the lung cancer mortality rates of unexposed cigarette smokers. Lung cancer mortality in these situations can be attributed to both cigarette smoking and the occupational exposure.

10. In the past few years, progress has been made in the development of animal models in which to study lung cancer. At the present time it is possible to reproduce in animals the major categories of respiratory tumors observed in man, using tobacco smoke, subfractions of tobacco tar, or specific compounds found in cigarette smoke.

Cancer of the Larynx

Approximately 1 percent of all deaths from cancer are from cancer of the larynx. It is estimated that in 1978 there were 3,350 deaths from cancer of the larynx, with 2,900 occurring in males and 450 occurring in females. The National Center for Health Statistics reported 3,351 deaths from cancer of the larynx in 1976. There were 2,808 deaths in males and 543 deaths in females (*150*). The most common histological lesion is squamous cell carcinoma. Approximately 70 percent are located in the glottis and 25 percent in the supraglottic region (*132*). Laryngeal cancer is predominantly a disease of males, although the incidence for females has increased somewhat over the past 20 years (*181, 238*). A typical patient with cancer of the larynx would be a 60-year-old male who was a heavy cigarette smoker and also a moderate-to-heavy alcohol drinker (*132*). The 5-year survival rate is improving and is presently at approximately 60 percent for all stages in both males and females.

TABLE 16.—Mortality ratios for cancer of the larynx—prospectiive studies

Study	Population size	Number of deaths	Mortality ratio		Comments
			Nonsmokers	Smokers	
A.C.S. 9-State Study(*68*)	188,000 males	24	—	—	All larynx cancer deaths occurred in smokers
British doctors(*47a*)	34,000 males	38	1.00	13.00	Includes cancer of larynx and other upper respiratory sites.
U.S. veterans(*90*)	239,000 males	54	1.00	9.95	
A.C.S. 25-State Study(*65*)	440,000 males	57	1.00	6.09-males, 8.99-males,	ages 45–64 ages 65–79
California males in 9 occupations (*228*)	68,000 males	11	—	—	All larynx cancer deaths occurred in smokers
Japanese study(*77a,80*)	122,200 males	38	1.00	11.83	
	142,800 females	6	1.00	9.00	

Epidemiological Studies

Many epidemiological studies have investigated the relationship between smoking habits and cancer of the larynx. The major prospective studies are outlined in Table 16. In these studies, cigarette smokers had a mortality ratio which was 6 to 13 times greater than that of nonsmokers. In three of the prospective studies, mortality ratios could not be calculated because all of the deaths from cancer of the larynx occurred in cigarette smokers.

Recent retrospective studies confirm prior evidence of a strong positive association between cancer of the larynx and cigarette smoking (*56, 238, 252, 253*). Wynder, et al. (*238*) found that the large sex difference has diminished somewhat over the past 20 years. This is most likely due to the increase in female cigarette smokers in age groups for which laryngeal cancer rates are high. The relative risk for developing laryngeal cancer for male cigarette smokers was 15.8; for female cigarette smokers it was 9.0. There was also a strong dose-response relationship in the relative risk of laryngeal cancer with both

the number of cigarettes smoked per day and the duration of smoking. A distinct synergism with combined alcohol and tobacco use was also described, with a relative risk of 22.1 for the smoker of more than 35 cigarettes a day who was also a heavy drinker. This study also examined the relative risks experienced by long-term filter cigarette smokers. At every level of consumption, both males and females who smoked filter cigarettes had a lower risk than did nonfilter smokers. Among men, the reduction in risk ranged from 25 to 49 percent for cancer of the larynx, and a substantial lowering of risk was also found for women. For ex-smokers, the risk of developing laryngeal cancer diminished gradually with time in a curve that paralleled that for cancer of the lung. The most rapid reduction in risk occurred during the first 5 years after cessation of smoking. After approximately 10 years, the risk approached that of nonsmokers. Several of these relationships are demonstrated in Figures 4 through 7.

Williams and Horm (*233*), using data from the Third National Cancer Survey, reported a strong dose-response relationship for the number of cigarettes smoked per day and the risk of developing cancer of the larynx. The relative risks for males, controlling for age and race, were 2.9 for level-one smokers, 3.3 for level-two smokers, and 17.7 for level-three smokers (the levels for cigarette-smoke exposure were established by using both the amount and the duration of cigarette use). Considering tobacco use at each level of alcohol consumption, the risk of developing cancer of the larynx increased as tobacco exposure increased. There was a positive association for the intake of alcoholic beverages and the development of cancer of the larynx. In previous reports of the U.S. Public Health Service (*212*, *217*), most of the older retrospective epidemiological studies have been reviewed (*22*, *56*, *172*, *174*, *184*, *185*, *193*, *196*, *203*, *205*, *218*, *237*, *246*, *250*).

Asbestos

Several authors have found an association between asbestos exposure and cigarette smoking with development of laryngeal carcinoma (*28*, *121*, *148*, *190*, *197*).

Animal Studies

The Syrian golden hamster has been found to be a suitable species for the investigation of cancer of the larynx. The distribution of malignant lesions in the upper airway of the hamster is not due to an unusual susceptibility of the larynx for tumor induction but rather reflects the distribution of smoke aerosol precipitation within the upper respiratory tract. The most recent experimental studies are those of Bernfeld, et al. (*18*), Dontenwill, et al. (*49*, *50*), Homburger (*86*), and Karbe and Koster (*93*). Cigarette smoke inhalation has not been found to induce laryngeal tumors in other rodents. Such tumors have been induced,

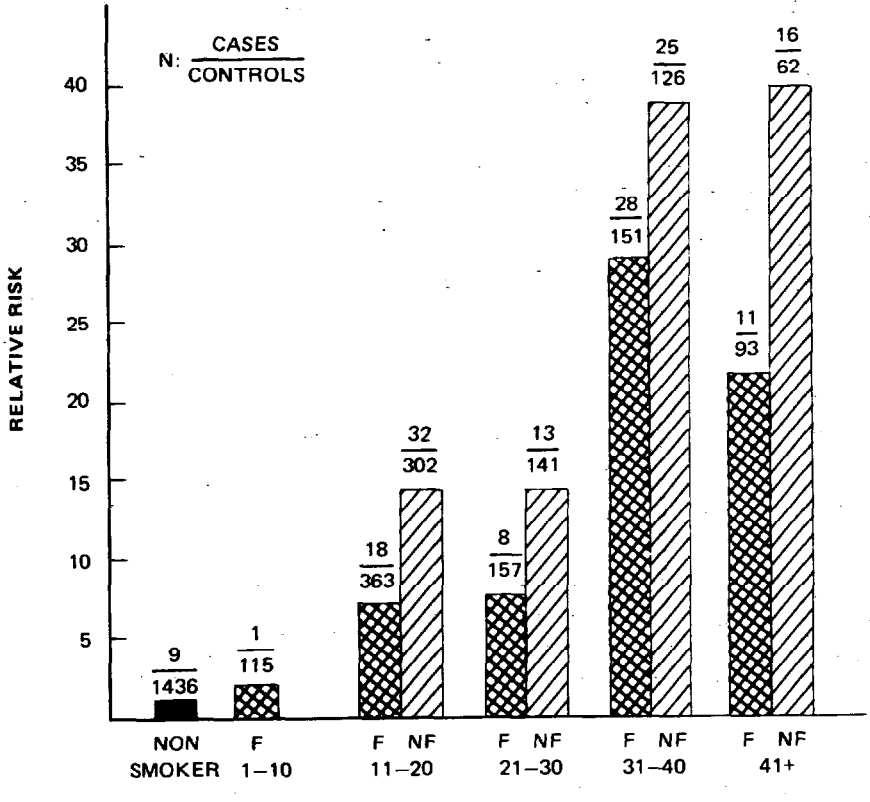


FIGURE 4.—Relative risk of developing larynx cancer for males, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes
SOURCE: Wynder, E.L. (*253*)

however, by the direct application of carcinogens known to be present in cigarette smoke. This is accomplished by the intratracheal instillation of benzo(*a*)pyrene in combination with particulate dusts into hamster lungs. In this animal model, laryngeal tumors, as well as tumors in other parts of the respiratory tract, are induced (*143*, *176*, *177*).

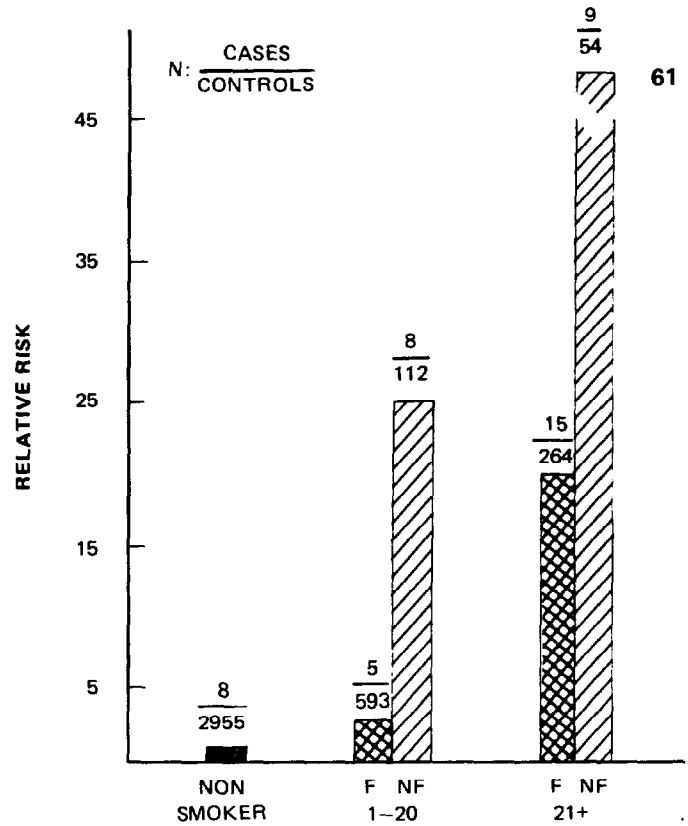


FIGURE 5.—Relative risk of developing larynx cancer for females, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes
SOURCE: Wynder, E.L. (*253*)

Conclusions

1. Epidemiological, experimental, and autopsy studies indicate that cigarette smoking is a significant causative factor in the development of cancer of the larynx.

2. The risk of developing cancer of the larynx in pipe and cigar smokers is similar to that for cigarette smokers.

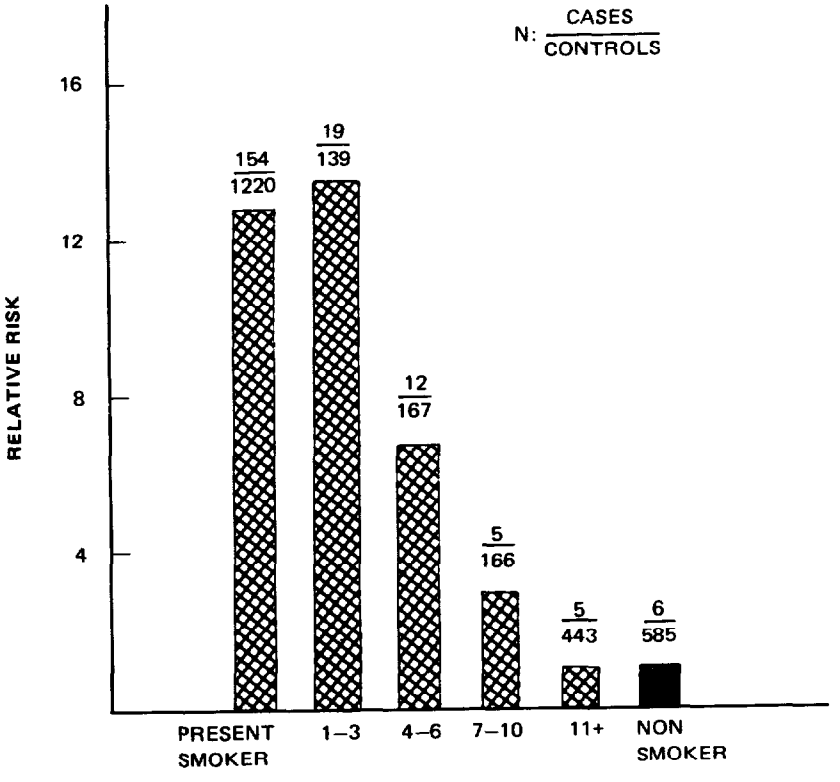


FIGURE 6.—Relative risk of developing larynx cancer for male ex-smokers, by years of smoking cessation
SOURCE: Wynder, E.L. *(253)*

3. There are positive dose-response relationships for the development of laryngeal cancer with the number of cigarettes smoked per day and the duration of cigarette smoking.

4. There is a synergistic effect with the use of cigarettes and alcohol. The risk of developing cancer of the larynx is much greater for heavy smokers who also drink heavily, compared with individuals who only have exposure to either substance.

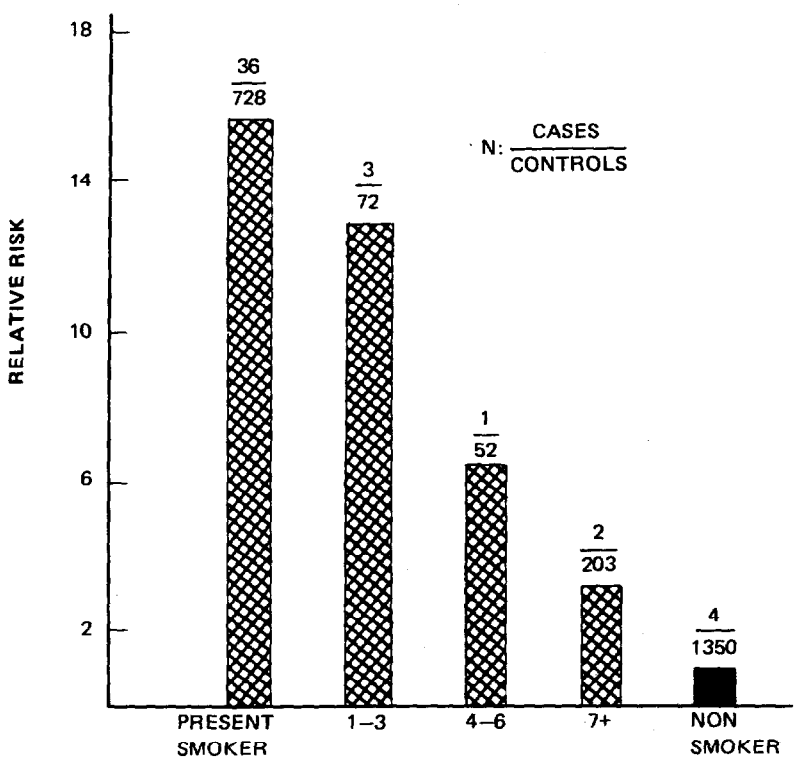


FIGURE 7.—Relative risk of developing larynx cancer for female ex-smokers, by years of smoking cessation
SOURCE: Wynder, E.L. (*253*)

5. There is a substantial decrease in the risk of developing cancer of the larynx with the long-term use of filter cigarettes (10 years or more), compared to the use of nonfilter cigarettes.

6. There is a gradual reduction in the risk of developing laryngeal cancer after cessation of smoking. After approximately 10 years, the risk of developing cancer of the larynx is similar to that of nonsmokers.

7. It has been reported that exposure to both asbestos and cigarette smoking synergistically increases the likelihood of an individual developing cancer of the larnyx.

8. Animal models have been found in which inhalation of cigarette smoke induces cancer of the larynx.

Oral Cancer

Cancers included in the oral cancer category are those malignant tumors of the lip, tongue, floor of the mouth, hard and soft palate, the gums, buccal mucosa, and oropharynx. The National Center for Health Statistics reported that in 1976 there were 8,114 deaths from cancer of the oral cavity, buccal surfaces, and pharynx. There were 5,731 deaths among males and 2,383 deaths among females (*150*). It is estimated that, in 1978, 24,400 new cases were diagnosed with a total of 8,400 deaths (*4*). The incidence in males is three times that in females. For the floor of the mouth, tongue, and pharynx, 5-year survival rates vary from 25 to 45 percent. A variety of histological types of malignant neoplasms can affect these tissues, but squamous cell carcinoma is the most common type, accounting for 90 percent of cancer of the oral cavity.

Epidemiological Studies

The use of tobacco in various forms has been associated with the development of cancer of the oral cavity and pharynx. Studies of cancer of the oral cavity are international. Many investigations have been carried out in Asian nations, as well as in the West. Data from the major prospective epidemiological studies show increased mortality ratios for these cancers among cigarette smokers, as well as among pipe and cigar smokers, compared to nonsmokers. There is some variation in mortality ratios, ranging from about 3.0 to 10.0. The results of these investigations are presented in Table 17.

There are a large number of retrospective studies which have examined the relationship of cigarette smoking to the development of cancer of the oral cavity (*26, 57, 94, 95, 116, 117, 119, 133, 134, 138, 139, 144, 145, 163, 170, 174, 178, 193, 220, 223, 239, 246*). These studies almost uniformly show a significant relationship between the various forms of tobacco use and cancer of the oral cavity and pharynx. One large survey recently conducted in India was reported by Bhargava, Smith, Malaowalla, and associates (*21, 130, 192*). The prevalence of oral cancer was determined in 57,518 industrial workers in Gujarat, India. A 2-year follow-up survey was conducted, and the incidence of oral cancer was determined. There was a strong association with tobacco use in various forms. In the Third National Cancer Survey (*233*), Williams and Horm reported a significant correlation between cancer of the gum and mouth and the use of pipes, cigars, cigarettes, and unsmoked tobacco.

In many of the studies dose-reponse relationships were examined. Increasing relative risks with increasing tobacco use were noted.

TABLE 17.—Mortality ratios for cancer of the oral cavity—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
A.C.S. 9-State Study(*68*)	188,000 males	55	1.00	18.00	Only 3 deaths among nonsmokers
British doctors(*47a*)	34,000 males	38	1.00	13.00	Includes lip, tongue, mouth, pharynx, larynx, and trachea
U.S. veterans(*90*)	239,000 males	61	1.00	4.09	
A.C.S. 25-State Study(*65*)	440,000 males	95	1.00	9.90	Ages 45–64
California males in 9 occupations (*228*)	68,000 males	19	1.00	2.76	
Japanese study(*77a,80*)	122,200 males 142,800 females	43 11	1.00 1.00	2.88 males 1.22 females	
Swedish study(*32*)	55,000 Swedish males and females	15	Mortality ratios not published		5 deaths in non-smoking males. 10 deaths in smoking males.

Other Forms of Tobacco

All forms of tobacco use expose the oral cavity to compounds found in raw tobacco or tobacco smoke. In most of the prospective and retrospective studies where other forms of tobacco use were accounted for, significant correlations were found between the use of tobacco and the development of oral cancer. These relationships are of the same general magnitude or slightly greater than those found with cigarette smoking. These relationships are examined in detail in the Chapter on Other Forms of Tobacco Use.

Other Risk Factors

Other than tobacco use, alcohol consumption and possibly poor dentition appear to be risk factors for the development of oral and pharyngeal cancers. The most recent investigations of the interaction

between alcohol and tobacco in the development of oral cancer are the studies of Rothman and Keller (*170*), Feldman, et al. (*58*), Graham, et al. (*62*), Browne, et al. (*28*), and the Third National Cancer Survey (*233*). In the latter survey, cancer of the oral cavity was associated significantly with both cigarettes and alcohol. The relative strength of each exposure after controlling for the other was evaluated by multiple regression analysis. For cancer of the pharynx, the standardized regression slope (based on standard deviation units) in males, after controlling for age, race, education, and cigarettes or alcohol, was 0.104 for alcohol and 0.084 for cigarettes. For cancer of the oral cavity and gums, the values were: alcohol 0.081 and cigarettes 0.018. For cancer of the lip and tongue, the values were: alcohol 0.057 and cigarettes 0.043. Hence, in this survey, oral cancer in males was somewhat more related to drinking than to smoking.

Rothman and Keller (*170*) also reported a strong synergy between the two exposures. They attributed 76 percent of oral cancer in males to the interaction of tobacco and alcohol. Feldman, et al. (*58*) found that nonsmoking alcohol users had only a slightly increased risk for head and neck cancer, whereas smokers who did not use alcohol still had two to four times the risk of abstainers from alcohol and tobacco. The risk for the heavy drinker who smokes, however, was from 6 to 15 times greater than for the individual who did not use tobacco or alcohol. In the study of Graham, et al. (*62*), the relative risk for heavy smoking alone was only 1.54; for heavy drinking alone it was 1.70. Heavy smoking and heavy drinking resulted in a relative risk of 2.49. When this was combined with inadequate dentition, the risk rose to 7.68. Browne, et al. (*28*) reported that alcohol and tobacco use was particularly prevalent among patients with oral squamous cell carcinoma.

Leukoplakia

Leukoplakia of the oral mucosa represents an abnormal thickening and keratinization of the oral mucosa. Leukoplakia is generally recognized as a precursor of malignancy in the oral cavity and is associated with tobacco use in various forms. The largest survey of leukoplakia in a Western population has been conducted by Banoczy and associates (*13, 168, 199*). Leukoplakia is quite common in India where tobacco and betel-nut chewing occurs and where bidis are smoked. The prevalence and incidence of leukoplakia has been reviewed in several large studies (*21, 130, 137, 192*).

Animal Studies

An ideal animal model in which to study oral carcinogenesis has not been found. Cigarette smoke and cigarette-smoke condensates generally fail to produce malignancies when applied to the oral cavity of mice, rabbits, or hamsters. Mechanical factors, such as secretion of saliva,

interfere with the retention of carcinogenic agents. The only positive results with carcinogens have been obtained with benza(*a*)pyrene, 20-methyl-cholanthrene, and 9,10-dimetyl-1,2 benzanthracene applied to the cheek pouch of hamsters. The cheek pouch, however, lacks the salivary gland, and its structure and function differ from those of the oral mucosa. These studies have been reviewed in previous reports of the U.S. Public Health Service (*212, 217*).

Conclusions

1. Epidemiological studies indicate that smoking is a significant causal factor in the development of cancer of the oral cavity. Dose-response relationships with the number of cigarettes smoked per day have been described.
2. The use of pipes, cigars, and chewing tobacco is associated with the development of cancer of the oral cavity. The risk of using these forms is of the same general magnitude as that of using cigarettes.
3. There is a synergism between cigarette smoking and alcohol use and the development of cancer of the oral cavity. The use of alcohol and tobacco results in a higher risk of developing cancer than that resulting from the use of either substance alone.

Cancer of the Esophagus

The National Center for Health Statistics reported that there were 7,224 deaths from cancer of the esophagus in 1976. There were 5,343 deaths in males and 1,881 deaths in females (*150*). It has been estimated that these figures rose to 7,100 deaths from cancer of the esophagus in 1978 (*4*). In addition, esophageal cancer incidence and mortality in the United States are substantially higher for blacks than for whites (*39*). Epidermoid carcinoma is the most common cancer of the esophagus (*3*). The prognosis is extremely poor with a 5-year survival rate of only 3 percent; the median survival time is less than 6 months after diagnosis (*152*).

Epidemiological Studies

Data from the major prospective epidemiological studies demonstrate a significant relationship between smoking and esophageal cancer. The mortality ratios for male cigarette smokers range from 1.82 to 8.75. These relationships are shown in Table 18. In several of these studies a positive dose-response relationship for the number of cigarettes smoked per day is shown. Available evidence indicates a similar relationship for men and women.

A number of retrospective studies have been published concerning smoking and esophageal cancer. Risk ratios for smokers in these studies range from 1.3 to 11.1, compared to nonsmoking controls (*24, 105, 133, 174, 178, 186, 194, 204, 235, 246*).

TABLE 18.—Mortality ratios for cancer of the esophagus—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
A.C.S. 9-State Study(*68*)	188,000 males	1 nonsmoker 33 smokers	1.00	—	Esophagus and other respiratory sites
British doctors (*47a*)	34,000 males	65	1.00	8.75	Esophagus and other respiratory sites
U.S. veterans(*90*)	293,000	111	1.00	6.17	
A.C.S. 25-State Study(*65*)	440,000 males	46	1.00	4.17	
California males in 9 occupations (*228*)	86,000	32	1.00	1.82	
Japanese Study(*77a*)	122,200 males	215	1.00	2.35	
Swedish Study(*32*)	55,000 Swedish males and females	1 nonsmoker 12 smokers	1.00	—	

Other Forms of Tobacco Use

In most of the prospective and retrospective epidemiological investigations, the association of esophagus cancer with the use of tobacco in other forms was examined. These relationships are discussed in some detail in the Chapter on Other Forms of Tobacco Use. The mortality ratios for cancer of the esophagus are approximately equal in users of cigars, pipes, and cigarettes.

Other Risk Factors

Numerous investigations have been made into the synergistic relationships between the use of tobacco in various forms, alcohol consumption, and the development of cancer of the esophagus (*78, 92, 105, 182, 183, 204, 208, 233, 235, 249*). Some investigators report that tobacco is a more important carcinogen than alcohol in the development of cancer of the esophagus, but others report that the reverse is true. Most of these studies support a synergism with the combined use of tobacco and alcohol, resulting in higher rates of cancer of the esophagus compared to those resulting from the use of either substance alone. The mechanism of the association is not known. Alcohol may act as a

solvent for carcinogenic hydrocarbons in tobacco smoke or alter microsomal enzymes in the mucosal cells of the esophagus (*234*). This hypothesis has received support from experimental observations by Kuratsune, et al. (*113*). The picture is complicated by the fact that alcoholism may be accompanied by severe nutritional deficiencies which may also predispose an individual to certain diseases.

Autopsy Studies

Histologic changes in the esophagus in relationship to smoking of tobacco in various forms were investigated by Auerbach, et al. (*11*). A total of 12,598 sections were made from esophageal tissue obtained from 1,268 subjects. It was found that tobacco smoking in any form resulted in the formation of atypical nuclei, disintegrating nuclei, hyperplasia, and hyperactive esophageal glands. Each of these parameters was significantly more abnormal in smokers than in nonsmokers; however, these changes were more frequently seen and more severe in cigarette smokers (*11*).

Animal Studies

There is experimental evidence that benzo(*a*)pyrene is able to penetrate the cell membranes of the esophageal epithelium, producing papillomas and squamous cell carcinomas. This process can be accelerated and better penetration achieved if the carcinogen is dissolved in an aqueous ethanol solution. This effect was reported by Kuratsune, Horie, and Kohchi (*88, 113*). Nitrosamine-induced esophageal cancer in experimental animals has also been reported by a number of investigators (*34, 52, 53, 54, 179*). These observations are significant because a variety of nitrosamine compounds have been identified in cigarette smoke.

Schmaehl (*179*) administered methyl-phenyl-nitrosamine orally or subcutaneously to Sprague-Dawley rats. Carcinomas of the esophagus were found in 46 to 87 percent of the animals. Simultaneous application of 25 percent ethyl alcohol did not affect the tumor incidence.

Mirvish (*140*) has reported that ^{3}H-thymidine incorporation in rat esophageal epithelium can be inhibited in the presence of nitrosamine *in vivo* and *in vitro*, lending further support to the role of these compounds in esophageal carcinogenic mechanisms.

Conclusions

1. Epidemiological studies demonstrate that cigarette smoking is a significant causal factor in the development of cancer of the esophagus. The risk of developing esophageal cancer increases with the amount smoked.

2. The risk of developing esophageal cancer with the use of other forms of tobacco, such as pipe and cigar smoking, is about the same order of magnitude as that for cigarette smokers.

3. Epidemiological studies also indicate a synergistic relationship between the use of alcohol and tobacco and the development of cancer of the esophagus.

4. Experimental studies show that chemical compounds found in cigarette smoke are capable of inducing carcinoma of the esophagus in experimental animals. In some experimental models, esophageal carcinogenesis is enhanced if the carcinogen is dissolved in a dilute alcohol solution.

Cancer of the Urinary Bladder and Kidney

Bladder Cancer

Most cancers of the urinary bladder are transitional or squamous cell carcinomas which appear either alone or in combination. Unless these produce hematuria or obstruct the bladder outlet, they remain undiagnosed until quite late, making a cure unlikely. For patients diagnosed with bladder cancer from 1960 to 1973, the 5-year survival rate was approximately 60 percent for whites and 30 percent for nonwhites (*240*). The average annual incidence for males is about three times that for females, but this ratio may change as the larger proportion of women who are now smoking reach the age where bladder cancer rates are high (*38*).

The National Center for Health Statistics reported that there were 9,673 deaths from bladder cancer in the United States in 1976. There were 6,759 deaths among males, and 2,914 deaths among females (*150*). It is estimated that 9,900 people died of bladder cancer in 1978 (*4*).

Epidemiological Studies

Epidemiological data on the relationship between smoking and cancer of the urinary bladder have been accumulating for well over 20 years. Bladder cancer mortality ratios from the larger prospective epidemiological studies are summarized in Table 19. On the average, cigarette smokers are about twice as likely to die from cancer of the bladder as nonsmokers.

There have been numerous retrospective studies of the effect of smoking on cancer of the bladder (*5, 36, 38, 41, 55, 101, 102, 124, 125, 147, 186, 195, 207, 240, 251, 253, 255*). Several of these studies show a positive dose-response relationship between the number of cigarettes smoked per day, the duration of cigarette smoking or the lifetime number of cigarettes smoked, and an increased risk of developing bladder cancer.

TABLE 19.—Bladder cancer mortality ratios—prospective studies

Population	Study size	Non-smokers	All cigarette smokers	Comments
ACS Males in 9-State Study(*68*)	187,783 White Males	1.00	2.00	Smokers of 10-20 cigarettes Includes all urinary tract cancers. Includes Prostate.
British doctors(*47a*)	34,000 Male Doctors	1.00	2.11	
Canadian Veterans(*20*)	78,000 Males	1.00	1.40	Genitourinary cancers considered as a group
ACS 25 State Study(*65*)	1,000,000 Males and Females	1.00 1.00	2.00 (Males 45–64) 2.96 (Females 65–79)	
U.S. Veterans(*90*)	2,265,000 Person-Years	1.00	2.15	
California Males in 9 occupations(*228*)	68,153 Males	1.00	2.89	
Japanese study(*77a,80*)	265,118 Males and Females	1.00 1.00	1.36 (Males) 2.71 (Females-P. O.O5)	
Swedish Study(*32*)	55,000 Males and Females	1.00 1.00	1.80 (Males) 1.60 (Females)	Bladder + other urinary organs

Wynder and Goldsmith (*240*) reported that the risk of developing bladder cancer decreased among ex-smokers and approached that of nonsmokers about 7 years after quitting smoking.

Several authors have calculated the percentage of bladder cancers which can conservatively be attributed to the cigarette smoking habit. Wynder and Goldsmith (*240*) estimated that 40 percent of male bladder cancers and 31 percent of female bladder cancers may be attributed to smoking cigarettes. This is in agreement with the estimates by Cole, et al. (*38*) of 39 percent in males and 29 percent in females.

In a cohort analysis of men and women in the United States, Denmark, England, and Wales, Hoover and Cole (*87*) examined the strength of the association between cigarette smoking, the development of bladder cancer, and successive birth cohorts. Increasing rates of bladder cancer were observed in populations characterized by an

increase in cigarette smoking among successive birth cohorts. The association was consistent in both men and women and was also found for different nationalities and for urban and rural groups. These findings are consistent with a causal role for cigarette smoking in the development of bladder cancer. It is interesting that the cohort analysis for bladder cancer is similar to and parallels that of cancer of the pancreas.

Other Risk Factors

Certain occupational exposures are associated with an increased risk of developing bladder cancer. Those who work with dyestuffs, rubber, leather, print, paint, petroleum, and other organic chemicals are particularly at risk. The common denominator appears to be aromatic amines. A number of specific carcinogens for the human bladder have been identified, including aminobiphenyl, 2-naphthylamine, benzidine, 1-naphthylamine, and 4-nitrobiphenyl (*35*). Some of these compounds are found in cigarette smoke. The relationship between cigarette smoking and occupational exposure is complex. It is likely that cigarette smoking can act as a sole agent in the development of bladder cancer; however, there may also be synergistic interactions between cigarette smoking and occupational exposures.

Animal Studies

Numerous experiments have been undertaken to examine the relationship of tobacco smoking to bladder carcinogenesis. The areas of major concern have centered upon aromatic amines, nitrosamines, tryptophan metabolism (*107*) and, more recently, non-nutritive sweetness, as in saccharin and cyclamates. The effect of these classes of compounds on the etiology of bladder cancer in experimental animals has been extensively reviewed in the literature.

Kidney Cancer

For 1978, the estimated incidence of kidney and other urinary cancers, exclusive of cancer of the bladder, was 9,400 for males and 5,700 for females. The estimated number of deaths for these same cancers was 4,600 in males and 2,800 in females (*4*). The 5-year survival rate following the diagnosis of kidney cancer is 40 to 50 percent (*151*).

Epidemiological Data

In most of the prospective studies, cancer of the kidney refers to tumors arising from the renal parenchyma as well as tumors in the renal pelvis and ureter. In some of the retrospective investigations, tumors at these various sites are considered separately in relationship to cigarette smoking. In several of the large prospective epidemiological studies, an association was found between cigarette smoking and

TABLE 20.—Kidney cancer mortality, ratios and relative risks: selected prospective and retrospective studies

Population	Study size and type	Number of kidney cancer deaths	Mortality ratio or relative risk ratio		Comments
			Non smokers	Cigarette smokers	
ACS 25 State Study(*65*)	440,558 males. Prospective study	104	1.00	1.42 1.57	Age 45–64 Age 65–79
U.S. Veterans(*90*)	2,265,000 person years. Prospective study	141	1.00	1.45	
California Males in 9 Occupations(*228*)	68,153 males. Prospective study	27	1.00	2.46	
Japanese study(*77a*)	122,261 males. Prospective study	30	1.00	1.20	
Bennington, Laubscher(*16a,17*)	Retrospective study of renal adenocarcinoma. 100 cases 190 controls	100	1.00	5.1	Risk ratio for Pipe - 10.3 Cigar - 12.9
Schmauz Cole(*180*)	Retrospective study. 43 cases of renal pelvis or ureter. 451 controls	18	1.00	10.0	For smokers of more than 2 1/2 pks/day
Armstrong(*8*)	Retrospective study. 106 adenocarcinoma of kidney.	106	1.00	1.06	
	30 carcinoma of renal pelvis. 139 controls	30	1.00	1.80	
Wynder et al.(*248a*)	Retrospective study 202 adenocarcinoma of kidney.		1.00	2.00	(Males)
	394 controls.		1.00	1.50	(Females)

cancer of the kidney. The mortality ratios for all cigarette smokers varied from 1.42 to 2.46, compared to nonsmokers. The results of these studies are summarized in Table 20.

TABLE 21.—Kidney cancer mortality ratios, by amount smoked: U.S. Veterans Study

Cigarettes smoked per day	Mortality ratios	Number of deaths
Nonsmokers	1.00	39
1-9	0.97	4
10-19	1.34	21
20-39	1.68	16
40+	2.75	5
All cigarette smokers	1.45	46

SOURCE: Kahn, H.A. (*90*)

Earlier retrospective reports of the association of renal adenocarcinoma with smoking reported a relative risk ratio of about 5.0 for cigarette smokers compared to nonsmokers (*16, 17*). They did find a positive association between cigarette smoking and cancer of the renal pelvis, as had Schmauz and Cole (*180*). Wynder, et al. (*248*) reported a moderate but significant association between cigarette smoking and renal adenocarcinoma for both males and females. There were positive dose-response relationships with the number of cigarettes smoked per day. The results of these studies are summarized in Table 20. A dose-response relationship with the number of cigarettes smoked per day was also found in the study of U.S. veterans (Table 21).

Conclusions

1. Epidemiological studies demonstrate a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. Supporting evidence from other disciplines supports the conclusion that cigarette smoking is one of the causes of cancer of the urinary bladder.

2. Epidemiologic studies show a positive dose-response relationship for developing bladder cancer with increases in the number of cigarettes smoked per day.

3. Cigarette smoking acts independently as a cause of bladder cancer and probably acts synergistically with other risk factors for bladder cancer, such as occupational exposure to certain aromatic amines.

4. Epidemiological studies have demonstrated an association of cigarette smoking with cancer of the kidney among men. There is some evidence of a dose-response relationship with the number of cigarettes smoked per day in the development of kidney cancer.

Cancer of the Pancreas

The National Center for Health Statistics reported that there were 19,738 deaths from cancer of the pancreas among men and women in the United States in 1976 (*150*). Deaths from cancer of the pancreas were expected to exceed 20,000 in the United States during 1978 (*4*). The incidence of cancer of the pancreas has increased threefold since 1930 (*100, 111*), and it now ranks fourth in frequency among fatal neoplastic diseases (*187*).

The most common form of pancreatic cancer in humans is adenocarcinoma, which originates from the epithelial duct cells of the pancreas. Acinar and islet cell tumors are relatively rare. Because of an extensive venous and lymphatic drainage system, metastases can occur relatively early in the course of the disease, contributing to the poor 3-year survival rate of 2 percent (*152*). Morgan and Wormsley (*149*) have reported that most studies have shown a mean survival time after diagnosis of less than 6 months.

Pancreatic cancer is more common among men than women in the United States, but the male-to-female ratio has been decreasing steadily from 1.6:1 during the period of 1940 to 1949 to 1.3:1 observed from 1965 to 1969 (*152*).

Epidemiological Studies

Several prospective epidemiologic investigations (*20, 32, 65, 79, 80, 90, 228*) have reported mortality ratios for cigarette smokers of approximately 2.0, compared to nonsmokers. These data are presented in Table 22. Not all of these investigations demonstrate a dose-response relationship with the number of cigarettes smoked per day; this is probably due to the small number of deaths in each smoking category. In a retrospective case control study with 81 cases of cancer of the pancreas, Wynder, et al. (*248*) showed a definite dose-response relationship with a relative risk of 5.0 for males smoking more than two packs of cigarettes a day. These data are presented in Figure 8. The dose-response data from the Swedish study are presented in Table 23.

Pancreatic cancer mortality in the United States was examined by cohort analysis for the period 1939 to 1969 by Bernarde and Weiss (*16*). White men were found to be at greater risk of developing pancreatic cancer than white women, and the same relationship existed for nonwhites. With the passage of time, there was a shift of the cohort mortality rate curve by age toward younger groups. These data appear to be compatible with an hypothesis which relates environmental factors to the etiology of pancreatic cancer. Air and water pollution, ionizing radiation, and improved diagnosis are unlikely to explain the observed differences, because these factors would be expected to influence both race and sexes more or less equally. Cigarette smoking,

TABLE 22.—Pancreatic cancer mortality ratios—prospective studies

Study population	Size of population	Nonsmokers	All cigarette smokers
Canadian veterans (*20*)	78,000 males	1.00	1.96
A.C.S. 25-State Study (*65*)	440,000 males	1.00	2.69
U.S. veterans (*90*)	239,000 males	1.00	1.84
Japanese study (*77a,80*)	122,000 males	1.00	1.41 males
	143,000 females	1.00	1.94 females
California occupations (*228*)	63,000 males	1.00	2.43
Swedish study (*32*)	55,000 males and females	1.00 1.00	3.1 males 2.5 females

high risk occupations, and dietary practices are more likely to explain these differences. Cigarette smoking is an exposure which is closely related to cohort and sex difference.

Other Risk Factors

There is epidemiologic evidence which links pancreatic cancer with increased dietary fat and protein intake (*80, 228*). An increased incidence of pancreatic cancer has been observed in chemists and industrial workers exposed to beta naphthylamine (*131*). A survey of death certificates of member chemists of the American Chemical Society indicates an increased relative frequency of pancreatic cancer (*120*). However, specific chemical exposures could not be traced.

Animal Studies

There are relatively limited numbers of experimental laboratory studies concerning cigarette smoking and cancer of the pancreas. Pour, et al. (*112, 166*), using a nitrosamine compound, induced pancreatic neoplasms in hamsters which were histologically similar to those in humans. Although the particular nitrosamine used in these experi-

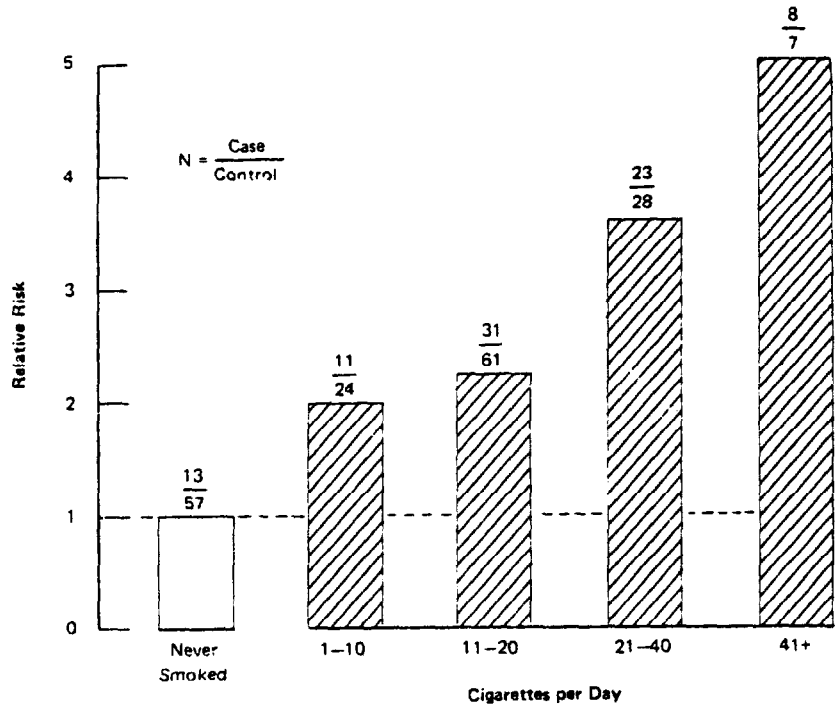


FIGURE 8.—Relative risk of pancreatic cancer in males, by number of cigarettes smoked
SOURCE: Wynder, E.L. (*248*)

TABLE 23.—Mortality ratios for cancer of the pancreas among Swedish subjects, aged 18–69, by sex and amount smoked

Number of cigarettes per day	Males	Females
Nonsmokers	1.0	1.0
1–7	1.6	2.4
8–15	3.4	2.5
15+	5.9	3.0
All cigarette smokers	3.1	2.5

SOURCE: Cederlof, R. (*32*)

ments is not found in tobacco smoke, a number of other nitrosamine compounds, such as dimethyl nitrosamine and methylethylnitrosamine,

have been found in cigarette smoke (*81*). This points to a class of compounds which should be investigated for their carcinogenic potential in cancer of the pancreas.

Konturek, et al. (*108*) has reported that nicotine inhibits pancreatic bicarbonate secretion in the dog by direct action on the organ. This has led to speculation that inhibition of duct cell secretion of bicarbonate could lead to intracellular pH changes and subsequently play a role in carcinogenesis.

Conclusions

1. Epidemiological data from prospective and retrospective investigations have demonstrated a significant association between cigarette smoking and cancer of the pancreas.
2. Several epidemiological studies contain evidence of a dose-response relationship for the number of cigarettes smoked per day. The relative risk of developing cancer of the pancreas is about five times greater for a two-pack-a-day smoker than for a nonsmoker.

Mechanisms of Carcinogenesis

Smoke Composition

Cigarette smoke for use in experimental studies is usually separated into a gas phase and a particulate phase by passing whole smoke through an appropriate filter. The compounds retained by the filter constitute the particulate phase and are referred to as "tar." More than 2,000 compounds have been identified in cigarette tar. The gas phase, which makes up more than 90 percent of the volume of whole smoke, contains a much smaller number of compounds. The particulate phase can be subdivided into categories based on the solubility of the compounds in acid, neutral, or basic solvents. Most of the chemical compounds which participate in the induction and maintenance of the malignant process are contained in the neutral portion of the particulate phase. A detailed analysis of the components of cigarette smoke is presented in the Chapter on the Constituents of Tobacco Smoke. This subject has also been reviewed in detail by Hoffmann and Wynder (*83*).

Experimental Models

Cigarette smoke, whole tobacco tars, the gas phase of cigarette smoke, various tobacco condensate subfractions, and single or multiple compounds known to be present in tobacco smoke have been used in studying the mechanisms of carcinogenesis in experimental animals. Rats, mice, hamsters, guinea pigs, rabbits, dogs, monkeys, donkeys, chickens, and other animals have been used in studying the carcinogenic properties of tobacco smoke.

It has not been possible to duplicate the same conditions of smoke inhalation in experimental animals as are found in humans. Many animals are obligate nose breathers, and under these circumstances turbulent precipitation of smoke particles in the nasal passages prevents most of the active compounds from reaching the lungs. A variety of alternate approaches have been used. The painting of shaved mouse skin with whole tobacco tar and various chemical constituents has been widely used. Other investigators have used subcutaneous injection, intratracheal instillation, implantation, and feeding. Tissue and organ cultures have also been used to study carcinogenesis. Chapter 14 contains a more complete discussion of this subject.

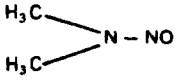
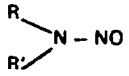
Concepts of Carcinogenesis

Carcinogenesis is a complex process involving multiple steps and various compounds operating at different points in the sequence. Chemical compounds have been classified as to the respective roles they play in the process of carcinogenesis. Cigarette smoke and tobacco tar act as complete carcinogens, since no additional compounds or steps are necessary to induce malignant changes in a variety of animal systems. When individual chemical compounds and subfractions are examined, however, the process of carcinogenesis becomes increasingly complex. Chemicals which can induce the first steps of malignant transformation are known as carcinogens or tumor initiators. Tumor promoters are compounds which continue the process of tumor formation when they are applied to tissue following initial treatment with a chemical carcinogen (*23*). Compounds known as co-carcinogens exert their effects when administered simultaneously with carcinogens or tumor initiators. Compounds which act as co-carcinogens do not necessarily have tumor-promoting properties. Mouse skin is frequently used for identifying co-carcinogens as well as promoters (*85*). Catechol is a potent co-carcinogen but is inactive as a tumor promoter. On the other hand, phenol, a tumor promoter, has no known co-carcinogenic activity (*219*). Data such as these support the idea that tumor promotion and co-carcinogenesis are independent phenomena with distinct mechanisms of action. Both promoters and co-carcinogens play an important role in tumor induction by tobacco products (*161*).

Additionally, Hoffmann and Wynder (*82, 244*) have described the property of tumor acceleration possessed by N-alkylated carbazoles and certain other compounds. These compounds are inactive as complete carcinogens, initiators, or promoters but accelerate the initiator-promoter activity of polynuclear aromatic hydrocarbons.

The carcinogens, tumor promoters, and ciliatoxic agents which have been identified in the gas phase of tobacco smoke are listed in Table 24. The major carcinogenic agents which have been identified in the particulate phase of tobacco smoke are listed in Table 25. The first part of Table 25 lists the 17 agents which are identified as tumor initiators;

TABLE 24.—Carcinogenic, promoting, and ciliatoxic agents in the gas phase of tobacco smoke*

	Smoke compounds	Amount in smoke of one cigarette
I. Carcinogens†		
	Dimethylnitrosamine	5–180ng**
	Dialkylnitrosamines (4 compounds)	2–80ng
	Nitrosopyrrolidine	1–110ng
	Nitrosopiperidine	0–9ng***
H_2N-NH_2	Hydrazine	24–43ng
$H_2C-CHCl$	Vinyl chloride	6–16ng
II. Tumor promoters		
HCHO	Formaldehyde	20–90μg
III. Ciliatoxic agents		
HCN	Hydrogen cyanide	100–700μg
HCHO	Formaldehyde	20–90μg
$H_2C-CH-CHO$	Acrolein	45–140μg
H_3C-CHO	Acetaldehyde	18–1,440μg

*List is based only on publications with unambiguous identifications of tumorigenic smoke compounds.
†Tobacco smoke is suspected of also containing H_3As (arsine), $Ni(CO)_4$ (nickel carbonyl) and possibly other volatile chlorinated olefins than vinylchloride and nitro-olefins.
**ng = 10^{-9}g
***μg = 10^{-6}g
SOURCE: Wynder, E.L. (*243*)

the second part contains a list of organ-specific carcinogens. The tumor promoters and co-carcinogens found in the particulate phase of tobacco smoke are listed in Table 26.

Many chemical carcinogens or initiators must be partially metabolized before they can exert their carcinogenic effects. Of the chemical carcinogens present in cigarette smoke, the metabolism of the polyaromatic hydrocarbons (PAH), in particular benzo(*a*)pyrene, has been most widely studied. The enzyme, aryl hydrocarbon hydroxylase (AHH), is responsible for the conversion of PAH into a number of hydroxylated derivatives (*60, 91, 191*).

TABLE 25.—Carcinogenic agents in the particulate phase of tobacco smoke[1]

Smoke compounds		Amount in smoke of one cigarette
Tumor Initiators[2]	Biol. Act.[2]	
Benzo(a)pyrene	(+++)	10–50ng
5-Methylchrysene	(+++)	0.6ng
Dibenz(a,h)anthracene	(++)	40ng
Benzo(b)fluoranthene	(++)	30ng
Benzo(j)fluoranthene	(++)	60ng
Dibenzo(a,h)pyrene	(++)	present
Dibenzo(a,i)pyrene	(++)	present
Dibenz(a,j)acridine	(++)	3–10ng
Indeno(1,2,3-cd)pyrene	(+)	4ng
Benz(a)anthracene	(+)	40–70ng
Chrysene	(+)	40–60ng
Methylchrysenes	(+)	18ng
Methylfluoranthenes	(+)	50ng
Dibenz(a,c)anthracene	(+)	present
Dibenz(a,h)acridine	(+)	0.1ng
Dibenzo(c,g)carbazole	(+)	0.7ng
Benzo(c)phenanthrene	(+)	present
Organ specific carcinogens[3]		
A. Esophagus		
N'-Nitrosonornicotine		140ng
Nitrosopiperidine		0–9ng
Nitrosopyrrolidine		1–110ng
Unknown Nitrosamines		?
B. Lung		
Polonium-210		0.03–1.3pCi[4]
Nickel compounds		0–600ng
Cadmium compounds		9–70ng
Unknowns		?
C. Pancreas		
Nitrosamines		?
Unknowns		?
D. Kidney and Bladder		
β-Naphthylamine		22ng
x-Aminofluorene		present
x-Aminostilbene		present
o-Toluidine		present
Unknown Aromatic Amines		?
o-Nitrotoluene		21μg
Unknown Nitro compounds		?
Di-n-butylnitrosamine		0.3ng
Unknown nitrosamines		?

[1]So far with certainty identified.

[2]Biol. Act. = Relative carcinogenic activity on mouse skin. + + + highly active; + + moderately active; + weakly active.

[3]These carcinogens also may act on other target organs

[4]pCi = picoCurie, 10^{-12}Curie

SOURCE: Wynder, E.L. (*243*)

TABLE 26.—Tumor promoters and co-carcinogens in the particulate phase of tobacco smoke[1]

Smoke compounds	Amount in smoke of one cigarette
Tumor promoters	
Volatile phenols	150–500μg
Unknown weakly acidic compounds	?
Unknown neutral compounds	?
Co-carcinogens	
Pyrene	50–200ng
Methylpyrenes	30–300ng
Fluoranthene	100–260ng
Methylfluoranthenes	180ng
Benzo(ghi)perylene	60ng
Benzo(e)pyrene	30ng
Other PAH	?
Napthalenes	0.3–6.3μg
1-Methylindoles	0.83μg
9-Methylcarbazoles	0.14μg
4,4'-Dichlorostilbene	1.5μg[2]
Other neutral compounds	?
Catechol	200–500μg
4-Alkylcatechol	10μg
Other acidic compounds	?

[1]So far with certainty identified.
[2]Values are decreasing because of lesser use of DDT and DDD for tobacco cultivation.
SOURCE: Wynder, E.L. (*243*)

Aryl Hydrocarbon Hydroxylase

AHH activity is present in most tissue of the body. It is induced by treatment *in vivo* or *in vitro* with a variety of PAH or related chemicals. Tobacco smoke inhalation elevates AHH activity in respiratory tissues of laboratory animals (*2, 51, 231*) and in human peripheral lymphocytes and pulmonary alveolar macrophages (*29, 129*). Inducible levels of the enzyme vary both with the tissue and with the individual (*60, 97, 156*).

Kellermann, et al. (*25, 96*) reported that the percentage of lung and laryngeal cancer patients with highly inducible AHH levels was much greater than in the normal population. On the other hand, there have been reports in which the inducibility of AHH in lung cancer patients either did not differ significantly from controlled populations (*123*) or was lower than in controls (*17*). Further research is necessary to clarify the relationship between cigarette smoking, AHH inducibility, and the development of cancer.

Multi-Stage Model of Carcinogenesis

One unifying hypothesis is the multi-stage model of carcinogenesis. This model has been proposed in various forms by several scientists and has recently been given attention by Armitage (*6*), Doll (*42*), and Peto (*165*). In the multi-stage model, carcinogenesis is considered a disease of interactions.

The transformation of a normal cell to a malignant one would require two or more separate stages, each with a characteristic probability of occurrence determined by one or more of the carcinogens present. The initiation and development of cancer would thus be a multi-stage, multi-causal process, in which both external and internal factors act in a sequence of several steps before the cancer would appear clinically. The multi-stage concept of carcinogenesis offers a plausible explanation for some of the peculiarities of the induction of lung cancer (such as the multiplicative effect of asbestos on cigarette smokers and the changing risks of ex-smokers). It is likely that development of cancer in each organ or tissue requires a different set of factors to induce malignant changes. It should not be surprising that cigarette smoking can induce malignant changes in as many organ systems as it does. Evidently, among the 2,000 chemical compounds found in cigarette smoke, there are sufficient carcinogens, tumor initiators, co-carcinogens, and tumor promoters to induce cancer in multiple-organ systems. Certainly, over the long time period in which the smoker is exposed to the products of tobacco combustion, there is sufficient time to satisfy the most complex multi-phased or multi-causal process. Given this model, it is not surprising that tobacco carcinogenesis is additionally influenced by a number of environmental factors (*76*). This would explain the synergism for lung cancer observed in cigarette smokers in various occupations, such as asbestos workers and uranium miners.

Cancer: References

(1) ABELIN, T., GSELL, O.R. Relative risk of pulmonary cancer in cigar and pipe smokers. Cancer 20 (8): 1288-1296, August 1967.

(2) ABRAMSON, R.K., HUTTON, J.J. Effects of cigarette smoking on aryl hydrocarbon hydroxylase activity in lungs and tissues of inbred mice. Cancer Research 35: 23-29, January 1975.

(3) ACKERMAN, L.V., REGATO, J.A. Cancer diagnosis, treatment and prognosis. St. Louis, C.V. Mosby Company, 1970, p. 412.

(4) AMERICAN CANCER SOCIETY. 1978 Cancer Facts and Figures. American Cancer Society, Inc., New York, 1977, p. 12.

(5) ANTHONY, H.M., THOMAS, G.M. Bladder tumours and smoking. International Journal of Cancer 5 (2): 266-272, March 15, 1970.

(6) ARMITAGE, P., DOLL, R. Stochastic models for carcinogenesis. In: Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability. Biology and Problems of Health, Volume 4. Berkeley, University of California Press, 1961.

(7) ARCHER, V.E., WAGONER, J.K., LUNDIN, F.E., JR. Uranium mining and cigarette smoking effects on man. Journal of Occupational Medicine 15(3): 204-211, March 1973.

(8) ARMSTRONG, B., GARROD, A., DOLL, R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. British Journal of Cancer 33: 127-136, 1976.

(9) ASHLEY, D.J.B., DAVIES, H.D. Lung cancer in women. Thorax 24: 446-450, 1969.

(10) AUERBACH, O., GARFINKEL, L., PARKS, V.R. Histologic type of lung cancer in relation to smoking habits, year of diagnosis and sites of metastases. Chest 67 (4): 382-387, April 1975.

(11) AUERBACH, O., HAMMOND, E.C., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. II. Pulmonary neoplasms. Archives of Environmental Health 21 (6): 754-768, December 1970.

(11a) AUERBACH, O., STOUT, A.P., HAMMOND, E.C., GARFINKEL, L. Histologic changes in esophagus in relation to missing smoking habits. Archives of Environmental Health 11(1): 4-15, July 1965.

(12) BAIR, W.J. Inhalation of radionuclides and carcinogenesis. In: Hanna, M.G., Jr, Nettesheim, P., Gilbert, J.R. (Editors). Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. U.S. Atomic Energy Commission, Division of Technical Information, AEC Symposium Series No. 18, April 1970, pp. 77-101.

(13) BANOCZY, J., SUGAR, L. Progressive and regressive changes in Hungarian oral leukoplakias in the course of longitudinal studies. Community Dentistry and Oral Epidemiology 3: 194-197, August 1975.

(14) BEAMIS, J.F., STEIN, A., ANDREWS, J.L., JR. Changing epidemiology of lung cancer. Medical Clinics of North America 59(2): 315-325, March 1975.

(15) BELCHER, J.R. Adenocarcinoma and smoking. Communications to the Editor. Chest 67(5): 622-623, May 1975.

(16) BENARDE, M.A., WEISS, W. A cohort analysis of pancreatic cancer, 1939-1969. Cancer 39(3): 1260-1263, March 1977.

(16a) BENNINGTON, J.L., FERGUSON, B.R., CAMPBELL, P.B. Epidemiologic studies of carcinoma of the kidney. II. Association of renal adenoma with smoking. Cancer 22(4): 821-823, October 1968.

(17) BENNINGTON, J.L., LAUBSCHER, F.A. Epidemiologic studies on carcinoma of the kidney. I. Association of renal adenocarcinoma with smoking. Cancer 21(6): 1069-1071, June 1968.

(18) BERNFELD, P., HOMBURGER, F., RUSSFIELD, A.B. Strain differences in the response of inbred Syrian hamsters to cigarette smoke inhalation. Journal of the National Cancer Institute 53(4): 1141-1157, October 1974.

(19) BERRY, G., NEWHOUSE, M.L., TUROK, M. Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. Lancet 2(7775): 476-479, September 2, 1972.

(20) BEST, E.W.R. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966, pp. 65-86.

(21) BHARGAVA, K., SMITH, L.W., MANI, N.J., SILVERMAN, S., JR., MALAOWALLA, A.M., BILIMORIA, K.F. A followup study of oral cancer and precancerous lesions in 57,518 industrial workers of Gujarat, India. Indian Journal of Cancer 12(2): 124-129, June 1975.

(22) BLUEMLEIN, H., Zur kausalen pathogenese des larynxkarzinoms unter beruecksichtigung des tabakrauchens (Causal pathogenesis of laryngeal carcinoma with respect to tobacco smoking). Archiv fuer Hygiene und Bakteriologie 139(5): 349-404, 1955.

(23) BOCK, F.G. Tumor promoters in tobacco and cigarette-smoke condensate. Journal of the National Cancer Institute 48(6): 1849-1853, June 1972.

(24) BRADSHAW, E., SCHONLAND, M. Oesophageal and lung cancers in Natal African males in relation to certain socio-economic factors. An analysis of 484 interviews. British Journal of Cancer 23(2): 275-284, June 1969.

(25) BRANDENBURG, J.H., KELLERMANN, G. Aryl hydrocarbon hydroxylase inducibility in laryngeal carcinoma. Archives of Otolaryngology 104: 151-152, March 1978.

(26) BRODERS, A.C. Squamous-cell epithelioma of the lip. A study of five hundred and thirty-seven cases. Journal of the American Medical Association 74(10): 656-664, March 6, 1920.

(27) BROSS, I.D.J., GIBSON, R. Risks of lung cancer in smokers who switch to filter cigarettes. American Journal of Public Health 58(8): 1396-1403, August 1968.

(28) BROWNE, R.M., CAMSEY, M.C., WATERHOUSE, J.A.H., MANNING, G.L. Etiological factors in oral squamous cell carcinoma. Community Dentistry and Oral Epidemiology 5: 301-306, 1977.

(29) CANTRELL, E.T., WARR, G.A., BUSBEE, D.L., MARTIN, R.R. Induction of aryl hydrocarbon hydroxylases in human pulmonary alveolar macrophages by cigarette smoking. Journal of Clinical Investigation 52(8): 1881-1884, August 1973.

(30) CARNOW, B.W. The "urban factor" and lung cancer: Cigarette smoking or air pollution? Environmental Health Perspectives 22: 17-21, February 1978.

(31) CEDERLOF, R., DOLL, R., FOWLER, B., FRIBERG, L., NELSON, N., VOUK, V. (Editors). Air pollution and cancer: Risk assessment methodology and epidemiological evidence. Report of a task group. Environmental Health Perspectives 22: 1-12, February 1978.

(32) CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity. A Ten Year Follow-Up in a Probability Sample of 55,000 Swedish Subjects, Age 18-69, Part 1 and Part 2. Stockholm, The Karolinska Institute, 1975, pp. 1-91.

(33) CEDERLOF, R., FRIBERG, L., LUNDMAN, T. The interactions of smoking, environment and heredity and their implications for disease etiology. A Report of Epidemiological Studies on the Swedish Twin Registries. Acta Medica Scandinavica, Supplementum 612: 1-128, September 1977.

(34) CLAPP, N.K., CRAIG, A.W. Carcinogenic effects of diethylnitrosamine in RF mice. Journal of the National Cancer Institute 39(5): 903-912, November 1967.

(35) CLAYSON, D.B. Occupational Bladder Cancer. Preventive Medicine 5(2): 228-244, June 1976. (Abstract)

(36) COBB, B.G., ANSELL, J.S. Cigarette smoking and cancer of the bladder. Journal of the American Medical Association 193(5): 329-332, August 2, 1965.
(37) COLE, P. Cancer and occupation: Status and needs of epidemiologic research. Cancer 39(4): 1788-1791, April 1977.
(38) COLE, P., MONSON, R.R., HANING, H., FRIEDELL, G.H. Smoking and cancer of the lower urinary tract. New England Journal of Medicine 284(3): 129-134, January 21, 1971.
(39) DAY, N.E. Some aspects of the epidemiology of esophageal cancer. Cancer Research 35(2): 3304-3307, November 1975.
(40) DEANER, R.M., TRUMMER, M.J. Carcinoma of the lung in women. Journal of Thoracic and Cardiovascular Surgery 59(4): 551-554, April 1970.
(41) DEELEY, T.J., COHEN, S.L. The relationship between cancer of the bladder and smoking. In: Bladder Cancer. Proceedings of the 5th Inter-American Conference on Toxicology and Occupational Medicine. Coral Gables, Florida, University of Miami, School of Medicine, 1966, pp. 163-169.
(42) DOLL, R. The age distribution of cancer: Implications for statistical models of carcinogenesis. Journal of the Royal Statistical Society 134(Part 2): 133-166, 1971.
(43) DOLL, R. Atmospheric Pollution and Lung Cancer. Environmental Health Perspectives 22: 23-31, February 1978.
(44) DOLL, R. Cancer of the lung and nose in nickel workers. British Journal of Industrial Medicine 15(4): 217-223, October 1958.
(45) DOLL, R. Strategy for detection of cancer hazards to man. Nature 265(5595): 589-596, February 17, 1977.
(46) DOLL, R., HILL, A.B. A study of the aetiology of carcinoma of the lung. British Medical Journal 2: 1271-1286, December 12, 1952.
(47) DOLL, R., HILL, A.B., KREYBERG, L. The significance of cell type in relation to the aetiology of lung cancer. British Journal of Cancer II: 43-48, 1957.
(47a) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2(6051): 1525-1536, December 25, 1976.
(48) DONALDSON, A.W. The epidemiology of lung cancer among uranium miners. Health Physics 16: 563-569, 1969.
(49) DONTENWILL, W., CHEVALIER, H.-J., HARKE, H.-P., LAFRENZ, U., RECKZEH, G., SCHNEIDER, B. Investigations on the effects of chronic cigarette-smoke inhalation in Syrian golden hamsters. Journal of the National Cancer Institute 51(6): 1781-1806, December 1973.
(50) DONTENWILL, W., CHEVALIER, H.-J., HARKE, H.-P., KLIMISCH, H.-J., KUHNIGK, C., RECKZEH, G., SCHNEIDER, B. Untersuchungen ueber den effekt der chronischen zigare menrauchinhalation beim Syrischen goldhamster und ueber die bedentung des Vitamin A auf die bei berauchung gefundenen organveraenderungen (Studies on the effect of chronic cigarette smoke inhalation in Syrian golden hamsters and the importance of Vitamin A on morphological alterations after smoke exposure). Zeitschrift fuer Krebsforschung und Klinische Onkologie 89(2): 153-180, 1977.
(51) DRATH, D.B., HARPER, A., GHARIBIAN, J., KARNOVSKY, M.L., HUBER, G.L. The effect of tobacco smoke on the metabolism and function of rat alveolar macrophages. Journal of Cellular Physiology 95: 105-113, 1978.
(52) DRUCKREY, H., LANDSCHUETZ, C., PREUSSMANN, R. Oesophagus-carcinome nach inhalation von methyl-butyl-nitrosamin (MBNA) an ratten (Carcinomas of the oesophagus, induced by inhalation of methyl-butyl-nitrosamine (MBNA) in rats). Zeitschrift fuer Krebsforschung 71(2): 135-139, July 1968.

(53) DRUCKREY, H., PREUSSMANN, R., BLUM, G., IVANKOVIC, S., AFKHAM, J. Erzeugung von karzinomen der spelseroehre durch unsymmetrische nitrosamine (Esophageal carcinomas induced by asymmetric nitrosamines). Naturwissenschaften 50(3): 100-101, 1963.

(54) DRUCKREY, H., PREUSSMANN, R., IVANKOVIC, S., SCHMAEHL, D. Organotrope carcinogene wirkungen bei 65 verschiedenen N-nitroso-verbindungen an BD-ratten (Organotropic carcinogenic effects of 65 different N-nitroso- compounds on BD-rats). Zeitschrift fuer Krebsforschung 69(2): 103-201, March 22, 1967.

(55) DUNHAM, L.J., RABSON, A.S., STEWART, H.L., FRANK, A.S. YOUNG, J.L., JR. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. Journal of the National Cancer Institute 41(3): 683-709, September 1968.

(56) DUTTA-CHOUDHURI, R., ROY, H., SEN GUPTA B.K. Cancer of the larynx and hypopharynx. A clinicopathological study with special reference to aetiology. Journal of the Indian Medical Association 32 (9): 352-362, May 1, 1959.

(57) EBENIUS, B. Cancer of the lip. A clinical study of 778 cases with particular regard to predisposing factors and radium therapy. Acta Radiologica 24 (Supplement 48): 1-232, 1943.

(58) FELDMAN, J.G., HAZAN, M., NAGARAJAN, M., KISSIN, B. A case-control investigation of alcohol, tobacco, and diet in head and neck cancer. Preventive Medicine 4(4): 444-463, December 1975.

(59) FIGUEROA, W.G., RASZKOWSKI, R., WEISS, W. Lung cancer in chloromethyl methyl ether workers. New England Journal of Medicine 288(21): 1096-1097, May 24, 1973.

(60) GIELEN, J.E., GOUJON, F.M., NEBERT, D.W. Genetic regulation of aryl hydrocarbon hydroxylase induction. II. Simple Mendelian expression in mouse tissues *in vivo*. Journal of Biological Chemistry 247(4): 1125-1137, February 25, 1972.

(61) GLOYNE, S.R. Two cases of squamous carcinoma of the lung occurring in asbestosis. Tubercle 17: 5-10, October 1935.

(62) GRAHAM, S., DAYAL, H., ROHRER, T., SWANSON, M., SULTZ, H., SHEDD, D., FISCHMAN, S. Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. Journal of the National Cancer Institute 59(6): 1611-1618, December 1977.

(63) HAENSZEL, W., SHIMKIN, M.B., MANTEL, N. A retrospective study of lung cancer in women. Journal of the National Cancer Institute 21(5): 825-842, November 1958.

(64) HAENSZEL, W., TAEUBER, K.E. Lung-cancer mortality as related to residence and smoking histories. II. White females. Journal of the National Cancer Institute 32(4): 803-838, April 1964.

(65) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(66) HAMMOND, E.C., AUERBACH, O., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. I. Design of experiment, mortality, and findings in lung parenchyma. Archives of Environmental Health 21(6): 740-753, December 1970.

(67) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. Some recent findings concerning cigarette smoking. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). Origins of Human Cancer. Book A: Incidence of Cancer in Humans. New York, Cold Spring Harbor Laboratory, 1977, pp. 101-112.

(68) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. Journal of the American Medical Association 166(11): 1294-1308, March 15, 1958.

(69) HAMMOND, E.C., SELIKOFF, I.J. Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States. In: Bogovski, P., Davis, W., Gilson, J.C., Timbrell, V., Wagner, J.C. (Editors). Biological Effects of Asbestos. Lyon, France, International Agency for Research on Cancer, 1973, pp. 312-317.

(69a) HARRIS, C.C., HSU, I.C., STONER, G.D., TRUMP, B.F., SELKIRK, J.K. Human pulmonary alveolar macrophages metabolise benzo(a)pyrene to proximate and ultimate mutagens. Nature 272(5654): 633-634, April 13, 1978.

(70) HECHT, S.S., CHEN, C.B., HIROTA, N., ORNAF, R.M., TSO, T.C., HOFFMANN, D. Tobacco-specific nitrosamines: Formation from nicotine *in vitro* and during tobacco curing and carcinogenicity in strain A mice. Journal of the National Cancer Institute 60(4): 819-824, April 1978.

(71) HENRY, M.C., KAUFMAN, D.G. Clearance of benzo(a)pyrene from hamster lungs after administration on coated particles. Journal of the National Cancer Institute 51(6): 1961-1964, December 1973.

(72) HENRY, M.C., PORT, C.D., KAUFMAN, D.G. Importance of physical properties of benzo(a)pyrene-ferric oxide mixtures in lung tumor induction. Cancer Research 35: 207-213, January 1975.

(73) HIGGINSON, J. A hazardous society? Individual versus community responsibility in cancer prevention. American Journal of Public Health 66(4): 359-366, April 1976.

(74) HIGGINSON, J. Present trends in cancer epidemiology. Proceedings of the Canada Cancer Congress 8: 40-75, 1969.

(75) HIGGINSON, J., JENSEN, O.M. Epidemiological review of lung cancer in man. In: Davis, W., Mohr, U., Schmaehl, D., Tomatis, L. (Editors). Air Pollution and Cancer in Man. Lyon, France, International Agency for Research on Cancer, 1977, pp. 169-189.

(76) HIGGINSON, J., MUIR, C.S. The role of epidemiology in elucidating the importance of environmental factors in human cancer. Cancer Detection and Prevention 1(1): 79-105, 1976.

(77) HILFRICH, J., HECHT, S.S., HOFFMANN, D. A study of tobacco carcinogenesis. XV. Effects of N'-nitrosonornicotine and N'-nitrosoanabasine in Syrian golden hamsters. Cancer Letters 2: 169-175, 1977.

(77a) HIRAYAMA, T. Changing patterns of cancer in Japan with special reference to the decrease in stomach cancer mortality. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). Origins of Human Cancer. Book A: Incidence of Cancer in Humans. New York, Cold Springs Harbor Laboratory, 1977, pp. 55-75.

(78) HIRAYAMA, T. Prospective studies on cancer epidemiology based on census population in Japan. In: Bucalossi, P., Veronesi, U., Cascinelli, N. (Editors). Cancer Epidemiology, Environmental Factors. Volume 3. Proceedings XI International Cancer Congress, Florence, October 20-26, 1974. Amsterdam, Excerpta Medica, 1975, pp. 26-35.

(79) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo, National Cancer Center, Research Institute, Epidemiology Division. September 1967, 14 pp.

(80) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. A report on five years of follow-up. American Cancer Society's Fourteenth Science Writers' Seminar, Clearwater Beach, Florida, March 24-29, 1972, pp. 1-4.

(*80a*) HITOSUGI, M. Epidemiological study of lung cancer with special reference to the effect of air pollution and smoking habit. Bulletin of the Institute of Public Health 17(3): 237-256, September 1968.

(*81*) HOFFMANN, D., RATHKAMP, G., LIU, Y.Y. Chemical studies on tobacco smoke. XXVI. On the isolation and identification of volatile and non-volatile N-nitrosamines and hydrazines in cigarette smoke. In: Bogarski P., Walker E.A. (Editors). N-Nitroso Compounds in the Environment. World Health Organization, International Agency for Research on Cancer, IARC Scientific Publication No. 9, 1974, pp. 159-165.

(*82*) HOFFMANN, D., WYNDER, E.L. A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. Cancer 27(4): 848-864, April 1971.

(*83*) HOFFMANN, D., WYNDER, E.L. Environmental respiratory carcinogenesis. In: Searle, C.E. (Editor). Chemical Carcinogens. ACS Monograph No. 173. Washington, D.C., American Chemical Society, 1976, pp. 324-365.

(*84*) HOFFMANN, D., WYNDER, E.L. Smoking and occupational cancers. Preventive Medicine 5(2): 245-261, June 1976.

(*85*) HOFFMANN, D., WYNDER, E.L. Studies on gasoline engine exhaust. Journal of the Air Pollution Control Association 13(7): 322-327, July 1963.

(*86*) HOMBURGER, F. "Smokers' larynx" and carcinoma of the larynx in Syrian hamsters exposed to cigarette smoke. Laryngoscope 85(11, Part 1): :1874-1881, November 1975.

(*87*) HOOVER, R., COLE, P. Population trends in cigarette smoking and bladder cancer. American Journal of Epidemiology 94(5): 409-418, November 1971.

(*88*) HORIE, A., KOHCHI, S., KURATSUNE, M. Carcinogenesis in the esophagus. II. Experimental production of esophageal cancer by administration of ethanolic solution of carcinogens. Gann 56(5): 429-440, October 1965.

(*89*) HUEPER, W.C. Experimental studies in metal cancerigenesis. IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel. American Medical Association Archives of Pathology 65:600-607, June 1958.

(*90*) KAHN, H.A. The Dorn study of smoking and mortality among U.S. Veterans: Report on eight and one-half years of observation. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 1-125.

(*91*) KAPITULNIK, J., WISLOCKI, P.G. LEVIN, W., YAGI, H., JERINA, D.M., CONNEY, A.H. Tumorigenicity studies with diol-epoxides of benzo(a)pyrene which indicate that (±)-trans-7β,8α-dihydroxy-9α, 10α-epoxy-7, 8, 9, 10-tetrahydrobenzo(a)pyrene is an ultimate carcinogen in newborn mice. Cancer Research 38(2): 354-358, February 1978.

(*92*) KAMIONKOWSKI, M.D., FLESHLER, B. The role of alcoholic intake in esophageal carcinoma. American Journal of the Medical Sciences 249: 696-700, June 1965.

(*93*) KARBE, E., KOESTER, K. Carcinogenicity of inhaled cigarette smoke in the NMU-pretreated hamster larynx. In: Karbe, E., Park, J.F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. New York, Springer-Verlag. 1974, pp. 369-382.

(*94*) KELLER, A.Z. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. American Journal of Epidemiology 91(5): 486-499, May 1970.

(*95*) KELLER, A.Z. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. Cancer 20(6): 1015-1022, June 1967.

(96) KELLERMANN, G., SHAW, C.R., LUYTEN-KELLERMANN, M. Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. New England Journal of Medicine 289(18): 934-937, November 1, 1973.

(97) KELLERMANN, G., LUYTEN-KELLERMANN, M., SHAW, C.R. Genetic variation of aryl hydrocarbon hydroxylase in human lymphocytes. American Journal of Human Genetics 25: 327-331, 1973.

(98) KELLEY, T.F. Polonium-210 content of mainstream cigarette smoke. Science 149(3683): 537-538, July 30, 1965.

(99) KENDRICK, J., NETTESHEIM, P., HAMMONS, A.S. Tumor induction in tracheal grafts: A new experimental model for respiratory carcinogenesis studies. Journal of the National Cancer Institute 52(4): 1317-1320, April 1974.

(100) KENNEDY, A. Relationship between cigarette smoking and histological type of lung cancer in women. Thorax 28(2): 204-208, March 1973.

(101) KERR, W.K., BARKIN, M., LEVERS, P.E., WOO, S.K.-C., MENCZYK, Z. The effect of cigarette smoking on bladder carcinogens in man. Canadian Medical Association Journal 93(1): 1-7, July 3, 1965.

(102) KIDA, H., OMOTO, T., SAKAMOTO, K., MOMOSE, S. Fukuoka ken hokubu ni okeru boko shuyo no ekigaku to tokei (Statistical and epidemiological studies on tumor of the urinary bladder in the northern parts of Fukuoka Prefecture). Hifu to Hinyo 30(5): 883-889, October 1968.

(103) KILIBARDA, M., PETROVIC., D., PANOV, D., DJURIC, D. Contamination with polonium-210, uranium and radium-226 due to smoking. Health Physics 12(11): 1808, November 1966. (Abstract)

(104) KIRYU, S., KURATSUNE, M. Polycyclic aromatic hydrocarbons in the cigarette tar produced by human smoking. Gann 57: 317-322, August 1966.

(105) KISSIN, B., KALEY, M. M., SU, W. H., LERNER, R. Head and neck cancer in alcoholics. The relationship to drinking, smoking, and dietary patterns. Journal of the American Medical Association 224(8): 1174-1175, May 21, 1973.

(106) KNUDTSON, K.P. The pathologic effects of smoking tobacco on the trachea and bronchial mucosa. American Journal of Clinical Pathology 33(4): 310-317, April 1960.

(107) KOCHEN, W., HOCHBERG, K. Utersuchungen ueber den tryptophan-stoffwechsel beim blasen-carcinom (Studies about the tryptophan metabolism in carcinoma of the bladder). Zeitschrift fuer Krebsforschung 72(3): 251-264, January 29, 1970.

(108) KONTUREK, S.J., DALE, J., JACOBSON, E.D., JOHNSON, L.R. Mechanisms of nicotine-induced inhibition of pancreatic secretion of bicarbonate in the dog. Gastroenterology 62(3): 425-429, March 1972.

(109) KOTIN, P., FALK, H.L. Polluted urban air and related enviromental factors in the pathogenesis of pulmonary cancer. Diseases of the Chest 45(3): 236-246, March 1964.

(110) KRAIN, L.S. Crossing of the mortality curves for stomach and pancreatic carcinoma. International Surgery 57(4): 307-310, April 1972.

(111) KRAIN, L.S. The rising incidence of carcinoma of the pancreas. An epidemiologic appraisal. American Journal of Gastronenterology 54(5): 500-507, November 1970.

(111a) KREYBERG, L. Histological lung cancer types; A morphological and biological correlation. Acta Pathologica et Microbiologica Scandinavica (Supplement) 152, 1962, 92 pp.

(112) KRUEGER, F.W., POUR, P., ALTHOFF, J. Induction of pancreas tumours by Di-Isopropanolnitrosamine. Naturwissenschaften 61(7): 328, July 1974. (Abstract)

(113) KURATSUNE, M., KOHCHI, S., HORIE, A. Carcinogenesis in the esophagus. I. Penetration of benzo(a)pyrene and other hydrocarbons into the esophageal mucosa. Gann 56(2): 177-187, April 1965.

(*114*) LASKIN, S., KUSCHER, M., DREW, R.T., CAPPIELLO, V.P., NELSON, N. Tumors of the respiratory tract induced by inhalation of bis(chloromethyl)ether. Archives of Enviromental Health 23(2): 135-136, August 1971.

(*115*) LASKIN, S., KUSCHNER, M., DREW, R.T. Studies in pulmonary carcinogenesis. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee. October 8-11, 1968. U.S. Atomic Energy Commission, Division of Technical Information, AEC Symposium Series No. 18, April 1970, pp. 321-351.

(*116*) LEDERMANN, S. Cancers, tabac, vin, et alcohol. Conjuguarte leurs influences, li cas echeant... (Cancers, tobacco, wine, and alcohol. Combining their influences, should the case arise...). Le Concours Medical 77(10): 1218-1225, March 5, 1955.

(*117*) LEE, W.Y., TERRIS, M., KELLER, A.Z. Relation of alcohol and tobacco to cancer of the mouth and pharynx. Paper presented to the Epidemiology Section at the Annual Meeting of the American Public Health Association, Atlantic City, New Jersey, November 14, 1972, 10 pp.

(*118*) LINDEN, G. The increasing rate of lung cancer mortality in California women. California School Health: 12-16, January 1966.

(*119*) LEVIN, M.L., GOLDSTEIN, H., GERHARDT, P.R. Cancer and tobacco smoking. A preliminary report. Journal of the American Medical Association 143(4): 336-338, May 27, 1950.

(*120*) LI, F.P., FRAUMENI, J.F., JR., MANTEL, N., MILLER, R.W. Cancer mortality among chemists. Journal of the National Cancer Institute 43(5): 1159-1164, November 1969.

(*121*) LIBSHITZ, H.I., WERSHBA, M.S., ATKINSON, G.W., SOUTHARD, M.E. Asbestosis and carcinoma of the larynx. A possible association. Journal of the American Medical Association 228(12): 1571-1572, June 17, 1974.

(*122*) LICKINT, F. Der tabakrauch als ursache des lungenkrebses (Tobacco smoke as causes of lung cancer). In: Atiologie und Prophylaxe des Lungenkrebses. 2. Statistische Voraussetzungen zur Klaerung der Tabakrauchaetiologie des Lungenkrebses. Dresden, Theodor Steinkopff, 1953, pp. 76-102.

(*123*) LIEBERMAN, J. Aryl hydrocarbon hydroxylase in bronchogenic carcinoma. New England Journal of Medicine 298(12): 686-687, March 23, 1978.

(*124*) LILIENFELD, A.M., LEVIN, M.L., MOORE, G.E. The association of smoking with cancer of the urinary bladder in humans. American Medical Association Archives of Internal Medicine 98: 129-135, 1956.

(*125*) LOCKWOOD, K. On the etiology of bladder tumors in Kobenhavn-Frederiksberg. An inquiry of 369 patients and 369 controls. Acta Pathologica et Microbiologica Scandinavica 51 (Supplementum 145): 1-161, 1961.

(*126*) LUNDIN, F.E., JR., LLOYD, J.W., SMITH, E.M., ARCHER, V.E., HOLADAY, D.A. Mortality of uranium miners in relation to radiation exposure, hard-rock mining and cigarette smoking—1950 through September 1967. Health Physics 16(5): 571-578, 1969.

(*127*) LYNCH, K.M., SMITH, W.A. Pulmonary asbestosis III: Carcinoma of the lung in asbesto-silicosis. American Journal of Cancer 24(1): 56-64, May 1935.

(*128*) MCCONNELL, R.B., GORDON, K.C.T., JONES, T. Occupational and personal factors in the aetiology of carcinoma of the lung. Lancet 2(6736): 651-656, October 4, 1952.

(*129*) MCLEMORE, T.L., WARR, G.A., MARTIN, R.R. Induction of aryl hydrocarbon hydroxylase in human pulmonary alveolar macrophages and peripheral lymphocytes by cigarette tars. Cancer Letters 2: 161-167, 1977.

(*130*) MALAOWALLA, A.M., SILVERMAN, S., JR., MANI, N.J., BILIMORIA, K.F., SMITH, L.W. Oral cancer in 57,518 industrial workers of Gujarat, India. A prevalence and followup study. Cancer 37(4): 1882-1886, April 1976.

(*131*) MANCUSO, T.F., EL-ATTAR, A.A. Cohort study of workers exposed to betanaphthylamine and benzidene. Journal of Occupational Medicine 9: 277-285, June 1967.

(*132*) MARKS, R.D., JR., PUTNEY, F.J., SCRUGGS, H.J., ADKINS, W.Y., WALLACE, K.M. Management of cancer of the larynx. Journal of the South Carolina Medical Association 71(11): 333-336, November 1975.

(*133*) MARTINEZ, I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. Journal of the National Cancer Institute 42(6): 1069-1094, June 1969.

(*134*) MARTINEZ, I. Retrospective and prospective study of carcinoma of the esophagus, mouth, and pharynx in Puerto Rico. Boletin de la Asociacion Medica de Puerto Rico 62(6): 170-178, June 1970.

(*135*) MARTISCHNIG, K.M., NEWELL, D.J., BARNSLEY, W.C., COWAN, W.K., FEINMANN, E.L., OLIVER, E. Unsuspected exposure to asbestos and bronchogenic carcinoma. British Medical Journal 1(6063): 746-749, March 19, 1977.

(*136*) MAXWELL, J.C., JR. The 1976 Maxwell report on cigarettes. Tobacco Reporter 16: 16-17, 53-55, November 17, 1976.

(*137*) MEHTA, F.S., PINDBORG, J.J., BHONSLE, R.B., SINOR, P.N. Incidence of oral leucoplakias among 20,358 Indian villagers in a 7-year period. British Journal of Cancer 33(5): 549-554, May 1976.

(*138*) MILLS, C.A., PORTER, M.M. Tobacco smoking habits and cancer of the mouth and respiratory system. Cancer Research 10(9): 539-542, September 1950.

(*139*) MILLS, C.A., PORTER, M.M. Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. Cancer Research 17(10): 981-990, November 1957.

(*140*) MIRVISH, S.S. N-nitroso compounds: Their chemical and *in vivo* formation and possible importance as environmental carcinogens. Journal of Toxicology and Environmental Health 2(6): 1267-1277, 1977.

(*141*) MONTESANO, R., SAFFIOTTI, U. Carcinogenic response of the respiratory tract of Syrian golden hamsters to different doses of diethylnitrosamine. Cancer Research 28: 2197-2205, November 1968.

(*142*) MONTESANO, R., SAFFIOTTI, U., FERRERO, A., KAUFMAN, D.G. Brief communication: Synergistic effects of benzo(a)pyrene and diethylnitrosamine on respiratory carcinogenesis in hamsters. Journal of the National Cancer Institute 53(5): 1395-1397, November 1974.

(*143*) MONTESANO, R., SAFFIOTTI, U., SHUBIK, P. The role of topical and systemic factors in experimental respiratory carcinogenesis. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. Atomic Energy Commission, Division of Technical Information, AEC Symposium Series No. 18, April 1970, pp. 353-371.

(*144*) MOORE, C. Cigarette smoking and cancer of the mouth, pharynx, and larynx. A continuing study. Journal of the American Medical Association 218(4): 553-558, October 25, 1971.

(*145*) MOORE, G.E., BISSINGER, L.L., PROEHL, E.C. Intraoral cancer and the use of chewing tobacco. Journal of the American Geriatrics Society 1: 497-506, 1953.

(*146*) MORGAN, J.G. Some observations on the incidence of respiratory cancer in nickel workers. British Journal of Industrial Medicine 15: 224-234, 1958.

(147) MORGAN, R.W., JAIN, M.G. Bladder cancer: Smoking, beverages and artificial sweeteners. Canadian Medical Association Journal III: 1067-1070, November 16, 1974.

(148) MORGAN, R.W., SHETTIGARA, P.T. Occupational asbestos exposure, smoking, and laryngeal carcinoma. Annals of the New York Academy of Sciences 271: 308-310, 1976.

(149) MORGAN, R.G.H., WORMSLEY, K.G. Progress report. Cancer of the pancreas. GUT 18: 580-593, 1977.

(151) NATIONAL CANCER INSTITUTE. Cancer patient survival. Report No. 5. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-922, 1976, pp. 11-55.

(152) NATIONAL CANCER INSTITUTE. End results in cancer. Report No. 4. U. S. Department of Health Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH) 73-272, 1972, pp. 43-46, 81-84.

(153) NATIONAL CANCER INSTITUTE. NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Estimates of the fraction of cancer in the United States related to occupational factors. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, September 15, 1978, pp. 1-50.

(154) NATIONAL CANCER INSTITUTE. SEER Program: Cancer incidence and mortality in the United States 1973-1976. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH) 78-1837, 1978, 67 pp.

(154a) NATIONAL CENTER FOR HEALTH STATISTICS. Vital Rates of the United States, 1940–1960. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of Health Policy, Research, and Statistics, National Center for Health Statistics.

(154b) NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States, Volume II, Mortality, Part A, 1970. U. S. Department of Health, Education, and Welfare, Public Health Service, Office of Health Policy, Research, and Statistics, National Center for Health Statistics.

(154c) NATIONAL CENTER FOR HEALTH STATISTICS. Vital Statistics of the United States, Volume II, Mortality, Part A. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of Health Policy, Research, and Statistics, National Center for Health Statistics. (To be published)

(155) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U. S. Department of Health, Education, and Welfare, Public Health Service, June 1976. 23 pp.

(155a) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Patterns and Prevalence of Teen-age Cigarette Smoking: 1968, 1970, 1972, and 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, DHEW Publication No. (HSM) 74-8701, July 1974. 4 pp.

(156) NEBERT, D.W., GOUJON, F.M., GIELEN, J.E. Aryl hydrocarbon hydroxylase induction by polycyclic hydrocarbons: Simple autosomal dominant trait in the mouse. Nature New Biology 236(65): 107-109, March 29, 1972.

(157) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Re-Examination and Update of Information on the Health Effects of Occupational Exposure to Asbestos. U.S. Department of Health, Education, and Welfare, 1977. (In press)

(158) NETTESHEIM, P., CREASIA, D.A., MITCHELL, T.J. Carcinogenic and co-carcinogenic effects of inhaled synthetic smog and ferric oxide particles. Journal of the National Cancer Institute 55(1): 159-166, July 1975.

(159) OCHSNER, A. DEBAKEY, M. Primary pulmonary malignancy. Treatment by total pneumonectomy. Analysis of 79 collected cases and presentation of 7 personal cases. Surgery, Gynecology and Obstetrics 68: 435-451, 1939.

(160) ORMOS, J., KARACSONYI, G., BILICZKI, F., SZONYI, F. Lung cancer in the Hungarian plain. Neoplasma 16(6): 667-675, 1969.

(161) ORRIS, L., VAN DUUREN, B.L., KOSAK, A.I., NELSON, N., SCHMITT, F.L. The carcinogenicity for mouse skin and the aromatic hydrocarbon content of cigarette-smoke condensates. Journal of the National Cancer Institute 21(3): 557-561, September 1958.

(162) PALMER, W.G., ALLEN, T.J., TOMASZEWKI, J.E. Metabolism of 7, 12-dimethylbenz(a)anthracene by macrophages and uptake of macrophage-derived metabolites by respiratory tissues *in vitro*. Cancer Research 38: 1079-1084, April 1978.

(163) PEACOCK, E.E., JR., GREENBERG, B.G., BRAWLEY, B.W. The effect of snuff and tobacco on the production of oral carcinoma: An experimental and epidemiological study. Annals of Surgery 151(4): 542-550, April 1960.

(164) PERNU, J. An epidemiological study on cancer of the digestive organs and respiratory system. A study based on 7,078 cases. Annales Medicinae Internae Fenniae 49 (Supplementum 33): 1-117, 1960.

(165) PETO, R. Epidemiology, multistage models, and short-term mutagenicity tests. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). Origins of Human Cancer. Book C: Human Risk Assessment. New York, Cold Spring Harbor Laboratory, 1977, pp. 1403-1428.

(166) POUR, P., KRUEGER, F.W., ALTHOFF, J., CARDESA, A., MOHR, U. Cancer of the pancreas induced in the Syrian golden hamster. American Journal of Pathology 76(2): 349-354, August 1974.

(167) RANDIG, K. Untersuchungen zur atiologie des bronchialkarzinoms (Investigations on the etiology of bronchialcarcinoma). Oeffentliche Gesundheitsdienst 16(9): 305-313, December 1954.

(168) ROED-PETERSEN, B., BANOCZY, J., PINDBORG, J.J. Smoking habits and histological characteristics of oral leukoplakias in Denmark and Hungary. British Journal of Cancer 28(6): 575-579, December 1973.

(169) ROCKEY, E.E., SPEER, F.D. The ill effects of cigarette smoking in dogs. International Surgery 46(6): 520-530, December 1966.

(170) ROTHMAN, K., KELLER, A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. Journal of Chronic Disease 25: 711-716, 1972.

(171) ROYAL COLLEGE OF PHYSICIANS. Smoking and Health. Summary and Report of The Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases. New York, Pitman Publishing Corporation, 1962, 70 pp.

(172) ROZENBILDS, J.G. Carcinoma of the larynx and hypopharynx in South Australia, 1952-1966. Medical Journal of Australia 2(6): 244-249, August 5, 1967.

(173) SACCOMANNO, G. U.S. Congress hearings before the Subcommittee on Research, Development and Radiation of the Joint Committee on Atomic Energy. 91st Congress, First Session on Radiation Standards for Uranium Mining, March 17-18, 1969.

(174) SADOWSKY, D.A., GILLIAM, A.G., CORNFIELD, J. The statistical association between smoking and carcinoma of the lung. Journal of the National Cancer Institute 13(5): 1237-1258, April 1953.

(*175*) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis. Progress in Experimental Tumor Research 11: 302-333, 1969.

(*176*) SAFFIOTTI, U. Experimental respiratory tract carcinogenesis and its relation to inhalation exposures. In: Hanna, M.G., Jr., Nettesheim, P., Gilbert, J.R. (Editors). Inhalation Carcinogenesis. Proceedings of a Biology Division, Oak Ridge National Laboratory Conference, Gatlinburg, Tennessee, October 8-11, 1969. Atomic Energy Commission, Division of Technical Information, AEC Symposium Series No. 18, April 1970, pp. 27-54.

(*177*) SAFFIOTTI, U., CEFIS, F., KOLB, L.H. A method for the experimental induction of bronchogenic carcinoma. Cancer Research 28: 104-124, January 1968.

(*178*) SANGHVI, L.D., RAO, K.C.M., KHANOLKAR, V.R. Smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. British Medical Journal 1(4922): 1111-1114, May 7, 1955.

(*179*) SCHMAEHL, D. Investigations on esophageal carcinogenicity by methyl-phenyl-nitrosamine and ethyl alcohol in rats. Cancer Letters 1(4): 215-218, 1976.

(*180*) SCHMAUZ, R., COLE, P. Epidemiology of cancer of the renal pelvis and ureter. Journal of the National Cancer Institute 52(5): 1431-1434, May 1974.

(*181*) SCHNEIDERMAN, M.A. Time trends: United States 1953-1973. Laryngoscope 88(1, Supplement 8): 6, 44-49, 1978.

(*182*) SCHOENBERG, B.S., BAILAR, J.C., III, FRAUMENI, J.F., JR., Certain mortality patterns of esophageal cancer in the United States, 1930-67. Journal of the National Cancer Institute 46(1): 63-73, January 1971.

(*183*) SCHOTTENFELD, D., GANTT, R.C., WYNDER, E.L. The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx, and lung: A prospective study. Preventive Medicine 3(2): 277-293, June 1974.

(*184*) SCHREK, R., BAKER, L. A., BALLARD, G. P., DOLGOFF, S. Tobacco smoking as an etiologic factor in disease. I. Cancer. Cancer Research 10(1): 49-58, January 1950.

(*185*) SCHWARTZ, D., DENOIX, P.-F., ANGUERA, G. Recherche des localisations du cancer associees aux facteurs tabac et alcool chez l'homme (Research on the localizations of cancer associates with tobacco and alcoholic factors in man). Bulletin de l'Association Francaise pour l'Etude du Cancer 44(2): 336-361, June 1957.

(*186*) SCHWARTZ, D., FLAMANT, R., LELLOUCH, J., DENOIX, P.-F. Results of a French survey on the role of tobacco, particularly inhalation, in different cancer sites. Journal of the National Cancer Institute 26(5): 1085-1108, May 1961.

(*187*) SEIDMAN, H., SILVERBERG, E., HOLLEB, A. I. Cancer statistics, 1976. A comparison of white and black populations. CA—A Cancer Journal for Clinicians 26(1): 2-13, January/February 1976.

(*188*) SELIKOFF, I. J., BADER,, R. A., BADER, M. E., CHURG, J., HAMMOND, E. C. Asbestosis and neoplasia. American Journal of Medicine 42(4): 487-496, April 1967.

(*189*) SELIKOFF, I. J., HAMMOND, E. C., CHURG, J. Asbestos exposure, smoking, and neoplasia. Journal of the American Medical Association 204(2): 104-110, April 8, 1968.

(*190*) SHETTIGARA, P. T., MORGAN, R. W. Asbestos, smoking, and laryngeal carcinoma. Archives of Environmental Health 30(10): 517-519, October 1975.

(*191*) SIMS, P., GROVER, P. L., SWAISLAND, A., PAL, K., HEWER, A. Metabolic activation of benzo(a)pyrene proceeds by a diol-epoxide. Nature 252: 326-328, November 1974.

(192) SMITH, L. W., BHARGAVA, K., MANI, N. J., MALAOWALLA, A.M., SILVERMAN, S., JR. Oral cancer and precancerous lesions in 57,518 industrial workers of Gujarat, India. Indian Journal of Cancer 12(2): 118-123, June 1975.

(193) STASZEWSKI, J. Palenie a rak wargi, jamy ustnej, migdalkow i krtani (Tobacco smoking and its relation to cancer of the mouth tonsils and larynx). Nowotwory 10(2): 121-132, 1960.

(194) STASZEWSKI, J. Palenie tytoniu a rak przelyku i zoladka oraz choroba wrzodowa (Tobacco smoking and its relation to carcinoma of the esophagus and stomach and to peptic ulcer). Polski Tygodnik Lekarski 16(8): 287-292, 1961.

(195) STASZEWSKI, J. Smoking and cancer of the urinary bladder in males in Poland. British Journal of Cancer 20(1): 32-35, March 1966.

(196) STELL, P. M. Smoking and laryngeal cancer. Lancet 1(7751): 617-618, March 18, 1972.

(197) STELL, P. M., MCGILL, T. Asbestos and laryngeal carcinoma. Lancet: 416-417, August 25, 1973.

(198) STOCKS, P. Cancer incidence in North Wales and Liverpool region in relation to habits and environment. British Empire Cancer Campaign Thirty-Fifth Annual Report (Supplement to Part 2): 66-95, 1957.

(199) SUGAR, L., BANOCZY, J. Follow-up studies in oral leukoplakia. Bulletin of the World Health Organization 41(2): 289-293, 1969.

(200) SUNDERMAN, F. W., DONNELLY, A. J. Studies of nickel carcinogenesis metastasizing pulmonary tumors in rats induced by the inhalation of nickel carbonyl. American Journal of Pathology 46(6): 1027-1041, June 1965.

(201) SUNDERMAN, F. W., DONNELLY, A. J., WEST, B., KINCAID, J. F. Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl. A.M.A Archives of Industrial Health 20(1): 36-41, July 1959.

(202) SUNDERMAN, F. W., KINCAID, J. F., DONNELLY, A. J., WEST, B. Nickel poisoning. IV. Chronic exposure of rats to nickel carbonyl; A report after one year of observation. A.M.A. Archives of Industrial Health 16(6): 480-485, December 1957.

(203) SVOBODA, V. An analysis of some possible epidemiological factors involved in carcinoma of the larynx. Neoplasma 15(6): 677-684, 1968.

(204) TAKANO, K., OSOGOSHI, K., KAMIMURA, N., KANDA, K., KANE, K., KAMIYAMA, R., SAKAMOTO, K., SATO, H., SHIRAI, Y., SEI, M., TANABE, T., HORINO, M., MINAMI, Y., MOTOJI, H., MORITA, R., ORIHATA, H., HIRAYAMA, T. Schokudogan no ekigaku, toku ni atsui inshokubutsu, inshu, kitsuen narabi, ni eiyo ketsubo ni tsuit (Epidemiology of esophageal cancer—with special reference to the significance of hot food and beverage drinking, smoking, and nutritional deficiency). Nihon Rinsho 26(8): 39-44, August 1968.

(205) TERRACOL, J., CALVET, J., MARQUES, P., COLL, J. Le tabac et le cancer du larynx (Tobacco and cancer of the larynx). Vie Medicale 48: 1149-1150, August 1967.

(206) TYLECOTE, F.E. Cancer of the lung. Lancet 2(4): 256-257, July 30, 1927.

(207) TYRRELL, A.B., MACAIRT, J.G., MCCAUGHEY, W.T.E. Occupational and Non-occupational factors associated with vesical neoplasm in Ireland. Journal of the Irish Medical Association 64(410): 213-217, April 22, 1971.

(208) TUYNS, A.J. Cancer of the oesophagus: Further evidence of the relation to drinking habits in France. International Journal of Cancer 5: 152-156, 1970.

(209) U. S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review: 1967. U. S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696, Revised, January 1968, 227 pp.

(210) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1968. Supplement to the 1967 Public Health Service Review. U. S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696, 1968, 117 pp.

(211) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1969. Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696-2, 1969, 98 pp.

(212) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report to the Surgeon General: 1971. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 71-7513, 1971, 458 pp.

(212a) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

(213) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1973. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 73-8704, 1973, 249 pp.

(214) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. (CDC)74-8704, 1974, 124 pp.

(215) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 76-8704, 1976, 235 pp.

(216) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. (CDC) 78-8357, 1976, 657 pp.

(217) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. 1103, 1964, 387 pp.

(218) VALKO, P. Koureni a vyskyt zhoubnych novotvaru hrtanu (Smoking and occurence of malignant tumors of the larynx). Ceskoslovenska Otolaryngologie 1: 92-105, 1952.

(219) VAN DUUREN, B.L. Tumor-promoting and co-carcinogenic agents in chemical carcinogenesis. In: Searle, C.E. (Editor). Chemical Carcinogens. ACS Monograph No. 173. Washington, D.C., American Chemical Society, 1976, pp. 24-51.

(220) VINCENT, R.G., MARCHETTA, F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx or larynx. American Journal of Surgery 106(3): 501-505, September 1963.

(221) VINCENT, R.G., PICKREN, J.W., LANE, W.W., BROSS, I., TAKITA, H., HOUTEN, L., GUTIERREZ, A.C., RZEPKA, T. The changing histopathology of lung cancer. A Review of 1682 cases. Cancer 39(4): 1647-1655, April 1977.

(222) VINCENT, T.N., SATTERFIELD, J.V., ACKERMAN, L.V. Carcinoma of the lung in women. Cancer 18(5): 559-570, May 1965.

(223) VOGLER, W.R., LLOYD, J.W., MILMORE, B.K. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. Cancer 15(2): 246-258, March-April 1962.

(224) WAGONER, J.K., ARCHER, V.E., CARROLL, B.E., HOLADAY, D.A., LAWRENCE, P.A. Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. Journal of the National Cancer Institute 32(4): 787-801, April 1964.

(225) WAGONER, J.K., ARCHER, V.E., LUNDIN, F.E., JR., HOLADAY, D.A., LLOYD, J.W. Radiation as the cause of lung cancer among uranium miners. New England Journal of Medicine 273(4): 181-188, July 22, 1965.

(226) WAGONER, J.K., MILLER, R.W., LUNDIN, F.E., JR., FRAUMENI, J.F., JR., HAIJ, M.E. Unusual cancer mortality among a group of underground metal miners. New England Journal of Medicine 269(6): 284-289. August 8, 1963.

(227) WATSON, W.L., CONTE, A.J. Smoking and lung cancer. Cancer 7(2): 245-249, March 1954.

(228) WEIR, J.M., DUNN, J.E., JR. Smoking and mortality: A prospective study. Cancer 25(1): 105-112, January 1970.

(229) WEISS, W. Lung cancer mortality and urban air pollution. American Journal of Public Health 68(8): 773-775, August 1978.

(230) WEISS, W., BOUCOT, K.R., SEIDMAN, H., CARNAHAN, W.J. Risk of lung cancer according to histologic type and cigarette dosage. Journal of the American Medical Association 222(7): 799-801, November 13, 1972.

(231) WELCH, R.M., LOH, A., CONNEY, A.H. Cigarette smoke: Stimulatory effect on metabolism of 3, 4-benzpyrene by enzymes in rat lung. Life Science 10(Part I): 215-221, 1971.

(232) WICKEN, A.J. Environmental and personal factors in lung cancer and bronchitis mortality in Northern Ireland, 1960-62. London, Tobacco Research Council, Research Paper No. 9, 1966, 84 pp.

(233) WILLIAMS, R.R., HORM, J.W. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. Journal of the National Cancer Institute 58(3): 525-547, March 1977.

(234) WYNDER, E.L. The epidemiology of cancers of the upper alimentary and upper respiratory tracts. Laryngoscope 88(1, Part 2): 50-51, January 1978.

(235) WYNDER, E.L., BROSS, I.J. A study of etiological factors in cancer of the esophagus. Cancer 14(2): 389-413, March-April 1961.

(236) WYNDER, E.L., BROSS, I.J., CORNFIELD, J., O'DONNELL, W.E. Lung cancer in women. A study of environmental factors. New England Journal of Medicine 255(24): 1111-1121, December 13, 1956.

(237) WYNDER, E.L., BROSS, I.J., DAY, E. A study of environmental factors in cancer of the larynx. Cancer 9(1): 86-110, January-February 1956.

(238) WYNDER, E.L., COVEY, L.S., MABUCHI, K., MUSHINSKI, M. Environmental factors in cancer of the larynx. A second look. Cancer 38(4): 1591-1601, October 1976.

(239) WYNDER, E.L., BROSS, I.J., FELDMAN, R.M. A study of the etiological factors in cancer of the mouth. Cancer 10(6): 1300-1323, November-December 1957.

(240) WYNDER, E.L., GOLDSMITH, R. The epidemiology of bladder cancer. A second look. Cancer 40(3): 1246-1268, September 1977.

(241) WYNDER, E.L., GORI, G.B. Contribution of the environment to cancer incidence: An epidemiological exercise. Journal of the National Cancer Institute 58(4): 825-832, April 1977.

(242) WYNDER, E.L., GRAHAM, E.A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. Journal of the American Medical Association 143(4): 329-336, May 27, 1950.

(243) WYNDER, E.L., HECHT, S. (Editors). Lung Cancer. A Series of Workshops on the Biology of Human Cancer. Report No. 3. UICC Technical Report Series-Volume 25. Geneva, International Union Against Cancer, 1976, 170 pp.

(244) WYNDER, E.L., HOFFMANN, D. The epidermis and the respiratory tract as bioassay systems in tobacco carcinogenesis. British Journal of Cancer 24(3): 574-587, September 1970.

(245) WYNDER, E.L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, 730 pp.

(246) WYNDER, E.L., HULTBERG, S., JACOBSSON, F., BROSS, I.J. Environmental factors in cancer of the upper alimentary tract. A Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. Cancer 10(3): 470-487, May-June 1957.

(247) WYNDER, E.L., MABUCHI, K., BEATTIE, E.J., JR. The epidemiology of lung cancer. Recent trends. Journal of the American Medical Association 213(13): 2221-2228, September 28, 1970.

(248) WYNDER, E.L., MABUCHI, K., MARUCHI, N., FORTNER, J.G. A case control study of cancer of the pancreas. Cancer 31(3): 641-648, March 1973.

(248a) WYNDER, E.L., MABUCHI, K., WHITMORE, W.F., JR. Epidemiology of adenocarcinoma of the kidney. Journal of the National Cancer Institute 53(6): 1619-1634, December 1974.

(249) WYNDER, E.L., MUSHINSKI, M.H., SPIVAK, J.C. Tobacco and alcohol consumption in relation to the development of multiple primary cancers. Cancer 40(4): 1872-1878, October 1977.

(250) WYNDER, E.L., NAVARRETE, A., AROSTEGUI, G.E., LLAMBES, J.L. Study of environmental factors in cancer of the respiratory tract in Cuba. Journal of the National Cancer Institute 20(4): 665-673, April 1958.

(251) WYNDER, E.L., ONDERDONK, J., MANTEL, N. An epidemiological investigation of cancer of the bladder. Cancer 16(11): 1388-1407, November 1963.

(252) WYNDER, E.L., STELLMAN, S.D. Comparative epidemiology of tobacco-related cancers. Cancer Research 37: 4608-4622, December 1977.

(253) WYNDER, E.L., STELLMAN, S.D. The impact of long-term filter cigarette usage on lung and larynx cancer. Journal of the National Cancer Institute 62(3): March 1979. (In press)

(254) YESNER, R. Histologic typing of lung cancer with clinical implications. Frontiers of Radiation Therapy and Oncology 9: 140-150, 1974.

(255) YOSHIDA, O., MIYAKAWA, M., HARADA, T., OKADA, K. Bokogan no ekigaku ni okeru mondaiten (Problem points in epidemiology of bladder cancer). Nihon Rinsho 26(8): 66-77, August 1968.

6. NON-NEOPLASTIC BRONCHOPULMONARY DISEASES.

CONTENTS

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Introduction

The chronic non-neoplastic bronchopulmonary diseases pose a major worldwide health challenge. The chronic obstructive lung diseases (COLD), chronic bronchitis, and emphysema comprise the majority of these illnesses and rank second only to coronary artery disease as a cause of Social Security-compensated disability (*73*). Previous reports on the health consequences of smoking (*141-149*) have reviewed the relationship between smoking and these disorders. They are summarized below.

Cigarette smoking is the most important cause of COLD. Cigarette smokers have higher mortality rates from chronic bronchitis and emphysema, an increased prevalence of respiratory symptoms, and diminished performance on pulmonary function testing compared to nonsmokers. These differences become more marked as the number of cigarettes smoked increases. Cigarette smokers without respiratory symptoms have evidence of small airway dysfunction more frequently than do nonsmokers. The relationship between cigarette smoking and COLD has been demonstrated in many different national groups and is more striking in men than in women. Pipe and cigar smokers have higher morbidity and mortality rates from COLD than do nonsmokers but are at lower risk for COLD than are cigarette smokers.

Certain occupational exposures are associated with an increased incidence of COLD, but the relationship is not as strong as for cigarette smoking. The combination of these occupational hazards and cigarette smoking has been observed in many studies to result in additive effects on morbidity from COLD. Exposures to cotton fiber, asbestos, and coal dust in particular appear to act in concert with cigarette smoking in promoting the development of pulmonary disease. The impact of cigarette smoking in the development of coal workers' pneumoconiosis is unclear. Although air pollution may contribute to the prevalence of symptoms of respiratory disease, cigarette smoking is far more important in producing respiratory disease. Cigarette smoking and air pollution may interact to produce higher rates of pulmonary disease than are seen with either factor alone.

Cigarette smokers experience an increased risk for respiratory problems other than COLD. They experience more frequent respiratory tract infections. In response to mild viral respiratory illness cigarette smokers develop abnormal but reversible changes in certain pulmonary function tests. Cigarette smokers have more protracted respiratory symptoms following mild viral illness and are at greater risk for developing postoperative respiratory complications and possibly spontaneous pneumothorax as compared to nonsmokers.

Cigarette smokers who die from diseases other than COLD have anatomic evidence of COLD more frequently than do nonsmokers. Autopsy studies have shown a dose-response relationship between cigarette smoking and the microscopic changes of COLD. Histologic

evidence of bronchiolitis may be more common in cigarette smokers than in nonsmokers.

Increased susceptibility to and premature development of emphysema occurs in individuals with severe genetically determined deficiencies of an antiprotease, alpha-1-antitrypsin. There is some evidence that smoking hastens the development of COLD in such individuals but it is unknown whether smoking places subjects with less severe types of deficiency at a greater risk for developing emphysema.

Experimental animal and human data have demonstrated that inhalation of cigarette smoke impairs pulmonary clearance, ciliary function, and alveolar macrophage activity. Pathological changes of emphysema and fibrosis have been noted in dogs trained to inhale cigarette smoke through a tracheostoma; these changes follow a dose-response relationship.

Many recent studies confirm and extend these observations. In addition, there have been considerable advances in our understanding of the relationship of smoking to the natural history and pathogenesis of these disorders. In the following discussion, these relationships will be examined in subjects of all ages as well as in animal models. Evidence will be presented documenting the effects of smoking on the integrity of the bronchopulmonary system, and the proposed pathogenetic mechanisms will be reviewed. Finally, a number of other risk factors which may interact with smoking in producing lung damage will be scrutinized.

Definitions

The terms chronic bronchitis and emphysema have been used diagnostically for many years, but the criteria on which each diagnosis rests have only recently been stated clearly (*54*). Physicians often use these terms interchangeably to describe a patient with chronic airflow obstruction. The confusion between chronic bronchitis and emphysema has been compounded further by the manner in which they have been defined by various scientific societies, in different studies, and in different nations (*55*).

Clinically pure forms of chronic bronchitis and emphysema are the exceptions rather than the rule. They are often difficult to distinguish from each other in patients with chronic airflow obstruction because (1) some degree of each may coexist in the same patient; (2) both disorders are usually characterized by expiratory flow obstruction; and (3) patients with either disorder frequently present the same symptom: dyspnea on exertion. Consequently the clinician often labels the patients with chronic expiratory flow obstruction as having COLD.

The most widely accepted definitions in the United States are those of a joint committee of the American College of Chest Physicians and the American Thoracic Society (*4*):

Bronchitis: A non-neoplastic disorder of structure or function of the bronchi resulting from infectious or noninfectious irritation. The term bronchitis should be modified by appropriate words or phrases to indicate its etiology, its chronicity, the presence of associated airways dysfunction, or type of anatomic change. The term chronic bronchitis, when unqualified, refers to a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucous hypersecretion and certain structural alterations in the bronchi. Anatomic changes may include hypertrophy of the mucous secreting apparatus and epithelial metaplasia, as well as more classic evidence of inflammation. In epidemiologic studies, the presence of cough or sputum production on most days for at least three months of the year has sometimes been accepted as a criterion for the diagnosis.

Pulmonary Emphysema: An abnormal enlargement of the air spaces distal to the terminal nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls. The term emphysema may be modified by words or phrases to indicate its etiology, its anatomic subtype, or any associated airways dysfunction.

COLD: This term refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration. It is recommended that a more specific term, such as chronic obstructive bronchitis or chronic obstructive emphysema, be used whenever possible.

It should be noted that these definitions may have serious inadequacies (*138*), particularly when applied to longitudinal studies assessing the natural history of COLD (*56*). In the following discussion, cognizance is taken of these limitations.

Smoking and Respiratory Mortality

Numerous retrospective and prospective studies have shown a greatly increased mortality from COLD among smokers as compared to nonsmokers. Results from the major prospective studies relating smoking to mortality from COLD are presented in the Chapter on Mortality and reproduced in Table 1. These studies represent over 13 million patient years of observation and approximately 270,000 deaths from all causes. The number of deaths related to COLD is probably underestimated since some of the deaths attributed to pneumonia or myocardial disease may have been due to complications of COLD. In addition, these mortality figures do not include a sizeable number of individuals for whom COLD may have been a major contributory cause of death. For example, it is not uncommon for individuals to have COLD and lung cancer simultaneously.

TABLE 1.—COLD mortality ratios in six prospective studies

	British Doctors	Men in 25 States 45–64	Men in 25 States 65–79	U.S. Veterans	Canadian Veterans	Men in 9 States	California Occupations
Emphysema and/or bronchitis	24.7	—	—	10.08	—	2.30	4.3
Emphysema without bronchitis	—	6.55	11.41	14.17	7.7	—	—
Bronchitis	—	—	—	4.49	11.3	—	—

SOURCE: See Table 41 of Chapter 2. Mortality.

TABLE 2.—Smoking habit when last asked and death from chronic bronchitis and emphysema

No. of deaths	Annual death rate per 100,000 men, standardized for age							X^2	
	Non-smokers	Current or ex-smoker	Ex-smoker	Current smokers any tobacco	Current smokers any tobacco (g/day)			Nonsmokers vs other	Trend (dose-response)
					1–14	15–24	25		
254	3	48	44	50	38	50	88	25.58*	47.23*

*$p<0.001$
SOURCE: Doll, R. (42)

Doll and Peto (42) have recently reported their 20-year followup of 34,440 British male physicians. The data, presented in Table 2, demonstrate an increased mortality ratio in all current smokers and a dose-response relationship to the number of cigarettes smoked. They also found a 1.5-fold higher death rate in smokers who inhaled as compared to smokers who did not inhale. The mortality in individuals who quit smoking increased during the fifth to ninth year but thereafter fell sharply (Table 3). The authors suggest that the men who died during this period from lung disease stopped smoking because they had irreversible disabling disease such that a few more years of normal functional decline resulted in their death.

Smoking and the Natural History of COLD

The adverse effects on the lungs of smoking have been demonstrated in very young, working age, and elderly populations. Although there is a clear relationship between the presence of COLD and a prior history of smoking, only a small proportion of smokers are severely disabled and die from COLD. Therefore, many investigators have scrutinized the natural history of smoking-related lung changes in an attempt to identify smokers at increased risk of developing COLD. Three methods have been employed: clinical, physiological, and pathological.

TABLE 3.—Mortality from chronic bronchitis, emphysema, and pulmonary heart disease in ex-cigarette smokers compared with mortality in lifelong nonsmokers

No. of deaths divided by number expected in lifelong nonsmokers. Years since stopped smoking					No. of deaths in lifelong nonsmokers
0*	5	5–9	10–14	>15	
35.6	34.2	47.7	7.3	8.1	2

*Current smokers are described as having stopped 0 years ago.
SOURCE: Doll, R. (*42*)

Clinical data are more readily obtained than pathological or physiological data. However, the relationship of early respiratory symptoms to subsequent development of COLD is unclear. Physiological data can be quite specific (disease versus no disease), but, until recently, functional tests were unable to detect the early effects of smoking on lung function. Tests of small airway function may identify such a stage, i.e., airways abnormality prior to symptoms and before airflow reduction can be measured by conventional spirometry. However, longitudinal studies demonstrating that individuals with abnormal tests of small airway function are at greater risk for COLD are unavailable. Pathological data are the most specific and sensitive parameters relating smoking to lung changes but generally are inaccessible during life. A few studies are now available relating lung pathology to smoking in young individuals.

Youthful Smoking and Respiratory Morbidity

A number of recent studies have established a higher prevalence of respiratory symptoms in adolescent, teenage, and young adult smokers as compared to nonsmokers. Bewley and Bland (*13*) examined the relationships between smoking and the prevalence of respiratory symptoms in 14,033 children aged 10 to 12-1/2 in two separate areas of the United Kingdom. In this questionnaire survey, 4.7 percent acknowledged smoking at least one cigarette per week ("smoker") and about 1 percent of the boys smoked more than one cigarette per day. Male smokers, who outnumbered female smokers threefold, reported more morning cough (17.4 to 6.4 percent), cough during the day or night (41.4 to 20.5 percent), and cough of 3 months duration (14.5 to 4.8 percent) than their nonsmoking classmates. These relationships were similar to those in females although based on smaller numbers of smokers.

Rush (*123*), in a survey of 12,595 high school students in Rochester, New York, found that reported respiratory symptoms (regular cough, phlegm production, and/or wheezing) strongly correlated with smok-

ing. In a re-survey (*122*) done a year later of a segment of this population (2,749 white students), he found a similar rate of smoking for both girls and boys (30.2 and 32.4 percent, respectively). Cessation of smoking resulted in only partial reversibility of respiratory symptoms within this time interval.

Kiernan, et al. (*80*) surveyed the respiratory symptoms and smoking habits of a British population of 25-year-olds followed since birth and previously examined at age 20. Current smokers had a 6.8 percent crude prevalence rate of cough, day or night, as compared to a 3.1 percent rate for those who had never smoked. Individuals who were smokers at age 20 and 25 had an 11.6 percent prevalence of symptoms, and individuals who had smoked at 20 but were ex-smokers at 25 had a 3.9 percent prevalence of symptoms.

In summary, these clinical data suggest that cigarette smoking even in these young age groups produces pulmonary symptoms. Cessation of smoking leads to at least partial resolution of symptoms. Pulmonary function (*127*) and histologic (*112*) abnormalities also have been observed in young smokers, confirming clinical suspicions of lung injury in this group.

Early Stages of Respiratory Dysfunction

In an effort to identify individuals at high risk for developing COLD, a number of investigators have examined the relationship of smoking to physiological changes not detectable by standard spirometry. Individuals with functional abnormalities in tests of small airway function may be such a high risk group. Anthonisen, et al. (*5*) observed abnormalities of regional gas exchange, as determined by inhaling ^{133}Xe, in a group of individuals with mild chronic bronchitis and well preserved lung function as measured spirometrically. The authors attributed these abnormalities to peripheral airway disease and suggested that the functionally important lesions in chronic bronchitis might be in the peripheral airways. Other investigators showed that airways less than 2 mm contributed little to the total pulmonary resistance in patients with normal lungs but were the main site of airflow obstructions in patients with chronic bronchitis and emphysema (*19*, *69*, *97*). These earlier reports led to the development of tests believed to measure small airway function.

A decrease in the ratio of dynamic to static compliance with increases in respiratory frequency was demonstrated by Woolcock, et al. (*160*) in a group of bronchitics with normal standard spirometry. This "frequency dependence of compliance" test appears to be a sensitive indicator of small airway dysfunction but it is cumbersome to perform and available in few laboratories.

The measurement of closing volume and of the slope of the alveolar plateau on a single breath nitrogen washout (*6*) are technically easier to record and have been widely applied in epidemiological surveys. The

closing volume is the lung volume at which the dependent lung zones stop contributing to the expired air flow and when expressed as a percent of total lung capacity is called closing capacity. The slope of the alveolar plateau is usually measured as the change in nitrogen concentration per liter. The precise physiologic event that this test measures is unclear, but it is thought to reflect the degree of homogeneity of ventilation and, when abnormal, to be a sensitive indicator of small airways dysfunction.

Maximum expiratory flow rates at 25 and 50 percent of vital capacity (*59*) measure flow at lung volumes where the resistance of the small airways comprises a larger proportion of the total resistance. Such measurements appear to be of particular value in assessing small airway function when performed before and after inhalation of an 80 percent helium and 20 percent oxygen mixture (*72*). Changes in both maximal flow rates and changes in the lung volume at which the same flow is achieved (volume of isoflow) indicate small airways dysfunction.

Several reports have demonstrated a higher prevalence of abnormalities in these tests of small airways function in smokers as compared to nonsmokers. However, as can be seen in Table 4, studies show wide variability in the percent of smokers demonstrating an abnormal test. Such variability most likely reflects testing of different populations (random vs. selected), the use of different standards of normalcy, and the application of different techniques for the same test. As can be seen from Table 4, a dose-response relationship often exists between the intensity of smoking and the percent of smokers with abnormal tests.

In a recent study, Dosman, et al. (*43*) examined the relationship between respiratory symptoms and tests of small airway function in clinically healthy cigarette smokers. They found that the presence of individual symptoms (cough, sputum, wheezing, and shortness of breath) correlated poorly or not at all with measured values for dynamic lung compliance, closing volume, closing capacity, slope of the alveolar plateau, and helium-oxygen flow curves. Moreover, 53 percent of their smoking population conformed to the American Thoracic Society criteria for a diagnosis of chronic bronchitis although all had a forced expiratory volume $FEV_1 \geq$ 70 percent. They suggested that symptoms could not be used to detect smokers who have abnormalities of small airway function.

The insensitivity of certain respiratory symptoms in the adult as a predictor of future development of COLD has been emphasized by Fletcher, et al. (*57*) in a prospective study of 792 men, aged 30 to 59, who were followed for 8 years. They found that smoking was strongly related to the presence of symptoms (mucous hypersecretion) and to the development of airflow obstruction (loss of forced expiratory volume), but they could find no relationship between mucous

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
Buist, A.S. 1973 USA (*20,21*)	524 cigarette smokers attending an emphysema screening center	all smokers	35	44	47				11	
		<20 pack years	28	31						
		20–40 pack years	33	45						
		>40 pack years	49	64						
Benson, M.K. 1974 Great Britain (*12*)	214 heavy male smokers, aged 20–55; 75 non-smoking controls	young (20–30)	12		6				4	
		middle aged (40–55)	34		21				20	
Dirksen, H. 1974 Sweden (*41*)	58 randomly selected smokers, aged 59; 38 nonsmoking controls		53	66					43	
Hutcheon, M. 1974 Canada (*72*)	17 mild smokers selected from hospital personnel, aged 27.6 ± 3.2 years; 18 age-matched controls[b]			23.5		48[c]–67[d]				12
Marco, M. 1976 Belgium (*103*)	71 volunteer smokers with *normal* spirometric testing	Smokers	18.5		20.3					0
		Ex-smokers	11.7		11.9					0
		All smokers	23.9		25					0

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers—Continued

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
McCarthy, D.J. 1976 Winnipeg (*106*)	131 volunteers from a smoking cessation clinic - varying smoking history[b]		48	9	42				30	13
Armstrong, J.G. 1976 Australia (*7*)	101 asymptomatic smokers and 20 nonsmoking controls aged 18–39	iight smokers heavy smokers	10 30		28 34				0 4	
Fairshter, R.D. 1977 USA (*50*)	18 asymptomatic mild smokers aged 29.8±5.4 yrs. 24 volunteer non-smoking controls	none				55.6				
Knudson, R.J. 1977 USA (*85*)	1900 white randomly selected subjects aged 25-54. (426 smokers)	symptomatic smokers (n=150) asymptomatic smokers (n=276)	9.1 6.0	12.9 8.7	30.4 15.4					
Cherniack, R.M. 1977 USA, Canada (*31*)	1456 randomly selected subjects from 3 cities (40% smokers) aged 25-54.	Montreal (n=275) Men Women	 15 14	 28 17	 14 19					 10 14
		Portland (n=208) men women	 15 36	 22 30	 17 47					 3 15

TABLE 4.—Prevalence of abnormalities in tests of small airway function in smokers—Continued

Author Year Country Reference	Number and type of population	Sub-groups	% smokers with abnormal test[a]							
			CV%	CC%	$\frac{\Delta N_2}{L}$	VisoV	V_{max25}	V_{max50}	$FEV_{1.0}$	FEV%
Cherniack, R.M. 1977 USA, Canada (*31*) (Cont'd)	1456 randomly selected subjects from 3 cities (40% smokers) aged 25-54.	Winnipeg (n = 112)								
		men	14	28	12					23
		women	20	26	20					26
		combined	17	25	23					
Oxhoj, H. 1977 Sweden (*114*)	502 randomly selected 50 and 60 year old male smokers - 129 nonsmoking controls[b]	50-year-old men								
		ex-smokers	13	18	32		2	5	10	10
		moderate smokers	9	15	41		3	5	18	7
		heavy smokers	12	20	58		7	10	37	22
"	"	60-year-old men								
		ex-smokers	10	17	18		2	4	15	10
		moderate smokers	19	24	38		2	17	22	18
		heavy smokers	23	22	45		1	18	22	22
Manfreda, J. 1977 Canada (*98,100*)	534 randomly selected smokers and ex-smokers aged 24–55	Men (n = 301)								
		Smokers	21.1	28.7	45.4		24.1	19.8	13.4	12.8
		ex-smokers	14.2	17.0	25.5		22.8	21.9	11.4	7.9
		Women (n = 233)								
		smokers	6.7	6.7	45.3		24.7	32.3	25.9	8.2
		ex-smokers	4.4	5.9	19.1		12.0	20	18.7	6.7

Footnotes on following page.

TABLE 4.—Footnotes

FEV = Forced expiratory volume
$FEV_{1.0}$ = FEV in 1 second
VC = vital capacity
FVC = forced vital capacity
FEV% = $FEV_{1.0}$/FVC x 100
V_{max} = maximum flow
V_{max} 50 = maximum flow at 50% of vital capacity
V_{max} 25 = maximum flow at 25% of vital capacity
CV = closing volume
RV = residual volume
TLC = total lung capacity
CV% = CV/VC x 100
CC% = (RV + CV)/TLC x 100
$\Delta N_2/L$ = slope of the alveolar plateau
VisoV = volume of isoflow

[a]abbreviations and definitions of pulmonary function tests
[b]estimated from bar graph
[c]obtained from spirometry
[d]obtained from plethysmography

hypersecretion and airflow obstruction. They suggested that there is a susceptible population of smokers who develop a more rapid decline in forced expiratory volume, eventuating in severe obstructive lung disease.

Pathological evidence of the effects of smoking on small airway histology was presented by Niewoehner, et al. (*112*) in an autopsy study of 39 men (20 nonsmokers, 19 smokers) who died suddenly from nonrespiratory causes. They observed a respiratory bronchiolitis in the lungs of smokers but rarely observed these changes in nonsmokers ($p<0.002$). They postulated that these changes were precursors of emphysema and responsible for the subtle function abnormalities observed in young smokers. In a second autopsy study of 168 male victims of sudden death aged 16 to 65, Kleinerman and Rice (*83*) age-matched 18 nonsmokers and 18 smokers. They observed significantly more chronic bronchiolitis, emphysema, and parenchymal pigmentation in lung tissue in smokers versus nonsmokers.

Prospective pathological evidence that abnormalities in tests of small airway function reflect structural alterations in small airways has recently been presented by Cosio, et al. (*37*). They examined the relationship between preoperative pulmonary function tests and graded pathologic lesions in the small airways (Group I-IV) in 36 patients (30 smokers, 4 ex-smokers, 2 nonsmokers) who went to surgery for an open lung biopsy (localized disease). These data are presented in Figure 1. Subjects with the lowest pathological score (Group I) were younger, had smoked fewer cigarettes, and had a normal FEV_1 percent. Subjects with minimal pathologic changes, Group II, could be separated from Group I (least pathological changes) by several tests of small airway function (closing capacity, volume of isoflow comparing air and helium on the flow volume curve, and slope of the alveolar plateau). The mean cigarette consumption in Group II was more than twice that of Group I. Group II-IV subjects demonstrated progressively abnormal function tests but only Group IV demonstrated a substantial amount of emphysema. The authors concluded that structural abnormalities in the small airways can be detected in living patients with normal FEV_1 percent by tests of small airway function. However, as noted by Thurlbeck (*140*), the maximum mid-expiratory flow rates also showed changes that were close to significant in Group I and II diseases.

These findings lend support to the postulated natural history of smoking induced lung changes advanced by Dosman, et al. (*44, 45*). They suggest that the effects of smoking on the lung are sequential, beginning with changes in the peripheral airways and progressing through stages of alterations in the mechanical properties of alveolar walls and loss of elastic recoil, and finally leading to the overt development of chronic bronchitis and emphysema with a reduction of

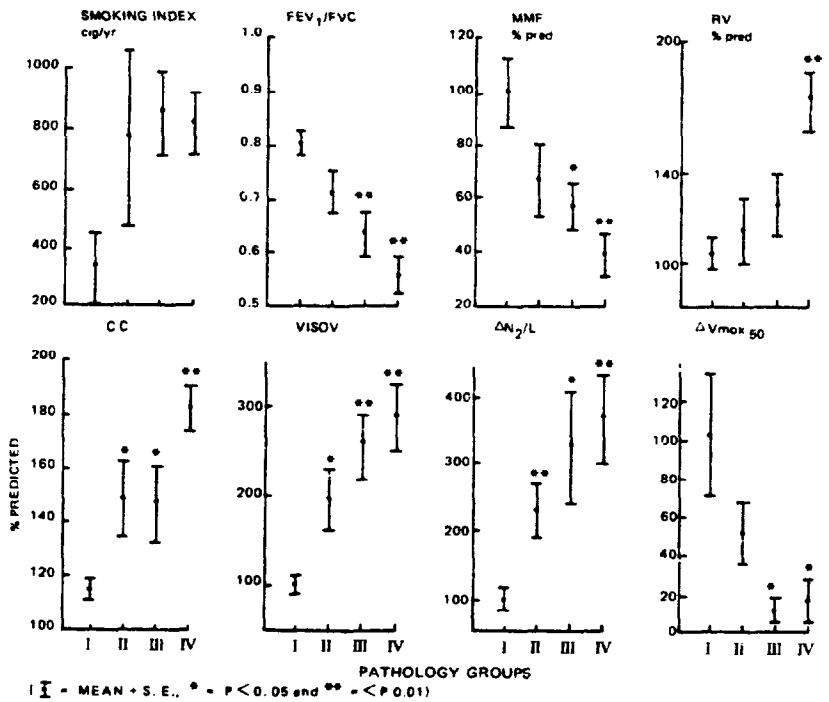

FIGURE 1.—Comparison of increasing small airways disease (Group I–IV) to smoking and pulmonary function

SOURCE: Cosio, M. (*37*)

FEV_1 percent. However, the mechanisms responsible and the demonstration of such a sequence remain to be demonstrated.

In summary, a variety of function abnormalities believed to represent small airway dysfunction occur in smokers. Many such individuals demonstrate normal expiratory flow rates as measured by conventional spirometry. In one prospective study abnormalities in tests of small airway function appeared to correlate well with pathologic abnormalities of the peripheral airways. It has been suggested that such changes may be precursors of further abnormality if smoking were continued; however, prospective studies relating small airway physiological and/or pathological abnormalities to the subsequent development of COLD are lacking.

Respiratory Morbidity in the Adult

In 1970, in the United States, the combined prevalence of chronic bronchitis for members of both sexes over age 17 was 29.5 per 1,000

population, and for emphysema it was 9.8 per 1,000 population. In 1970, persons with chronic bronchitis lost, on the average, 1.4 workdays per year, while those with emphysema lost more than 5 workdays per year due to disability from these diseases.

The relationship between smoking and an increased prevalence of respiratory symptoms in the adult has been well established in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community (*141, 145*). Such symptoms, particularly cough and sputum production, increase with increasing dosage of cigarettes smoked. The association of smoking with wheezing is similar, though less marked, to that seen with cough and sputum. Chest illness during the past 3 years, cough lasting 2 weeks or more, and breathlessness are usually more prevalent in smokers than in nonsmokers, but evidence for a dose-response is inconsistent. This may be related to a decision by the smoker to reduce cigarette consumption upon recognition of such symptoms (*67*).

COLD is more common in men than in women; however, these differences must be corrected for differences in the smoking habit, since there are more male than female smokers. A number of earlier studies found conflicting data regarding the prevalence of symptoms in women with smoking habits equivalent to those in men (*139*).

Lebowitz and Burrows (*90*), in a recent study of 2,857 randomly selected subjects aged 14 to 96, found no significant differences in the prevalence of symptoms in younger men and women with equivalent smoking habits. However, male symptom rates were consistently higher above the age of 60 and in ex-smokers with a greater than 20 pack-year smoking history.

In a survey of 500 working women, aged 25 to 54, Woolf (*161*) noted a strong correlation between the number of cigarettes smoked and the prevalence of respiratory symptoms (cough, sputum production, wheezing, and shortness of breath). In comparing these results to published data on men, Woolf concluded that smoking had similar adverse effects on the respiratory system in women and men.

The relationship between smoking and acute respiratory infection was examined by Monto, et al. (*110*) in individuals with COLD and in two similar groups (comparable in age, sex, number of family members) with no history of flow obstruction or chronic bronchitis. The presence of respiratory illness was ascertained weekly, usually by telephone. The presence of infection was evaluated by serological tests for several viruses, Mycoplasma pneumoniae, and Hemophilus influenzae performed three times during the year. Among bronchitics, infections (as measured by serological tests) were more frequent in smokers than in nonsmokers; however clinical respiratory illness was greater in nonsmokers. The authors suggest that this disparity may be due to different perception of mild symptoms as disease in the two groups.

In summary, these data suggest that adult cigarette smokers have respiratory symptoms more frequently than do nonsmokers and that at least some symptoms (i.e., cough and sputum production) increase with a greater dosage of cigarettes. While it is clear that COLD is more common in men than in women, it is uncertain whether men and women with equivalent smoking histories have a similar increase in the prevalence of respiratory symptoms and COLD.

Ventilatory Function

Subtle, functional abnormalities (i.e., in tests of small airway function) have been recognized in smokers in whom standard spirometric measures are normal. These studies were reviewed in a previous section. It is generally recognized that the standard pulmonary function tests only become abnormal late in the pathological process, perhaps after some irreversible structural changes have occurred.

The majority of epidemiological surveys investigating the prevalence of functional abnormalities in smokers have employed measurements of ventilatory capacity, usually FEV. Measurements of airways resistance, diffusing capacity, lung volumes, and nitrogen mixing have been used much less frequently.

These studies, which were recently reviewed by Higgins (*67*), have confirmed that lung function is consistently worse in smokers than in nonsmokers. One major exception to this finding was a report on a study from the Kaiser Permanente multiphasic health check clinic (*128*) in which 65,086 white, black, and oriental smokers and nonsmokers, aged 20 to 79, answered a self-administered questionnaire about smoking habits and underwent pulmonary function testing. Significant differences were observed between white male and female smokers and nonsmokers with respect to their performance on pulmonary function tests. However, differences were not observed between black and oriental smokers and nonsmokers. An explanation was not readily apparent.

In a survey of New York City postal and transit workers, Densen, et al. (*40*) found the lowest values for FEV_1 among cigarette smokers. Stebbings (*133*), in a further analysis of Densen's data, noted significantly less decline in FEV_1 among black smokers when compared to white smokers. This difference persisted even when corrections were made for differences in amount smoked, age at which smoking began, inhalation patterns, and smaller initial lung volumes in blacks. Black and white nonsmokers did not differ in the rate of decline in FEV_1. By age 60, blacks who smoked one pack per day had a .34 liter smaller cumulative decrease in FEV_1 than whites who smoked the same amount.

In a study of male-female differences in pulmonary function of young smokers with similar smoking history, Enjeti, et al. (*47*) found abnormalities in tests of small airway function in males, but not in

female smokers. They suggested that men respond differently to habitual cigarette smoking at an earlier stage than do women.

Few reports have shown a consistent dose-response relationship between cigarette smoking and functional abnormality. In a recent study, Burrows, et al. (*23*) demonstrated an inverse relationship between ventilatory function and pack-years, even in subjects who denied cough and sputum.

The long-term effects of cigarette smoking on lung function have been examined in several prospective studies. These have usually shown that the rate of decline of FEV in smokers is greater than in the nonsmoker (*67*). This was again suggested in the 10-year followup of the Framingham cohort (*8*).

In a large prospective study of London working men, Fletcher, et al. (*57*) recognized a "susceptible" group of smokers whose rate of decline in FEV was steeper than that for nonsmokers. However, there was another group of smokers who lost FEV almost as slowly as did nonsmokers. The authors suggest that the effect of smoking on FEV in "susceptible" individuals may be underestimated by focusing on the mean FEV of all smokers, as is usually done in prevalence surveys. As noted earlier, they found no relationship between the rate of decline in FEV and productive cough when smoking habits were taken into account. This is in conflict with Gregg's data (*62*), in which only smokers with bronchial hypersecretion were likely o develop functional decline.

In summary, the majority of epidemiological surveys have found a higher prevalence of functional abnormalities in smokers as compared to nonsmokers. There are conflicting data as to the effect of smoking on pulmonary function in different racial groups and whether men and women with equivalent smoking habits have similar reductions in pulmonary function. It is clear that cigarette smoking produces a more rapid decline in FEV and a higher prevalence of productive cough. However, it is unclear whether the presence of productive cough by itself predicts the risk for a more rapid decline in FEV independent of that increased risk associated with cigarette smoking. It has been suggested that there may be a "susceptible" group of smokers whose rate of decline in FEV is much greater than that in both "unsusceptible" smokers and nonsmokers and that "unsusceptible" smokers and nonsmokers have similar rates of decline in FEV. Therefore, prevalence surveys of functional abnormalities in all smokers may underestimate the impact of cigarette smoking in the "susceptible" population.

Cessation and Reversibility of Functional Changes

Smoking cessation results in a reduced prevalence of symptoms in all age groups and in reduced mortality rates. The effects of smoking cessation on pulmonary function have been considered at various stages of functional abnormality.

Buist, et al. (*22*) followed a group of 75 smokers attending a smoking cessation clinic and observed significant improvement in closing volume, closing capacity, and the slope of the alveolar plateau at 6 and 12 months in subjects who stopped smoking. McCarthy, et al. (*105*) found similar improvement in 131 subjects who stopped smoking; resumption of smoking led to subsequent development of abnormalities in the slope of the alveolar plateau and closing capacity. These findings are especially pertinent in view of the suggestion by Cosio, et al. (*37*) that some of the pathologic changes present when tests of small airway functions are abnormal can be reversed.

As a group, ex-smokers usually perform better on conventional pulmonary function testing than smokers, but they do not perform as well as nonsmokers (*67*). Several studies have confirmed that there is improvement in performance on standard spirometric function tests following cessation of smoking in small numbers of patients (*85*, *115*, *159*), but there is still debate as to whether the normal decline in ventilatory function (i.e., FEV) is accelerated in ex-smokers as compared to nonsmokers. In the Framingham study, Ashley, et al. (*8*) observed that men and women who continued to smoke had a greater decline in forced vital capacity (FVC) than those who stopped; however, they could not demonstrate consistent changes in the FEV_1 following smoking cessation. They attributed this to the impreciseness and insensitivity of the FEV_1 measurement. In women ex-smokers, the decline in FVC was similar to that of female nonsmokers; in male ex-smokers, the decline in FVC was slightly greater than that of male nonsmokers. Fletcher, et al. (*57*) observed that cessation of smoking halved the rate of loss of FEV and returned the rate of decline in FEV to normal in "susceptible" smokers. However, the lost FEV was not recovered. Smoking cessation had no effect on the normal rate of decline in "unsusceptible" individuals. Similarly, in a two-year followup of 118 continuing ex-smokers, aged 27 to 56, Manfreda, et al. (*100*) noted that subjects who continued to refrain from smoking had a smaller decline in $FEV_{1.0}/FVC$ ratio than did smokers; in the male ex-smokers, the decline in ventilatory function fell at about the same rate as that for nonsmokers.

In summary, it is clear that smoking cessation leads to improved performance on standard pulmonary function tests. However there is still debate as to whether the normal decline in ventilatory function is accelerated in ex-smokers as compared to nonsmokers.

Lung Pathology

Auerbach, et al. (*10*) studied the relationship between age, smoking habits, and emphysematous changes in whole lung sections obtained at autopsy from 1,443 males and 388 females. A total of 7,324 sections 1

mm thick were graded on a scale of 0 to 9 according to the severity of emphysema. No distinction was made between centrilobular and panlobular emphysema. The men were classified by age, type of smoking (pipe, cigar, or cigarette), and amount of cigarette smoking. Smoking habits were ascertained by interviews with relatives. Within each of the six smoking categories, the mean degree of emphysema increased with age. Adjusting the data for age revealed that the mean degree of emphysema was lowest among men who never smoked, was higher in pipe or cigar smokers, and highest among regular cigarette smokers. A dose-response relationship was found for the number of cigarettes smoked per day and the severity of emphysema. These data are presented in Tables 5 and 6.

In a subsequent histologic study of tissue from 1,582 men and 368 women, Auerbach, et al. (*9*) were able to show that rupture of alveolar septa (emphysema) and fibrosis and thickening of the small arteries and arterioles were far greater in smokers than in nonsmokers and increased with increasing amount smoked (Tables 7 and 8).

When these researchers examined former cigarette smokers, they found that those who had stopped more than 10 years prior to death had less marked pathologic changes than those who had stopped less than 10 years before death. But even in those who had stopped for more than 10 years, there was a greater degree of pathological change in those who had been smoking more than one pack per day than in those who had been smoking less than one pack per day (Table 9).

In a clinicopathologic study of 196 men and 46 women, Mitchell, et al. (*107*) found that the total exposure to cigarettes was related to clinical symptoms of chronic airway obstruction and to both alveolar and airway pathologic features. The severity of pathologic change was related to the amount of smoking.

Several recent studies have shown evidence of small airway abnormalities in young smokers. Cosio, et al. (*37*) found squamous metaplasia of the airway epithelium as well as chronic inflammatory infiltrate and a slight increase in the connective tissue in the walls of the small airways. Kleinerman and Rice (*83*) found significantly more emphysema, parenchymal pigment, and chronic bronchiolitis in the lungs of smokers as compared to age-matched nonsmokers (median age 27.5 years).

In summary, cigarette smokers demonstrate more frequent abnormalities in macroscopic and microscopic lung sections at autopsy than do nonsmokers. Furthermore, there is a dose-response relationship between these changes and the intensity of smoking. Histologic evidence of small airways pathology was more common in cigarette smokers than in age-matched nonsmokers in an autopsy study of sudden-death victims.

TABLE 5.—Degree of emphysema in current smokers* 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

*Subjects who smoked regularly up to time of terminal illness.
†Packages/day.
SOURCE: Auerbach, O. (*10*)

Smoking and the Pathogenesis of Lung Damage

In recent years, numerous investigators have examined the mechanisms by which smoking might induce lung damage. Three major pathogenetic possibilities by which smoking may damage the lungs

TABLE 6.—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, O. (*10*)

TABLE 7.—Means of the numerical values given lung sections at autopsy of male current smokers and nonsmokers, standardized for age

	Subjects who never smoked regularly	Current pipe or cigar smokers	Current cigarette smokers			
			<.5 Pk.	.5–1 Pk.	1–2 Pk.	>2 Pk.
Number of subjects	175	141	66	115	440	216
Emphysema	0.09	0.90	1.43	1.92	2.17	2.27
Fibrosis	0.40	1.88	2.78	3.73	4.06	4.28
Thickening of arterioles	0.10	1.11	1.35	1.66	1.82	1.89
Thickening of arteries	0.02	0.23	0.42	0.68	0.83	0.90

NOTE: Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of arterioles, 0–7 for fibrosis, and 0–3 for thickening of arteries.
SOURCE: Auerbach, O. (*9*)

have been scrutinized. They are: (1) altering protease-antiprotease balance in the lungs, (2) compromising immune mechanisms, and (3) interfering with pulmonary clearance mechanisms.

Proteolytic Lung Damage

Emphysema is characterized by irreversible destruction of alveolar septal tissue. If severe, this disruption may result in loss of elastic

TABLE 8.—Means of the numerical values given lung sections at autopsy of female current smokers and nonsmokers, 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, O. (*9*)

TABLE 9.—Means of the numerical values given lung sections at autopsy of male former cigarette smokers, standardized for age

Formerly Smoked	Stopped ≥ 10 yr.		Stopped < 10 yr.	
	<1 Pk.	Pk.	<1 Pk.	Pk.
Number of subjects	35	66	51	131
Emphysema	0.24	0.70	1.08	1.69
Fibrosis	1.14	1.74	2.44	3.30
Thickening of arterioles	0.57	0.93	1.25	1.59
Thickening of arteries	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, O. (*9*)

recoil, enhanced collapsibility of the airways, and airflow obstruction. The elastic properties of the lung are attributed to the appropriate distribution of elastin in its connective tissue framework. Recent data suggest that the lung damage observed in emphysema may be due to injury of this elastic framework by proteolytic enzymes released (and not inhibited) in the lung. Formulation of this hypothesis was catalyzed by the discovery that emphysema is extremely common in individuals who are severely deficient in alpha-1-antitrypsin (*48*), a glycoprotein that inhibits several proteases. Subsequently, it was postulated that conditions interfering with the normal balance between protease and antiprotease activity could give rise to an excess of free protease (i.e., elastase) in the lung and initiate lung destruction (*109*).

The proteases are a group of enzymes which probably serve a wide range of functions in the normal host. Proteases with particular elastolytic capability (elastases) are synthesized and released by alveolar macrophages which are found in increased numbers in bronchopulmonary lavage fluid of smokers. They are also present in significant concentrations in polymorphonuclear leukocytes (PMNs).

The antiproteases, of which alpha-1-antitrypsin is the most abundant, are found primarily in blood although alveolar macrophages and bronchial secretions are additional sources of antiproteases. An excess of protease within the lung may arise from any circumstances in which there is increased release of protease which is not matched by availability of antiprotease activity at the site of such release. Various types of experimental support for the proteolytically mediated hypothesis of lung damage have been presented in recent years (*15, 75, 77, 132*).

Crude leukocyte extracts can digest lung tissue (*76, 92*) and homogenates of leukocytes can produce emphysema (*101, 103*) when instilled into the lungs of animals. The degree of damage depends on the proteolytic activity of the instillate (*82*). Recently, Senior, et al. (*129*) instilled purified human leukocyte elastase into the tracheas of hamsters. At two months the lungs of the animals showed mild, patchy emphysema. In a related study, Schuyler, et al. (*126*) administered elastase to hamsters intravenously and demonstrated significant loss of elastic recoil at low lung volumes when their lung histology was normal. The authors suggested that submicroscopic lesions may antedate obvious morphologic evidence of emphysema.

The mechanisms by which cigarette smoking may alter the protease-antiprotease balance have been the subject of several recent investigations. Janoff and Carp (*74a*) demonstrated that unfractionated cigarette smoke condensate suppressed antiprotease activity *in vitro*. Elastin-agarose gels were impregnated with cigarette smoke condensate. Elastases were then allowed to diffuse through the gels toward a counter-diffusing sample of antiproteases. The effectiveness of the antiproteases in blocking the enzyme was determined by the extent of elastin destruction in the plates. Elastins, proteases, and antiproteases from different sources, including purified human leukocyte elastase and human alpha-1-antitrypsin, were tested. In all situations, the cigarette smoke condensate suppressed the inhibitory activity of the antiprotease. In a followup study, Carp and Janoff (*26*) demonstrated that fresh cigarette smoke also suppressed elastase-inhibitory activity of human serum. In addition, treatment of serum with model oxidants caused a similar suppression of elastase inhibition. These *in vitro* observations suggested to the researchers that emphysema in cigarette smokers might be due in part to the suppression of antiprotease activity by oxidizing agents present in cigarette smoke.

In another study from the same laboratory, Blue and Janoff (*16*) demonstrated that cigarette smoke condensates elicited the release of elastase from human PMNs. When human PMNs were incubated *in vitro* with cigarette smoke condensate, three enzymes were released: beta-glucuronidase, acid phosphatase, and elastase. The elastase was active in digesting elastin, even in the continuing presence of cigarette smoke condensate. When mixtures of human PMNs and cigarette smoke condensate were instilled into rat lung *in vitro*, elastase was released and could be traced to connective tissue targets using immunohistochemical and enzyme-histochemical techniques. This study appears to be particularly relevant in view of previous studies demonstrating that cigarette smoke recruits leukocytes into the lung airways (*81*, *124*), immobilizes them (*46*), and inhibits their chemotaxis *in vitro* (*17*).

The role of the pulmonary macrophage in proteolytic lung damage has been evaluated by several investigators. Alveolar macrophages are normally important in cleansing the lower airways by phagocytising and digesting foreign particulate matter. Bronchopulmonary lavage studies have documented increased total numbers of macrophages in lavage fluid of smokers as compared to nonsmokers (*65*, *156*). Keast and Holt (*79*) exposed mice to smoke via a special apparatus and found sustained elevations in bronchopulmonary macrophage populations.

Changes in the ultrastructure of macrophages have been reported in smokers. Pratt, et al. (*116*) observed pigmented cytoplasmic inclusions in macrophages from cigarette smokers. Brody and Craighead (*18*) observed that the pigmentation appeared to be due, at least in part, to an increased number of lysosomes and phagolysosomes. In addition, distinctive "smoker's" inclusions were observed within these cytoplasmic organelles which appeared plate-like and crystallographically consistent with kaolinite. The authors presented some preliminary evidence that these particles are derived from inhaled tobacco smoke. Kaolinite is a common clay mineral found in the soil in many tobacco growing regions and is sometimes used as a tobacco additive in the production of cigarettes for the purpose of reducing tar content. A few studies have shown that when macrophages engulf kaolinite they release beta-gulcuronidase and lactic acid dehydrogenase, lysosomal enzymes believed to play a role in cell death and fibrogenesis *in vivo* (*3*, *66*, *157*). In a recent study, Matulionis and Traurig (*104*) exposed pulmonary macrophages of mice *in situ* to cigarette smoke and found: (1) an increase in number, variety, and size of lysosome-like bodies in the macrophage; (2) the appearance of multinucleation; and (3) an increased size of the macrophages. After cessation of smoke exposure, macrophage morphology and population size returned toward normal.

A considerable increase in elastase-like esterase and protease activity was demonstrated by Harris, et al. (*64*) in human alveolar macrophages in smokers as compared to nonsmokers. In a subsequent

study, Rodriguez, et al. (*119*) demonstrated that human alveolar macrophages from smokers released elastase into serum-free culture medium, unlike those from nonsmokers. Elastase was not detectable in cell homogenates from either smokers or nonsmokers, implying that this enzyme is not stored. The authors suggested that cigarette smokers have the potential for a 20-fold increase in elastase released in the lungs when the increased number of macrophages in lungs of smokers also is considered.

Potentially important effects of cigarette smoke also have been demonstrated on alveolar macrophage pinocytosis (*164*), cell adhesion (*61*), cell migration (*154*), and protein synthesis (*94, 95, 163*). The data relating the effect of cigarette smoke to alveolar macrophage phagoocytosis and bacteriocidal activity are conflicting (*61, 130, 135, 137*) but generally have shown cigarette smoke to have a suppressant effect. At least some of the toxic effects of the gas phase of cigarette smoke on macrophage activity may be due to the oxidant, acrolein (*74*).

In summary, a number of recent investigations have suggested that a destruction of the elastic framework of the lungs seen in COLD may result from a protease-antiprotease imbalance. Although definitive evidence is lacking, it appears that alveolar macrophages and PMNs are the most important sources for the proteases. Cigarette smoke appears to increase the rate of synthesis and release of elastase *in vitro* from human alveolar macrophages and increases their numbers. Antiproteases are inhibited from counteracting protease activity in the presence of cigarette smoke *in vitro*. Possible deleterious effects of cigarette smoke also have been demonstrated on a variety of functions of the human alveolar macrophage.

Interference with Immune Mechanisms

The lungs have a highly developed lymphatic system and the capacity to effect local immune responses. Inhalation of tobacco smoke produces significant changes in cellular and humoral immunity in both animal and man. However, the role of such changes in the pathogenesis of lung disease remains speculative. Waldman, et al. (*151*) reported that cigarette smokers of more than 1/2 pack per day had an increased risk of influenza-like illnesses although the length of illness was no different than for nonsmokers.

Finklea, et al. (*52*) noted that smokers had more frequent subclinical influenza than nonsmokers; subsequently he observed that the serological response (hemaglutination antibody titers) to either vaccination or natural infection with A-2 antigens was similar to that in nonsmokers but not as long lasting (*51*).

Cigarette smoke appears to adversely affect the nonspecific (phagocytosis) defense mechanisms provided by the alveolar macrophage. Evidence for an effect on the specific (immune) defense roles

played by both macrophages and lymphocytes has been offered by several investigators.

The alveolar macrophage system plays an important role in the overall immune response as an antigenic "processor." Warr and Martin (*154*) studied alveolar macrophages lavaged from four healthy smokers and four healthy nonsmokers. Only two members of each group were reactive to skin tests with Candida albicans. The migration of macrophages from nonsmokers was inhibited by migration inhibitory factor (MIF) whereas macrophages from smokers did not respond to MIF. The cells from smokers were noted to migrate three times faster than those from nonsmokers. When Candida antigen was added to the medium, cells from the nonreactive subjects (both smokers and nonsmokers) were not inhibited. The cells from the reactive nonsmokers were inhibited, but not those from reactive smokers. Thus, macrophages from smokers did not respond normally either to MIF or antigenic challenge.

The B and T lymphocytes participate in humoral and cell-mediated immune mechanisms, respectively. Warr, et al. (*155*) noted that a greater number of T cells and B cells were recovered by human bronchopulmonary lavage from smokers than from nonsmokers. Daniele, et al. (*39*) examined the T and B cell populations in peripheral blood of smokers versus nonsmokers and found no difference in either the absolute number of cells or the lymphocyte response to phytohemaglutinin (PHA) or concanavalin A. In a lavage study of five smokers the lymphocyte subpopulation did not differ from that in nonsmoking subjects (n=8), but cells from smokers showed a diminished response to PHA and concanavalin A. They concluded that cigarette smoking may impair cellular immune defenses.

In contrast, Silverman, et al. (*131*) found that young smokers had an increased number of T lymphocytes in peripheral blood and an enhanced response to PHA. No differences were found in the response of older smokers or those with a history of heavier cigarette consumption as compared to controls. A number of other studies have examined the relationship of smoking to T-cell function; these are reviewed in the Chapter on Allergy and Immunity.

Roszman and Rogers (*121*) noted that both the nicotine and the water-soluble fraction of whole cigarette smoke suppressed the immunoglobulin response of lymphoid cell cultures to antigen challenge. When concentrations of over 200 micrograms per milliliter of nicotine of the water-soluble fraction were added, they were able to suppress completely the immunoglobulin response; this suppression also occurred in cells exposed 2 hours prior to the antigenic challenge. In a subsequent experiment, they found suppression of mitogen-induced blastogenesis by cigarette smoke (*120*). Warr, et al. (*156*) examined immunoglobulin levels in bronchopulmonary lavage fluid in

19 smokers and 36 nonsmokers. They could find no difference in IgA levels; however, IgG levels were twice as high in smokers.

In summary, a variety of alterations in the specific immune system have been observed that are presumably due to cigarette smoking. Macrophages from smokers respond abnormally to MIF or antigen challenges. T lymphocytes obtained by bronchopulmonary lavage in smokers showed a diminished response to PHA compared to those of nonsmokers. Cigarette smoke suppresses production of immunoglobulin by B lymphocytes in lymphoid cell culture. However, the role of these abnormalities in the pathogenesis of lung damage is unclear.

Effect on Clearance Mechanisms

The mucociliary transport system protects the lung against inhaled particulate matter. Its two major components are the respiratory mucus blanket (secreted by submucosal and goblet cells) and the ciliated columnar epithelial cells lining the larger airways. Denudation of epithelium, an increased number of goblet cells, and squamous metaplasia have been demonstrated by Auerbach, et al. (*11*) in dogs exposed to cigarette smoke via a tracheostoma, and by Leuchtenberger, et al. (*91*) and Rylander (*124*) in mice and guinea pigs exposed to cigarette smoke via their upper airway passages. Similar morphologic abnormalities have been observed in human cigarette smokers (*58*).

A number of investigators have examined the effects of cigarette smoke on mucociliary function, employing a wide variety of experimental techniques. These studies have scrutinized the effects of gas and particulate elements of cigarette smoke in both acute and chronic situations.

Short-term exposure to cigarette smoke causes ciliostasis and decreased mucociliary transport in most animals (*152*). The ciliotoxic effects of cigarette smoke are not peculiar to tobacco cigarettes; they have been observed in protozoans following exposure to smoke from lettuce and grass cigarettes (*60*). The data relating these effects to specific particulate or gas phase elements of cigarette smoke are conflicting (*38*). Moreover, the relevance to human conditions of animal models demonstrating altered mucociliary function in "smoking" (tracheostomized) animals has been questioned, since, in humans, cigarette smoke passes the upper airways which might alter its ciliotoxic capacity for the lower airways (*152*). Data regarding the effects of acute cigarette exposure on mucociliary clearance in man also are conflicting (*152*).

Long-term exposure to cigarette smoke has been examined in animals and in man. Tracheal mucous velocity has been shown to be decreased in purebred beagle dogs (*153*) exposed to 100 cigarettes per week for 13.5 months. In donkeys (*2*), low level exposure to whole cigarette smoke accelerated tracheobronchial clearance; at intermedi-

ate and high levels whole cigarette smoke had twice the effect of filtered smoke in decreasing clearance.

The long-term effects of cigarette smoking on mucociliary function in man are unclear. Most of the evidence indicates that long-term smoking reduces mucociliary transport (*152*). Animal and human studies have suggested that cessation of smoking may allow partial recovery of mucociliary function (*1, 25*).

Interaction of Smoking with Other Risk Factors for COLD

Alpha-1-antitrypsin Deficiency

It would be useful to identify the populations at special risk of developing COLD from smoking so that such populations might be made aware of the risk. Persons with significant deficiencies of alpha-1-antitrypsin may be such a population.

Eriksson (*48*) was the first investigator to observe a relationship between the presence of markedly decreased serum trypsin inhibitory capacity and panlobular emphysema. Since Eriksson's paper, much research has been published concerning this intriguing observation.

Severe alpha-1-antitrypsin deficiency is due to a rare genetic trait which occurs in approximately 1 in 2,000 people (*49*). Less severe reductions are found in approximately 2 to 10 percent of the population. Alpha-1-antitrypsin inheritance patterns indicate multiple codominant alleles at one gene locus. Some alleles (notably Z, S, and "null") are associated with substantially reduced serum levels of alpha-1-antitrypsin. The autosomal codominant inheritance allows multiple combinations of alleles associated with low or normal serum levels of the antiprotease. For example, extremely low levels are associated with the ZZ homozygous state, intermediate levels with the MZ heterozygous state, and normal levels with the MM state. Thus, a wide range of serum levels may be encountered which depend upon the particular alleles involved. The particular phenotype of a given patient can be identified by antigen-antibody crossed gel electrophoresis but not by measurement of serum levels alone, because alpha-1-antitrypsin is an acute phase reactant. The pathophysiologic implications of a reduction in antiprotease activity have been discussed in previous sections.

Severe deficiency of alpha-1-antitrypsin has been associated with a particular type of pulmonary emphysema. While the majority of lungs of emphysematous patients reveal bullous or centrilobular deformities, particularly of the upper lobes, this hereditary disorder reveals a panacinar change, most severe in the lower lobes (*63, 136, 158*). Populations with this genetically related form of emphysema have a greater percentage of females than is usually observed in the general emphysema population. Their disease begins earlier, is more severe, is characterized by dyspnea rather than cough, and frequently is

unassociated with a history of preceding bronchitis (*63, 136, 158*). Radiographic studies of alpha-1-antitrypsin deficient patients have revealed decreased vascularization of the lower lobes (*134*).

Several retrospective studies in patients with severe deficiency have demonstrated an association between smoking and the age at which emphysema becomes manifest. However, control nonsmoking subjects with a similar phenotype have not been included. Black and Kueppers (*14*) evaluated 18 patients with alpha-1-antitrypsin deficiency who had never smoked and had little or no exposure to occupational or urban air pollution and compared them to 36 individuals with similar phenotype (PiZZ) who were (or had been) smokers. A larger percentage of individuals who smoked had impaired lung function early in life. However, there was considerable variability as to clinical course, degree of pulmonary function abnormality, and appearance of the roentgenogram among the nonsmokers. The authors recognized that their study was biased in favor of individuals with symptomatic disease; however, they noted that the rarity of the PiZZ phenotype and the need to identify nonsmokers with no other exposure to respiratory irritants would have required an enormous screening program. Prospective studies scrutinizing these relationships are lacking.

The natural history of the states with less severe deficiencies of alpha-1-antitrypsin is unclear (*86*). Cross-sectional studies have found such a deficiency more frequently in patients with COLD than would be expected by chance alone (*87, 93*). However, several other reports obtained from population studies have suggested that mild forms of antitrypsin deficiency are not important risk factors for emphysema (*30, 34, 111*). Mittman (*108*) recently reviewed the controversy as to whether the MZ phenotype is a significant risk factor for COLD but could not resolve the issue based on current evidence. Longitudinal studies in such individuals have not been reported. Because the natural history of the mild deficiency state is unclear, the effect of smoking on such individuals remains unsettled.

In summary, individuals with severe alpha-1-antitrypsin deficiency have an excessive risk for developing COLD; the onset of symptomatic COLD is probably abbreviated by smoking. The natural history of individuals with mild deficiency states for alpha-1-antitrypsin is unclear, as is the question of whether they represent a group at special risk from cigarette smoking.

Other Genetic Factors

Continued interest has been shown in the possible contribution of genetic factors (other than alpha-1-antitrypsin deficiency) to the pathogenesis of COLD. In earlier studies (*71, 88, 89*), the existence of kindreds with a high incidence of COLD had been noted, but the relative importance of genetic factors and smoking habits was unclear.

TABLE 10.—Expected and observed prevalence rate (percent) of "cough" among smoking partners to co-twins who either had or had not the symptom "cough" Monozygotic pairs

"Coughing" status in non-smoking partner	No. at risk	Prevalence rate for "coughing" among smoking co-twins, percent	
		Expected	Observed
No "cough"	497	4	12
"Cough"	41	24	37

SOURCE: Cederlof, R. (*29*)

Cohen, et al. (*32, 33*), in a family study in Baltimore, Maryland, found an increased prevalence of pulmonary function abnormalities in first-degree relatives of COLD cases as compared to first-degree relatives of nonpulmonary cases, even when Pi variant relatives were excluded. In all groups, smokers demonstrated a higher frequency of function abnormalities. The authors suggested that there is some interaction of familial factors with smoking. In a similar study in rural areas outside Rochester, Minnesota, Miller, et al. (*106*) found a twofold increased prevalence of functional abnormalities in family members of subjects with COLD as compared to families of controls matched for age, sex, occupation, and smoking exposure.

Cederlof, et al. (*27, 28*) examined the relationship of smoking to symptom prevalence among monozygotic and dizygotic twins who were both discordant and concordant for smoking habits. They observed that the hypermorbidity for COLD symptoms related to smoking persisted even after controlling for zygosity; they concluded that a causal relationship of smoking and COLD symptoms was supported. However, genetic factors had an appreciable influence.

In a more recent analysis of their twin data, Cederlof, et al. (*29*) examined the prevalence of cough among monozygotic pairs discordant for smoking. The results are presented in Table 10. They assumed that the nonsmoking symptomatic co-twin had a predisposition to cough. The smoking co-twin had a threefold increase in prevalence of cough compared to his asymptomatic nonsmoking co-twin—a 1-1/2 times increase compared to the symptomatic nonsmoking co-twin. The prevalence rates were higher in the smoking groups than in non-smoking groups but highest in the "predisposed" smoker. The authors suggested that hereditary factors were equally as important as smoking for the development of cough in the smaller "predisposed" group.

These findings lend support to earlier suspicions that genetic factors may play a role in determining the risk for COLD. Kazazian (*78*) has

suggested that common lung diseases may be due to a combination of risk factors, varying from one individual to another, and that this risk may be modulated by different genes in combination and by different environmental factors (e.g., smoking). Long-term prospective studies are necessary to answer these questions.

Occupational Exposures

Exposure to certain occupational environments has been shown to be associated with several forms of non-neoplastic bronchopulmonary disease. An increased prevalence of COLD is found with exposures to coal and granite dust and cotton fiber. This risk is increased further by cigarette smoking. However, in none of these studies is the relationship of COLD to occupation as strong as that to smoking.

A discussion on the proposed modes by which smoking interacts with occupational exposures is presented in the Chapter on the Interaction Between Smoking and Occupational Exposures.

Air Pollution

The relationships among air pollution, smoking, and COLD remain controversial. Reasons for this controversy include difficulties in controlling such variables as socioeconomic class, degree of crowding, ethnic differences, and age distribution, as well as in determining the exact type and amount of individual pollution exposure. Measuring individual pollution exposure, even within a small area, is difficult since both amount and type can vary dramatically from street to street (e.g., proximity of a street to a heavily traveled expressway).

In an effort to control as many of these variables as possible, two basic approaches in study design have been utilized. The first approach has been to find areas where different pollution levels have been well-measured and then to select populations that are as similar as possible in these areas. Thus, a population in a low-pollution area can be compared with a similar population in a high-pollution area. The second approach has been to select a population that is as uniform as possible (for example, twins), and then measure individual responses to different pollution exposures.

Using the first approach, the Community Health and Environmental Surveillance System evaluated the excess COLD (i.e., rate of COLD experienced above that of nonsmokers) in subjects in two communities of differing air pollution: Salt Lake City (high), and the Rocky Mountain Area (low). Finklea, et al. (*53*) commenting on the data, noted that smoking was the most important risk factor in developing abnormal pulmonary function but that smoking and exposure to air pollution had a synergistic effect.

The relationship among smoking, air pollution, and COLD were analyzed in an autopsy study of tissue samples from St. Louis, Missouri (high pollution) and Winnipeg, Canada (low pollution) (*162*). Three

hundred lungs were evaluated as to the extent and degree of emphysema; urban groups were matched for smoking habits, length of residence, age at immigration, and employment history; 25 to 26 percent of each group were nonsmokers. In nonsmokers, emphysema was more frequent and severe in the St. Louis than in the Winnipeg group. In male smokers the incidence of severe emphysema was fourfold higher in the St. Louis than in the Winnipeg group. The author concluded that tobacco smoke may have a cumulative or synergistic action with air-pollution exposure.

Increased prevalence of COLD has been demonstrated in areas of high pollution in the Netherlands (*150*), Yokkaichi, Japan (*113*), and Cracow, Poland (*125*). However, these studies were poorly controlled for socioeconomic status.

Several studies have used the second major method of investigating the relationship between smoking, air pollution, and COLD, i.e., to select a uniform population and then to measure individual differences to pollution exposure. Comstock, et al. (*36*), in an attempt to control for occupational exposure and socioeconomic class, studied three separate, uniform populations of telephone workers and used as a measure of pollution the location of the place of work and residence. The populations studied were telephone installers and repairmen in Baltimore, New York City, Washington, D.C., and rural Westchester County, New York, in 1962 (survey 1) and in 1967 (survey 2), and telephone installers and repairmen in Tokyo in 1967 (survey 3). The researchers were unable to find any relation between pulmonary symptoms and degree of urbanization of place of work or place of residence (either current or past). They were, however, able to establish a strong correlation between smoking habits and pulmonary symptoms. Given the crude estimation of pollution exposure used in this study (all workers in each city were treated as though they received the same exposure), a small difference in symptoms due to air pollution could have been missed, whereas the difference due to smoking could be detected both because it was larger and because it was possible to determine individual exposure more exactly.

Hrubec, et al. (*70*), in a study of twins from the U.S. Veterans Registry, were unable to show a difference in respiratory symptoms either between individuals with different exposures to air pollution or between members of twin pairs with different air-pollution exposures. However, they too used a crude measure of air-pollution exposure (by each zip code area), and so could have missed a small difference due to air pollution despite being able to relate respiratory symptoms to smoking, socioeconomic status, and alcohol intake.

Colley, et al. (*35*), in a study of 3,899 persons (20-year-olds born during the last week of March, 1946, in the United Kingdom), were also unable to show a relation between COLD and air pollution. As estimates of air-pollution exposure, they used the domestic coal

consumption in the towns where the subjects lived. This method of estimating air pollution is subject to the same limitations cited for the previous two studies, i.e., limited sensitivity to small risks due to air pollution.

In summary, if an increased risk of COLD due to air pollution exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed. The possibility remains that the two kinds of exposure may interact to increase the total effect beyond that contributed by each exposure separately.

Socioeconomic Status

In a morbidity survey (*117*) of the non-institutionalized population of the United States (1964), socioeconomic status appeared to be an important risk factor in determining rates of reporting chronic bronchitis, asthma, and emphysema. Rates were higher among those in lower socioeconomic classes. This relationship had been previously recognized in the United Kingdom (*118*).

In a recent study, the relationship of smoking to socioeconomic status and chronic respiratory diseases was examined in 9,226 residents of Tecumseh, Michigan, observed from 1962 to 1965 (*68*). The prevalence of chronic bronchitis was higher in cigarette smokers than in nonsmokers, higher in blue-collar workers than in white-collar workers, and least among men with the most education (Table 11). There was no significant association between the prevalence of asthma and smoking habits, occupation, education, or income. Most of the differences in the prevalence of chronic bronchitis in subjects of differing occupational, educational, or income classes were attributable to differences in smoking habits. Compared with smoking, poor occupations, educational background, and economic circumstances have only a weak deleterious effect.

Childhood Respiratory Illness and Adult Respiratory Disease

A connection between pediatric respiratory illness and adult respiratory disease has long been suspected on clinical grounds. Burrows, et al. (*24*) recently reported that physician-confirmed chronic bronchitis and/or emphysema and abnormalities in measures of expiratory flow are more common in older subjects with such history. They suggested that childhood respiratory illness leads to an increased susceptibility to the effects of bronchial irritants and respiratory infections.

In a prospective study of 10-year-olds followed since age 2 (n=3899), Colley, et al. (*35*) found that subjects with a history of respiratory tract illness before age 2 had an increased likelihood of developing respiratory symptoms by age 20. However, cigarette smoking appeared to be an even more important factor in increasing risk for developing these symptoms (Table 12).

TABLE 11.—The age-adjusted* prevalence (percent) of chronic bronchitis score by occupation and smoking habits in men 25 to 64 years of age, Tecumseh, 1962–65

Occupation	No. examined	Chronic bronchitis: All	Chronic bronchitis: Non-smokers	Chronic bronchitis: Cigarette smokers
Professional and managerial	421	12.3	4.9	26.7
Farmers	41	16.2	—	—
Clerical and sales	114	16.1	5.4	32.0
Craftsmen and operatives	782	18.2	5.3	31.5
Service	33	28.1	—	—
Laborers	35	30.0	—	—
White-collar	535	12.9	4.9	27.1
Blue-collar	850	18.9	5.4	31.6
Agricultural	48	19.4	—	—

*Adjusted to the age distribution of men and women in Tecumseh 25 to 64 years of age. Includes 7 farm laborers.
SOURCE: Higgins, M. W. (*68*)

TABLE 12.—Prevalence (%) for cough day or night in both sexes in winter by cigarette smoking and by chest illness before age 2* (Figures in parenthesis are population)

Chest illness under 2 yrs. of age	Cigarette smoking: Never	Cigarette smoking: Present
No chest illness	5.2 (1361)	13.7 (1141)
One or more chest illness	9.1 (397)	16.5 (423)

*Excludes 577 persons—exsmokers and those where history of cigarette smoking and of chest illness before age 2 and history of cough day and night are unknown.
SOURCE: Colley, J.R.T. (*35*)

In a followup study of the same cohort (*80*), the association of cough prevalence with current smoking habits and with childhood respiratory tract illness was confirmed and strengthened.

Summary

Cigarette smoking, even in young age groups, produces lung damage. Cessation of smoking leads to at least partial resolution of symptoms. Pulmonary function and histologic abnormalities have been observed in young smokers, confirming clinical suspicions of lung damage in this group.

A variety of pulmonary functional abnormalities believed to represent small airway dysfunction occurs in smokers. Many such individuals demonstrate normal expiratory flow as measured by conventional spirometry. In one prospective study, abnormalities in tests of small airway function appeared to correlate well with pathologic abnormalities of the peripheral airways. It has been suggested that such changes may be precursors of more extensive anatomic-functional abnormalities if smoking were continued. However, prospective studies relating small airway physiological and/or pathological abnormalities to the development of COLD are lacking.

Adult cigarette smokers have respiratory symptoms more frequently than do nonsmokers; some symptoms (i.e., cough and sputum production) increase with a greater dosage of cigarettes. While it is clear that COLD is more common in men than in women, it is uncertain whether men and women with equivalent smoking histories have a similar increase in the prevalence of respiratory symptoms and COLD.

In the majority of epidemiological surveys, a higher prevalence of functional abnormalities has been found in smokers as compared to nonsmokers. There are conflicting data as to the effect of smoking on pulmonary function in different racial groups and whether men and women with equivalent smoking habits have similar reductions in pulmonary function. It is clear that cigarette smoking produces a more rapid decline in FEV and a higher prevalence of productive cough. However, it is unclear whether the presence of productive cough by itself predicts the risk for a more rapid decline in FEV independent of that increased risk associated with cigarette smoking. It has been suggested that there may be a "susceptible" group of smokers whose rate of decline in FEV is much greater than that in both "unsusceptible" smokers and nonsmokers and that "unsusceptible" smokers and nonsmokers have similar rates of decline in FEV. Therefore, prevalence surveys of functional abnormalities in all smokers may underestimate the impact of cigarette smoking in the "susceptible" population.

Several studies have confirmed that there is improvement in standard spirometric function tests following cessation of smoking, but there is still debate as to whether the normal decline in ventilatory function is accelerated in ex-smokers as compared to nonsmokers.

Cigarette smokers demonstrate more frequent abnormalities in macroscopic and microscopic lung sections at autopsy than do nonsmokers. Furthermore, there is a dose-response relationship between these changes and the intensity of smoking. Histologic evidence of small airways pathology is more common in cigarette smokers than in age-matched nonsmokers in one autopsy study of sudden death victims.

A number of recent investigations have suggested that destructive lung changes seen in the emphysematous form of COLD may result from excess liberation of, or failure to inhibit, proteases in the lung.

Although definitive evidence is lacking, it appears that PMNs and alveolar macrophages are the most important sources for the proteases. Cigarette smoke appears to increase the rate of synthesis and release of elastase *in vitro* by human alveolar macrophages. Antiproteases are inhibited in the presence of cigarette smoke *in vitro*. Cigarette smoke also has been demonstrated to impair a variety of functions of the human alveolar macrophage.

Inhalation of tobacco smoke produces detectable changes in components of the cellular and humoral immune systems in both animal and man. Macrophages obtained by lung lavage from smokers respond abnormally to MIF or antigen challenge. T lymphocytes obtained from bronchopulmonary lavage show a diminished response to PHA in smokers. Cigarette smoke suppresses production of immunoglobulin by B lymphocytes in lymphoid cell culture. However, the role of these abnormalities in the pathogenesis of lung damage is unclear.

Individuals with severe alpha-1-antitrypsin deficiency have an excessive risk for developing COLD; the onset of symptomatic COLD is probably accelerated by smoking. The natural history of individuals with mild or moderate alpha-1-antitrypsin deficiencies is unclear, as is the effect of smoking on such individuals.

Genetic factors other than alpha-1-antitrypsin deficiency appear to play a role in determining the risk for COLD. Common lung diseases may be due to a combination of risk factors varying from one individual to another. The risk may be modulated by different genes in combination and by different environmental factors (e.g., smoking).

A recent study examined the relationship of smoking to socioeconomic status and chronic respiratory disease. The prevalence of chronic bronchitis was higher in cigarette smokers than in nonsmokers, higher in blue-collar workers than white-collar workers, and least among men with the most education. However, most of the differences in the prevalence of chronic bronchitis in subjects of differing occupational, educational, or income classes was attributable to differences in smoking habits. Compared with smoking, poor occupations, educational background, and economic circumstances have only a weak deleterious effect.

Childhood respiratory disease appears to be a risk factor for respiratory symptoms as an adult. However, cigarette smoking appears to be a more important factor in increasing risk for developing these symptoms.

Research Recommendations

The extensive studies already performed have identified several areas that merit particular investigational attention because of their promise in elucidating the effects of smoking and other risk factors upon the development of COLD:

(1) Current data suggest that early detection of pulmonary functional and histologic changes in asymptomatic smokers may identify populations which are particularly susceptible to COLD. Investigations documenting the relationships between tests for small airways dysfunction, pulmonary histology, and symptoms should be extended. In addition, longitudinal studies are needed to (a) document the impact of smoking cessation upon these early abnormalities, and, most important, to (b) define the relationship of these early abnormalities to the development of COLD.

(2) Similar longitudinal studies in patients with well-defined COLD should be carried out to define the effects of smoking cessation on clinical, physiologic, and anatomic parameters.

(3) The protease antiprotease imbalance hypothesis for the pathogenesis of pulmonary elastic tissue injury has received substantial support from investigations reported to date. Observations are available which suggest mechanisms by which cigarette smoke might promote an injury-inducing imbalance in man. Appropriate extensions of both *in vitro* and *in vivo* investigations which bear upon this relationship should be performed. It would appear particularly important to assure that *in vivo* research be carried out to determine the biologic importance of the expanding body of promising *in vitro* research.

(4) Subjects with genetically-determined severe and mild-moderate deficiencies of alpha-1-antitrypsin appear to be a particularly promising population in which to study the natural history of COLD, the role of cigarette smoking and other risk factors, and the mechanisms responsible for COLD. Carefully designed studies, cross-sectional and longitudinal, of subjects with severe and mild-moderate deficiencies should be undertaken. Multi-center studies with pooling of data should be encouraged.

(5) There are *in vitro* effects of smoking and cigarette smoke on both the humoral and cellular components of the immune system. Extension of relevant *in vitro* and *in vivo* investigations dealing with smoking-immune system interactions should be encouraged.

(6) Further investigations of the relationship between cigarette smoking and the mucociliary ("clearance") apparatus are warranted.

In all of the above areas, research planning should include attention to the primary goal, i.e., elucidation of the mechanisms responsible for the development of COLD in man and the manner in which smoking impacts upon these mechanisms to promote COLD. Thus, research support should seek a balanced program providing for *in vitro* and *in vivo* investigations (in animal models and in man). Such a balanced program also should provide for effective interchange of information among investigators pursuing research *in vitro*, in animals, and in man.

Non-Neoplastic Bronchopulmonary Diseases: References

(1) ALBERT, R.E., ALESSANDRO, D., BERGER, J., LIPPMANN, M. Long-term smoking in the donkey: Effect on tracheobronchial particle clearance. Archives of Environmental Health 22: 12-19, 1971.

(2) ALBERT, R.E., BERGER, J., SANBORN, K., LIPPMANN, M. Effects of cigarette smoke components on bronchial clearance in the donkey. Archives of Environmental Health 29: 96-101, 1974.

(3) ALLISON, A.C., HARINGTON, J.S., BIRBECK, M. An examination of the cytotoxic effects of silica on macrophages. Journal of Experimental Medicine 124: 141-153, 1966.

(4) AMERICAN COLLEGE OF CHEST PHYSICIANS. AMERICAN THORACIC SOCIETY. Pulmonary terms and symbols. A report of the ACCP-ATS Joint Committee on Pulmonary Nomenclature. Chest 67: 583-593, 1975.

(5) ANTHONISEN, N.R., BASS, H., ORIOL, A., PLACE, R.E.G., BATES, D.V. Regional lung function in patients with chronic bronchitis. Clinical Science 35(3): 495-511, 1968.

(6) ANTHONISEN, N.R., DANSON, J., ROBERTSON, P.C., ROSS, W.R.D. Airway closure as a function of age. Respiratory Physiology 8: 58-65, 1969-1970.

(7) ARMSTRONG, J.G., WOOLCOCK, A.J. Lung function in asymptomatic cigarette smokers—The single breath nitrogen test. Australia and New Zealand Journal of Medicine 6(2): 123-126, 1976.

(8) ASHLEY, F., KANNEL, W.B., SORLIE, P.D., MASSON, R. Pulmonary function: Relations to aging, cigarette habit, and mortality. The Framingham Study. Annals of Internal Medicine 82(5): 739-745, 1975.

(9) AUERBACH, O., GARFINKEL, L., HAMMOND, E.C. Relation of smoking and age to findings in lung parenchyma: A microscopic study. Chest 65(1): 29-35, 1974.

(10) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L., BENANTE, C. Relation of smoking and age to emphysema. Whole-lung section study. New England Journal of Medicine 286(16): 853-857, April 20, 1972.

(11) AUERBACH, O., HAMMOND, E.C., KIRMAN, D., GARFINKEL, L., STOUT, A.P. Histologic changes in bronchial tubes of cigarette-smoking dogs. Cancer 20: 2055-2066, 1967.

(12) BENSON, M.K. The closing volume as a screening test in smokers. Scandinavian Journal of Respiratory Disease 95(Supplement): 84-90, 1974.

(13) BEWLEY, B., BLAND, J.M. Smoking and respiratory symptoms in two groups of schoolchildren. Preventive Medicine 5: 63-69, 1976.

(14) BLACK, L.F., KUEPPERS, F. Alpha-1-antitrypsin deficiency in nonsmokers. American Review of Respiratory Disease 117: 421-427, 1978.

(15) BLACKWOOD, C.F., HOSANNAH, Y., PERMAN, E., KELLER, S., MANDL, I. Experimental emphysema in rats: Elastolytic titer of inducting enzyme as determinent of the response. Proceedings of the Society for Experimental Biology and Medicine 144: 450-454, 1973.

(16) BLUE, M.L., JANOFF, A. Possible mechanism of emphysema in a cigarette smokers. Release of elastase from human polymorphonuclear leukocytes by cigarette smoke condensate in vitro. American Review of Respiratory Disease 117(2): 317-325, February 1978.

(17) BRIDGES, R.B., KRAAL, J.H., HUANG, L.J.T., CHANCELLOR, M.B. Effects of tobacco smoke on chemotaxis and glucose metabolism of polymorphonuclear leukocytes. Infection and Immunity 15(1): 115-123, 1977.

(18) BRODY, A.R., CRAIGHEAD, J.E. Cytoplasmic inclusions in pulmonary macrophages of cigarette smokers. Laboratory Investigation 32(2): 125-132, 1975.

(19) BROWN, R., WOOLCOCK, A.J., VINCENT, N.J., MACKLEM, P.T. Physiological effects of experimental airway obstruction with beads. Journal of Applied Physiology 27: 328-335, 1969.

(20) BUIST, A.S., FLEET, L.V., ROSS, B.B. A comparison of conventional spirometric tests and the test of closing volume in an emphysema screening center. American Review of Respiratory Disease 107: 735-743, 1973.

(21) BUIST, A.S., ROSS, B.B. Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. American Review of Respiratory Disease 108: 1078-1087, 1973.

(22) BUIST, A.S., SEXTEN, G.J., NAGY, J.M., ROSS, B.B. The effect of smoking cessation and modification on lung functions. American Review of Respiratory Disease 114: 115-122, 1976.

(23) BURROWS, B., KNUDSON, R.J., CLINE, M.G., LEBOWITZ, M.D. Quantative relationships between cigarette smoking and ventilatory function. American Review of Respiratory Disease 115: 195-204, 1977.

(24) BURROWS, B., LEBOWITZ, M.D., KNUDSON, R.J. Epidemiologic evidence that childhood problems predispose to airways disease in the adult (An association between adult and pediatric respiratory disorders). Pediatric Research 11(3): 218-220, 1977.

(25) CAMNER, P., PHILIPSON, K., ARVIDSSON, T. Withdrawal of cigarette smoking. Archives of Environmental Health 26: 90-92, 1973.

(26) CARP, H., JANOFF, A. Possible mechanisms of emphysema in smokers in vitro suppression of serum elastase-inhibitory capacity by fresh cigarette smoke and prevention by antioxidants. American Review of Respiratory Disease 118: 617-621, 1978.

(27) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. Archives of Environmental Health 18(6): 934-940, June 1969.

(28) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIJ, L. Respiratory symptoms and 'angina pectoris' in twins with reference to smoking habits. An epidemiological study with mailed questionnaire. Archives of Environmental Health 13(6): 726-737, December 1966.

(29) CEDERLOF, R., FRIBERG, L., LUNDMAN, T. The interactions of smoking, environment, and heredity, and their implications for disease etiology. Acta Medica Scandinovica 612(Supplement): 1-128, 1977.

(30) CHAN-YEUNG, M., ASHLEY, M.J., COREY, P., MALEDY, H. Pi Phenotypes and the prevalence of chest symptoms and lung function abnormalities in workers employed in dusty industries. American Review of Respiratory Disease 117(2): 239-245, 1978.

(31) CHERNIACK, R.M. Smoking and chronic airways obstruction. National Heart, Lung and Blood Institute, Division of Lung Diseases. National Technical Information Service PB 272 154, September 1, 1977, pp. 1-41.

(32) COHEN, B.H., BALL, W.C., JR., BIAS, W.B., BRASHEARS, S., CHASE, G.A., DIAMOND, E.L., HSU, S.H., KREISS, P., LEVY, D.A., MENKES, H.A., PERMUTT, S., TOCKMAN, M.S. A genetic epidemiologic study of chronic obstructive pulmonary disease I. Study design and preliminary observations. Johns Hopkins Medical Journal 137: 95-104, 1975.

(33) COHEN, B.H., BALL, W.C., JR., BRASHEARS, S., DIAMOND, E.L., KREISS, P., LEVY, D.A., MENKES, H.A., PERMUTT, S., TOCKMAN, M.S. American Journal of Epidemiology 105(3): 223-231, 1977.

(34) COLE, R.B., NEVIN, N.C., BLUNDELL, G., MERRETT, J.D. MCDONALD, J.R., JOHNSTON, W.P. Relation of alpha-1-antitrypsin phenotype to the performance of pulmonary function tests and to the prevalence of respiratory illness in a working population. Thorax 31: 149-157, 1976.

(35) COLLEY, J.R.T., DOUGLAS, J.W.B., REID, D.D. Respiratory disease in young adults: Influence of early childhood lower respiratory tract illness, social class, air pollution, and smoking. British Medical Journal 3(5873): 195-198, July 28, 1973.

(36) COMSTOCK, G.W., STONE, R.W., SAKAI, Y., MATSUYA, T., TONASCIA, J.A. Respiratory findings and urban living. Archives of Environmental Health 27(3): 143-150, September 1973.

(37) COSIO, M., GHEZZO, R.H., HOGG, J.C., CORBIN, R., LOVELAND, M., DOSMAN, J., MACKLEM, P.T. The relationships between structural changes in small airways and pulmonary function tests. New England Journal of Medicine 298: 1277-1281, 1978.

(38) DALHAMN, T. Effect of cigarette smoke on ciliary activity. American Review of Respiratory Disease 93(3)(Supplement): 108-114, 1966.

(39) DANIELE, R.P., DAUBER, J.H., ALTOSE, M.D., ROWLANDS, D.T., GORENBERG, D.J. Lymphocyte studies in asymptomatic cigarette smokers. A comparison between lung and peripheral blood. American Review of Respiratory Disease 116: 997-1105, 1977.

(40) DENSEN, P.M., JONES, E.W., BASS, H.E., BREUER, J., REED, E. A survey of respiratory disease among New York City postal and transit workers. 2. Ventilatory function tests results. Environmental Research 2(4): 277-296, July 1969.

(41) DIRKSEN, H., JANZON, L., LINDELL, S.E. Influence of smoking and cessation of smoking in lung function. A population study of closing volume and nitrogen wash-out. Scandinavian Journal of Respiratory Disease 85(Supplement): 266-274, 1974.

(42) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2: 1525-1536, 1976.

(43) DOSMAN, J., BODE, F., GHEZZO, R.H., MARTIN, R., MACKLEM, P.T. The relationship between symptoms and functional abnormalities in clinically healthy cigarette smokers. American Review of Respiratory Disease 114(2): 297-304, August 1976.

(44) DOSMAN, J.A., GHEZZO, R.H., BODE, F., MARTIN, R.R., MACKLEM, P.T. Tests of early diagnosis of airway obstruction: A perspective. Revue Francais Maladies Respiratoires 5: 377-389, 1977.

(45) DOSMAN, J., MACKLEM, P.T. Diseases of small airways. Advances in Internal Medicine 22: 355-376, 1977.

(46) EICHEL, B., SHAHRIK, H.A. Tobacco smoke toxicity: Loss of human oral leukocyte function and fluid-cell metabolism. Science 166(3911): 1424-1428, 1969.

(47) ENJETI, S., HAZELWOOD, B., PERMUTT, S., MENKES, H., TERRY, P. Pulmonary function in young smokers. Male-female differences. American Review of Respiratory Disease 118: 667-675, 1978.

(48) ERIKSSON, S. Pulmonary emphysema and alpha-1-antitrypsin deficiency. Acta Medica Scandinavica 175: 197-205, 1964.

(49) ERIKSSON, S. Studies in α_1-antitrypsin deficiency. Acta Medica Scandinavica 177(Supplement 432): 1-85, 1965.

(50) FAIRSHTER, R.D., WILSON, A.F. Volume of isoflow: Effect of distribution of ventilation. Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology 43(5): 807-811, 1977.

(51) FINKLEA, J.F., HASSELBLAD, V., RIGGAN, W.B., NELSON, W.C., HAMMER, D.I., NEWILL, V.A. Cigarette smoking hemagglutination inhibition response to influenza after natural disease and immunization. American Review of Respiratory Disease 104(3): 368-376, September 1971.

(52) FINKLEA, J.F., SANDIFER, S.H., SMITH, D.D. Cigarette smoking and epidemic influenza. American Journal of Epidemiology 90: 390-399, 1969.

(53) FINKLEA, J.F., SHY, C.M., LOVE, C.J., HAYES, C.G., NELSON, R.S., HOUSE, D.E. Health consequences of sulfur oxides: Summary and conclusions based upon CHESS studies of 1970-1971. In: Health Consequences of Sulfur Oxides: A Report from CHESS, 1970-1971. U.S. Environmental Protection Agency Publication No. EPA-650/1-74-004, 1974.

(54) FLETCHER, C.M. (Editor). Terminology, definitions, classification of chronic pulmonary emphysema and related conditions. A report of the conclusions of a Ciba Guest Symposium. Thorax 14: 286-299, 1959.

(55) FLETCHER, C.M., JONES, N.L., BURROWS, B, NIDEN, A.H.. American emphysema and British bronchitis. A standardized comparative study. American Review of Respiratory Disease 90: 1-13, 1964.

(56) FLETCHER, C., PETO, R. The natural history of chronic airflow obstruction. British Medical Journal 1: 1645-1648, 1977.

(57) FLETCHER, C., PETO, R., TINKER, C., SPEIZER, F.E. The Natural History of Chronic Bronchitis and Emphysema: An Eight-Year Study of Early Chronic Obstructive Lung Disease in Working Men in London. Oxford, Oxford University Press, 1976, 272 pp.

(58) FRASCA, J.M., AUERBACH, O., PARKS, V.R., JAMIESON, J.D. Alveolar cell hyperplasia in the lungs of smoking dogs. Experimental and Molecular Pathology 21: 300-312, 1974.

(59) GELB, A.F., GOLD, W.M., WRIGHT, R.R., BRUCH, H.R., NADEL, J.A. Physiologic diagnosis of subclinical emphysema. American Review of Respiratory Disease 107(1): 50-63, 1973.

(60) GRAY, J.P., KENNEDY, J.R. Ultrastructure and physiological effects of nontobacco cigarettes on tetrahymena. Archives of Environmental Health 28: 283-291, 1974.

(61) GREEN, G.M., CAROLIN, D. The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. New England Journal of Medicine 276(8): 421-427, 1967.

(62) GREGG, I. A study of the causes of progressive airways obstruction in chronic bronchitis. In: Current Research in Chronic Respiratory Disease, 11th Aspen Emphysema Conference, U.S. Public Health Service, Publication No. 10721, 1968, pp. 235-248.

(63) HAMMARSTEN, J.F., WELCH, M., RICHARDSON, R.H., PATTERSON, C.D., GUENTER, C.A. Familial alpha-1-antitrypsin deficiency and pulmonary emphysema. Transactions of the American Clinical and Climatological Association 80(1): 7-14, 1969.

(64) HARRIS, J.O., OLSEN, G.N., CASTLE, J.R., MALONEY, A.S. Comparison of proteolytic enzyme activity in pulmonary alveolar macrophages and blood leukocytes in smokers and nonsmokers. American Review of Respiratory Disease 111: 579-586, 1975.

(65) HARRIS, J.O., SWENSON, E.W., JOHNSON, J.E., III. Human alveolar macrophages: Comparison of phagocytic ability, glucose utilization, and ultrastructure in smokers and nonsmokers. Journal of Clinical Investigation 49(11): 2086-2096, November 1970.

(66) HEPPLESTON, A.G., STYLES, J.A. Pathology: Activity of a macrophage factor in collagen formation by silica. Nature 214: 521-522, April 29, 1967.

(67) HIGGINS, I.T.T. Epidemiology of chronic respiratory disease: A literature review. U.S. Environmental Protection Agency, Office of Research and Development, 1974, pp. 1-129.

(68) HIGGINS, M.W., KELLER, J.B., METZNER, H.L. Smoking, socioeconomic status, and chronic respiratory disease. American Review of Respiratory Disease 116: 403-410, 1977.

(69) HOGG, J.C., MACKLEM, P.T., THURLBECK, W.M. Site and nature of airway obstruction in chronic obstructive lung disease. New England Journal of Medicine 278(25): 1355-1360, 1968.

(70) HRUBEC, Z., CEDERLOF, R., FRIBERG, L., HORTON, R., OZOLINS, G. Respiratory symptoms in twins. Archives of Environmental Health 27(3): 189-195, September 1973.

(71) HURST, A. Familial emphysema. American Review of Respiratory Disease 80(1): 179-180, 1959.

(72) HUTCHEON, M., GRIFFIN, P., LEVISON, H., ZAMEL, N. Volume of isoflow. A new test in detection of mild abnormalities of lung mechanics. American Review of Respiratory Disease 110(4): 458-465, October 1974.

(73) IMBODEN, C.A., Jr. Rising mortality from chronic respiratory disease. American Journal of Public Health 58: 221-222, 1968. (Letter)

(74) JAKAB, G.J. Adverse effect of a cigarette smoke component, acrolein, on pulmonary antibacterial defenses and on viral-bacterial interactions in the lung. American Review of Respiratory Disease 115: 33-38, 1977.

(74a) JANOFF, A., CARP, H. Possible mechanisms of emphysema in smokers. Cigarette smoke condensate suppresses protease inhibition in vitro. American Review of Respiratory Disease 116: 65-72, 1977.

(75) JANOFF, A., ROSENBERG, R., GALDSTON, M. Elastase-like, esteroprotease activity in human and rabbit alveolar macrophage granules. Proceedings of the Society for Experimental Biology and Medicine 136(3): 1054-1058, 1971.

(76) JANOFF, A., SANDHAUS, R.A., HOSPELHORN, V.D., ROSENBERG, R. Digestion of lung proteins by human leukocyte granules in vitro. Proceedings of the Society for Experimental Biology and Medicine 140: 516-519, 1972.

(77) KAPLAN, P.D., KUHN, C., PIERCE, J.A. The induction of emphysema with elastase. I. The evolution of the lesion and the influence of serum. Journal of Laboratory and Clinical Medicine 82(3): 349-356, 1973.

(78) KAZAZIAN, H.H. A geneticist's view of lung disease. American Review of Respiratory Disease 113: 261-266, 1976.

(79) KEAST, D., HOLT, P. Smoking and immune response. New Scientist 61: 806-807, March 28, 1974.

(80) KIERNAN, K.E., COLLEY, J.R.T., DOUGLAS, J.W.B., REID, D. Chronic cough in young adults in relation to smoking habits, childhood environment, and chest illness. Respiration 33: 236-244, 1976.

(81) KILBURN, K.H., MCKENZIE, W. Leukocyte recruitment to airways by cigarette smoke and particle phase in contrast to cytotoxicity of vapor. Science 189: 634-637, 1975.

(82) KIMBEL, P., WEINBAUM, G. Role of leucoproteases in the genesis of emphysema. In: Junod, A., De Haller, R. (Editors). Lung Metabolism. New York, Academic Press, 1975, pp. 25-41.

(83) KLEINERMAN, J., RICE, D.B. Evidence for preclinical lesions in lungs of young smokers: A postmortem epidemiologic-pathologic correlative study. In: Steinfeld, J., Griffith, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 161-169.

(84) KNUDSON, R.J., LEBOWITZ, M.D., BURTON, A.P., KNUDSON, D.E. The closing volume test: Evaluation of nitrogen and bolus methods in a random population. American Review of Respiratory Disease 115(3): 423-434, 1977.

(85) KRUMHOLZ, R.A., CHEVALIER, R.B., ROSS, J.C. Changes in cardiopulmonary functions related to abstinence from smoking. Annals of Internal Medicine 62(2): 197-207, 1965.

(86) KUEPPERS, F., BLACK, L. Alpha-1-antitrypsin and its deficiency. American Review of Respiratory Disease 110: 176-194, 1974.

(87) KUEPPERS, F., FALLAT, R., LARSON, R.K. Obstructive lung disease and alpha-1-antitrypsin deficiency gene heterozygosity. Science 165: 899-900, 1969.

(88) LARSON, R.K., BARMAN, M.L. The familial occurrence of chronic obstructive pulmonary disease. Annals of Internal Medicine 63(6): 1001-1008, December 1965.

(89) LARSON, R.K., BARMAN, M.L. KUEPPERS, F., FUDENBERG, H.H. Genetic and environmental determinants of chronic obstructive pulmonary disease. Annals of Internal Medicine 72(5): 627-632, May 1970.

(90) LEBOWITZ, M.D., BURROWS, B. Quantitative relationships between cigarette smoking and chronic productive cough. International Journal of Epidemiology 6(2): 107-113, 1977.

(91) LEUCHTENBERGER, C., LEUCHTENBERGER, R., DOOLIN, R. A correlated histological, cytological and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. 1. Bronchitis with atypical epithelial changes in mice exposed to cigarette smoke. Cancer 11: 490-506, 1958.

(92) LIEBERMAN, J., GAWAD, M.A. Inhibitors and activators of leukocytic proteases in purulent sputum: Digestion of human lung and inhibition of alpha-1-antitrypsin. Journal of Laboratory and Clinical Medicine 77(4): 713-727, 1971.

(93) LIEBERMAN, J., MITTMAN, C., SCHNEIDER, A.S. Screening for homozygous and heterozygous alpha-1-antitrypsin deficiency. Journal of the American Medical Association 210: 2055-2060, 1969.

(94) LOW, R.B. Effect of a phagocytic load on macrophage protein and nucleic acid biosynthesis. Journal of Cell Biology 67: 248a, 1975. (Abstract)

(95) LOW, R.B. Protein biosynthesis by the pulmonary alveolar macrophage: Comparison of suspended and adhered cells. American Review of Respiratory Disease 109(4): 741, 1974. (Abstract)

(96) LOW, R.B., BULMAN, C.A. Substrate transport by the pulmonary alveolar macrophage. Effects of cigarette smoke. American Review of Respiratory Disease 116: 423-431, 1977.

(97) MACKLEM, P.T., MEAD, J. Resistance of central and peripheral airways measured by a retrograde catheter. Journal of Applied Physiology 22(1): 395-401, 1967.

(98) MANFREDA, J., NELSON, N., CHERNIACK, R.M. Prevalence of respiratory abnormalities in a rural and an urban community. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, Division of Lung Disease. National Technical Information Service, PB 272 154, September 1, 1977, pp. 42-80.

(99) MANFREDA, J., NELSON, N., CHERNIACK, R.M. Prevalence of respiratory abnormalities in a rural and an urban community. American Review of Respiratory Disease 117: 215-226, 1978.

(100) MANFREDA, J., NELSON, N., CHERNIACK, R.M. Two year followup: The general population of Charleswood and Portage La Prairie. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, Division of Lung Diseases. National Technical Information Service, PB 272 154, September 1, 1977, pp. 97-105.

(101) MARCO, V., MASS, B., MERANZE, D.R., WEINBAUM, G., KIMBEL, P. Induction of experimental emphysema in dogs using leukocyte homogenates. American Review of Respiratory Disease 104: 595-598, 1971.

(*102*) MARCO, M., MINETTE, A. Lung function changes in smokers with normal conventional spirometry. American Review of Respiratory Disease 114: 723-738, 1976.

(*103*) MASS, B., IKEDA, T., MERANZE, D.R., WEINBAUM, G., KIMBEL, P. Induction of experimental emphysema: Cellular and species specificity. American Review of Respiratory Disease 106: 384-391, 1972.

(*104*) MATULIONIS, D.H., TRAURIG, H.H. *In situ response of lung macrophages* and hydrolase activities in cigarette smoke. Laboratory Investigation 37(3): 314-326, 1977.

(*105*) MCCARTHY, D.S., CRAIG, D.B., CHERNIACK, R.M. Effect of modification of the smoking habit on lung function. American Review of Respiratory Disease 114: 103-113, 1976.

(*106*) MILLER, R., KUEPPERS, S.F., HEPPER, N.G. A comprehensive study of host factors for chronic obstructive pulmonary disease in a North American rural community: Genetic characteristics. Bulletin of the International Union Against Tuberculosis 51(1, Tome 2): 629, 1976.

(*107*) MITCHELL, R.S., STANFORD, R.E., JOHNSON, J.M., SILVERS, G.W., DART, G., GEORGE, M.S. The morphologic features of the bronchi, bronchioles and alveoli in chronic airway obstruction: A clinicopathologic study. American Review of Respiratory Disease 114(1): 137-145, July 1976.

(*108*) MITTMAN, C. The PiMZ phenotype: Is it a significant risk factor for the development of chronic obstructive lung disease? American Review of Respiratory Disease 118: 649-652, 1978.

(*109*) MITTMAN, C. (Editor). Pulmonary emphysema and proteolysis. New York, Academic Press, 1972, 562 pp.

(*110*) MONTO, A.S., HIGGINS, M.W., ROSS, H.W. The Tecumseh Study of respiratory illness. VIII. Acute infection in chronic respiratory disease and comparison groups. American Review of Respiratory Disease 111(1): 27-36, January 1975.

(*111*) MORSE, J.O., LEBOWITZ, M.D., KNUDSON, R.J., BURROWS, B. Relation of protease inhibitor phenotypes to obstructive lung diseases in a community. New England Journal of Medicine 296(21): 1190-1194, 1977.

(*112*) NIEWOEHNER, D.E., KLEINERMAN, J., RICE, D.B. Pathologic changes in the peripheral airways of young cigarette smokers. New England Journal of Medicine 291: 755-758, 1974.

(*113*) OSHIMA, H., IMAI, M., KAWAGISHI, T. A study on air pollution effects on the respiratory symptoms in the city of Yokkaichi, Central Japan. Mie Igaku 16(1): 25-29, June 1972.

(*114*) ÖXHOJ, H., BAKE, B., WILHELMSEN, L. Ability of spirometry, low-volume curves, and the nitrogen closing volume test to detect smokers. Scandinavian Journal of Respiratory Disease 58: 80-96, 1977.

(*115*) PETERSON, D.I., LONERGAN, L.H., HARDINGE, M.G. Smoking and pulmonary function. Archives of Environmental Health 16: 215-218, 1968.

(*116*) PRATT, S.A., FINLEY, T.N., SMITH, M.H., LADMAN, A.J. A comparison of alveolar macrophages and pulmonary surfactant (?) obtained from the lungs of human smokers and nonsmokers by endobronchial lavage. Anatomical Record 163(4): 497-508, 1969.

(*117*) Prevalence of selected chronic respiratory conditions, United States–1970. DHEW Publication No. (HRA) 74-1511, 1973, Series 10, No. 84.

(*118*) The Registrar General's Decennial Supplement, England and Wales, Occupational Mortality. 1931, Her Majesty's Stationery Office, London, 1951.

(*119*) RODRIGUEZ, R.J., WHITE, R.R., SENIOR, R.M., LEVINE, E.A. Elastase release from human alveolar macrophages: Comparison between smokers and nonsmokers. Science 198(4314): 313-314, 1977.

(120) ROSZMAN, T.L., ELLIOTT, L.H., ROGERS, A.S. Suppression of lymphocyte function by products derived from cigarette smoke. American Review of Respiratory Disease 111(4): 453-457, 1975.

(121) ROSZMAN, T.L., ROGERS, A.S. The immunosuppressive potential of products derived from cigarette smoke. American Review of Respiratory Disease 108: 1158-1163, 1973.

(122) RUSH, D. Changes in respiratory symptoms related to smoking in a teenage population: The results of two linked surveys separated by one year. International Journal of Epidemiology 5(2): 173-178, 1976.

(123) RUSH, D. Respiratory symptoms in a group of American secondary school students: The overwhelming association with cigarette smoking. International Journal of Epidemiology 3(2): 153-165, 1974.

(124) RYLANDER, R. Pulmonary cell responses to inhaled cigarette smoke. Archives of Environmental Health 29: 329-333, 1974.

(125) SAWICKI, F. Air pollution and prevalence of chronic nonspecific respiratory diseases. In: Brzezinski, Z., Kopczynski, J., Sawicki, F. (Editors). Ecology of Chronic Nonspecific Respiratory Diseases. International Symposium, September 7-8, 1971, Warsaw, Poland, Panstwowy Zaklad Wydawnictw Lekarskich, 1972, pp. 3-13.

(126) SCHUYLER, M.R., RYNBRANDT, D.J., KLEINERMAN, J. Physiologic and morphologic observations of the effects of intravenous elastase on the lung. American Review of Respiratory Disease 117: 97-102, 1978.

(127) SEELY, J.E., ZUSKIN, E., BOUHUYS, A. Cigarette smoking: Objective evidence for lung damage in teen-agers. Science 172: 741-743, 1971.

(128) SELTZER, C.C., SIEGELAUB, A.B., FRIEDMAN, G.D., COLLEN, M.F. Differences in pulmonary function related to smoking habits and race. American Review of Respiratory Disease 110(5): 598-608, November 1974.

(129) SENIOR, R.M., TEGNER, H., KUHN, C., OHLSSON, K., STARCHER, B.G., PIERCE, J.A. The induction of pulmonary emphysema with human leukocyte elastase. American Review of Respiratory Disease 116: 469-475, 1977.

(130) SHEA, J.W., HUBER, G.L., HOLMES, L., NOMANS, S.A. The effect of experimental tobacco smoke inhalation on *in vitro* alveolar macrophage bactericidal function. Journal of Laboratory and Clinical Medicine 92(2): 270-282, 1978.

(131) SILVERMAN, N.A., POTVIN, C., ALEXANDER, J.C., JR., CHRETIEN, P.B. In vitro lymphocyte reactivity and T-cell levels in chronic cigarette smokers. Clinical and Experimental Immunity 22(2): 285-292, November 1975.

(132) SNIDER, G.I., HAYES, J.A., FRANZBLAU, C., KAGAN, H.M., STONE, P.S., NORTHY, A.L. Relationship between elastolytic activity and experimental emphysema-inducing properties or papain preparations. American Review of Respiratory Disease 110: 254-262, 1974.

(133) STEBBINGS, J.H., JR. A survey of respiratory disease among New York City postal and transit workers. IV. Racial differences in the FEV_1. Environmental Research 6: 147-158, 1973.

(134) STERLING, G.M. Mechanism of bronchoconstriction caused by cigarette smoking. British Medical Journal 3: 275-277, July 29, 1967.

(135) STUART, R.S., HIGGINS, W.H., BROWN, P.W. In vitro toxicity of tobacco smoke solutions to rabbit alveolar macrophages. Archives of Environmental Health 33: 135-140, 1978.

(136) TALAMO, R.C., ALLEN, J.D., KAHAN, M.G., AUSTEN, K.F. Hereditary alpha-1-antitrypsin deficiency. New England Journal of Medicine 278(7): 345-351, February 15, 1968.

(137) THOMAS, W.R., HOLT, P.G., KEAST, D. Cigarette smoke and phagocyte function: Effect of chronic exposure in vivo and acute exposure in vitro. Infection and Immunity 20(2): 468-475, 1978.

(*138*) THURLBECK, W.M. Aspects of chronic airflow obstruction. Chest 72: 341-349, 1977.

(*139*) THURLBECK, W.M. Chronic airflow obstruction in lung disease. V. Major problems in pathology. Philadelphia, W.B. Saunders Co., 1976, pp. 235-287.

(*140*) THURLBECK, W.M. Small airways: Physiology meets pathology. New England Journal of Medicine 298: 1310-1311, 1978.

(*141*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. PHS Publication No. 1103, 1964, 387 pp.

(*142*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review: 1967. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. 1696, Revised, January 1968, 227 pp.

(*143*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1968. Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. 1696, 1968, 117 pp.

(*144*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1969. Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. 1969-2, 1969, 98 pp.

(*145*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1971. U.S. Department of Health, Education, and Welfare, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 71-7513, 1971, 458 pp.

(*146*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

(*147*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: 1973. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 73-8704, 1973, 249 pp.

(*148*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (CDC) 74-8704, 1974, 124 pp.

(*149*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (CDC) 76-8704, 1975, 235 pp.

(*150*) VAN DER LENDE, R., DE KROON, J.P.M., TAMMELING, G.J., VISSER, B.F., DE VRIES, K., WEVER-HESS, J., ORIE, N.G.M. Prevalence of chronic nonspecific lung disease in a nonpolluted and in air-polluted area of the Netherlands. In: Brzezinski, Z., Kopczynski, J., Sawicki, F. (Editors). Ecology of Chronic Nonspecific Respiratory Diseases. International Symposium, September 7-8, 1971, Warsaw, Poland, Panstwowy Zaklad Wydawnictw Lekarskich, 1972, pp. 27-33.

(*151*) WALDMAN, R.H., BOND, J.O., LEVITT, L.P. HARTWIG, E.C., PRATHER, R.L., BARATTA-NEILL, J.S., SMALL, P.A., JR. An evaluation of influenza immunization. Influence of route of administration and vaccine strain. Bulletin of the World Health Organization 41: 543-548, 1969.

(*152*) WANNER, A. State of the art. Clinical aspects of mucociliary transport. American Review of Respiratory Disease 116: 73-125, 1977.

(*153*) WANNER, A., HIRSCH, J.A., GREENELTER, D.E., SWENSON, E.W., FORE, T. Tracheal mucous velocity in beagles after chronic exposure to cigarette smoke. Archives of Environmental Health 27:370-371, 1973.

(*154*) WARR, G.A., MARTIN, R.R. In vitro migration of human alveolar macrophages: Effects of cigarette smoking. Infection and Immunity 8(2): 222-227, 1973.

(*155*) WARR, G.A., MARTIN, R.R., HOLLEMAN, C.L., CRISWELL, B.S. Classification of bronchial lymphocytes from nonsmokers and smokers. American Review of Respiratory Disease 113: 96-100, 1976.

(*156*) WARR, G.A., MARTIN, R.R., SHARP, P.M., ROSSEN, R.D. Normal human bronchial immunoglobulins and proteins. American Review of Respiratory Disease 116: 25-30, 1977.

(*157*) WEISSMANN, G. The role of lysosomes in inflammation and disease. Annual Review of Medicine 18: 97-112, 1967.

(*158*) WELCH, M.H., REINECKE, M.E. HAMMERSTEN, J.F., GUENTER, C.A. Antitrypsin deficiency in pulmonary disease: The significance of intermediate levels. Annals of Internal Medicine 71(3): 553-542, September 1969.

(*159*) WILHELMSEN, L. Effects on bronchopulmonary symptoms, ventilation, and lung mechanics of abstinence from tobacco smoking. Scandanavian Journal of Respiratory Disease 48: 407-414, 1967.

(*160*) WOOLCOCK, A.J., VINCENT, N.J., MACKLEM, P.T. Frequency dependence of compliance as a test for obstruction of the small airways. Journal of Clinical Investigation 48: 1097-1105, 1969.

(*161*) WOOLF, C.R. Clinical findings, sputum examinations, and pulmonary function tests related to the smoking habit of 500 women. Chest 66: 652-659, 1974.

(*162*) WYATT, J.P. Environmental factors in chronic lung disease. In: Lee, D.H.K. (Editor). Environmental Factors on Respiratory Disease. Fogarty International Center Proceedings No. 11, New York, Academic Press, 1972, pp. 119-137. (Abstract)

(*163*) YEAGER, H. Alveolar cells: Depressant effect of cigarette smoke on protein synthesis. Proceedings of the Society of Experimental Biology and Medicine 31(1): 247-250, 1969.

(*164*) YEAGER, H., ZIMMET, S.M., SCHWARTZ, S.L. Pinocytosis by human alveolar macrophages: Comparison of smokers and nonsmokers. Journal of Clinical Investigation 54(2): 247-251, 1974.

7. INTERACTION BETWEEN SMOKING AND OCCUPATIONAL EXPOSURES.

CONTENTS

LIST OF FIGURES

Introduction

Despite increasing recognition that both smoking and occupational exposures contribute independently to the development of certain disease states, few investigators have addressed the ways in which these two factors act together to produce disease. Some of the effects historically attributed to smoking may actually reflect an interaction between smoking and occupational exposure. This cannot always be quantified at the present time, but at least six different ways have been identified in which smoking may act with physical and chemical agents found in the workplace. These actions are not mutually exclusive and several may prevail for any given agent.

Six ways in which smoking may act with physical and chemical agents to produce or increase adverse health effects are:

1. Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent by inhalation, ingestion, and/or skin absorption.
2. Workplace chemicals may be transformed into more harmful agents by smoking.
3. Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent.
4. Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect.
5. Smoking may act synergistically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influences of the agent and smoking added together.
6. Smoking may contribute to accidents in the workplace.

Exposure to multiple physical and chemical agents in the workplace can compound these various types of actions.

Illustrative Examples of Different Modes of Action Between Smoking and Occupational Exposures

Tobacco products may serve as vectors by becoming contaminated with toxic agents found in the workplace, thus facilitating entry of the agent by inhalation, ingestion, and/or skin absorption.

Workplace chemicals may be transformed into more harmful agents by smoking.

Investigations of outbreaks of polymer fume fever provide clear illustrations of both of these modes of action. Polymer fume fever is a disease with influenza-like symptoms caused by inhalation of fumes from heated polytetrafluoroethylene, e.g., Teflon® (*59*). Typical symptoms include chest discomfort, fever, leukocytosis, headache, chills, muscular aches, and weakness. Since the symptoms are so similar to influenza, polymer fume fever may be difficult to diagnose.

Workers who continue to smoke may experience continuing reexposure and recurrent symptoms. Although complete recovery has been reported to occur usually within 12 to 48 hours after exposure is terminated, an autopsy report has attributed permanent lung damage to repeated episodes of polymer fume fever (*89*). Pulmonary edema following exposure to heated polytetrafluoroethylene has also been reported (*26, 73*). Polymer fume fever was first recorded in 1951 (*33*) as a result of two workers being exposed to the fluorocarbon polymer, polytetrafluoroethylene, heated to 450-500° C. The particular decomposition product(s) responsible for polymer fume fever have not yet been identified, but temperatures in excess of 315° C have been sufficient to cause symptoms. The temperature of the combustion zone of cigarettes is approximately 875° C (*82*).

Numerous outbreaks of polymer fume fever among smokers have been attributed to the decomposition of workplace polytetrafluoroethylene by lit cigarettes and inhalation of the harmful decomposition products with cigarette smoke. One report (*18*) describes aviation employees whose work involved contact with door seals that had been sprayed with an unspecified fluorocarbon polymer. In one case, a worker smoking during a break realized by the taste of his cigarette that it had become contaminated. Although the worker extinguished the cigarette, he experienced shivering and chills, which lasted approximately 6 hours, beginning 1/2 hour after this incident. Another illustrative report (*12*) describes outbreaks of polymer fume fever among workers who smoked when their hands were contaminated with polytetrafluoroethylene used as a mold release agent. There was no recurrence of symptoms after smoking at the plant was prohibited. An outbreak of polymer fume fever among workers using liquid fluorocarbon polymer in the production of imitation crushed velvet was likewise attributed to decomposition of fluorocarbon polymer by lit cigarettes (*85*). Processing temperatures at this plant were too low to pyrolyze the polymer. The seven affected workers were all cigarette smokers, whereas most of the workers without symptoms were nonsmokers. After work practices were changed to prohibit smoking in the work area and to require hand washing before smoking, no further symptoms at this facility were reported. Other outbreaks of polymer fume fever attributed to cigarette smoking have also been reported (*1, 11, 44, 76, 90*).

The effects of smoking cigarettes contaminated with known amounts of tetrafluoroethylene polymer have been studied with the assistance of human volunteers (*22*). Nine out of ten subjects were reported to exhibit typical polymer fume fever symptoms after each had smoked just one cigarette contaminated with 0.40 mg tetrafluoroethylene polymer. Onset of symptoms ranged from 1 to 3.5 hours after smoking; recovery time averaged 9 hours.

With respect to tobacco products serving as vectors, the National Institute for Occupational Safety and Health (NIOSH) has thus far identified the following agents as potential occupational contaminants of tobacco and tobacco products:

Agent	*Major Health Effects*
Formaldehyde (*61*)	Respiratory irritant, dermatitis
Boron Trifluoride (*57*)	Respiratory irritant, joint disease
Organotin (*66*)	Respiratory irritant
Methyl Parathion (*65*)	Reduced erythrocyte cholinesterase activity
Dinitro-*ortho*-Creosol (*60*)	Kidney damage, peripheral neuritis, CNS disturbances.
Carbaryl (*58*)	Inhibition of acetylcholinesterase
Inorganic Fluorides (*63*)	Fluoride osteosclerosis
Inorganic Mercury (*64*)	CNS disturbances, kidney damage, peripheral neuritis
Lead (*81, 94*)	Nervous system toxin, renal toxin, changes in hematopoietic system

Additional research is clearly warranted to identify other workplace chemicals which are transformed into more toxic agents by tobacco smoking.

Certain toxic agents in tobacco products and/or smoke may also occur in the workplace, thus increasing exposure to the agent.

Hydrogen Cyanide

Hydrogen cyanide has been found in cigarette smoke at concentrations as high as 1,600 ppm (*83*). In 1973 Pettigrew and Fell (*69*) found the plasma thiocyanate (a metabolite of cyanide) levels of smokers significantly elevated as compared to those in nonsmokers. In 1973 Radojicic (*71*) reported a study of 43 workers in the electroplating division of an electronics firm in Nes, Yugoslavia. He found that the majority of workers exposed to cyanide complained of fatigue, headache, asthenia, tremors of the hands and feet, and pain and nausea. The urinary thiocyanate concentrations of the exposed group of workers were higher at the end of the work shift than before exposure at work. Urinary thiocyanate concentrations were significantly higher among exposed smokers than unexposed smoking controls, significantly higher among exposed nonsmokers than unexposed nonsmokers, and significantly higher among exposed smokers than among exposed nonsmokers. These findings demonstrate that smoking and occupational exposure can each contribute to a worker's total exposure to and intake of cyanide.

Adverse effects from cyanide may occur from sublethal doses. Hydrogen cyanide and cyanide salts inhibit cytochrome oxidase. Cyanide can form complexes with heavy metal ions. Formations of these complexes in the body can rapidly cause disturbances in enzyme systems in which heavy metals act as co-factors either alone or as part of organic molecules (*2, 15, 27*). Thiocyanate itself has toxic effects, especially inhibition of uptake of inorganic iodide into the thyroid gland for incorporation into thyroxin (*91*). The National Institute for Occupational Safety and Health has estimated that over 20,000 workers in 75 different occupational groups have potential occupational exposure to cyanide (*62*).

Carbon Monoxide

Cigarette smoking causes increased exposure to carbon monoxide (CO). A CO concentration of 4 percent (40,000 ppm) in cigarette smoke leads to an alveolar CO concentration of 0.04 to 0.05 percent (400 to 500 ppm), which produces a carboxyhemoglobin (COHb) concentration of 3 to 10 percent (*21, 40, 68*). Goldsmith, et al. (*29*) estimated that the cigarette smoker is exposed to 475 ppm CO for approximately 6 minutes per cigarette.

In a study of COHb levels in British steelworkers, Jones and Walters (*39*) found a 4.9 percent end of shift COHb saturation in nonsmoking blast furnace workers compared to 1.5 percent saturation in nonsmoking unexposed controls. For heavy cigarette smokers, the levels were 7.4 percent for blast furnace workers and 4.0 percent for smoking unexposed controls. The COHb levels of blast furnace workers who smoked were in a critical range. Studies by Aronow (*5-9*), Anderson (*3*), and Horvat (*36*) and their associates have shown that levels of COHb in excess of 5 percent can cause cardiovascular alterations which are dangerous for persons with cardiovascular disease.

Potential occupational exposure to CO is common (*37*). Since a significant number of workers have coronary heart disease and many smoke, additional occupational exposure to CO may increase cardiovascular morbidity and mortality.

Methylene Chloride

Methylene chloride is metabolized to CO in the body (*28*). COHb levels in blood increase with increasing environmental concentrations of methylene chloride as well as with increasing physical activity at the time of exposure (*10, 80*). Maximum COHb levels occur 3 to 4 hours *after* exposure is discontinued.

Mean methylene chloride concentrations of 778 ppm over a 3-hour exposure period produced a maximum COHb level of 9.1 percent 4 hours after exposure was discontinued. Twenty hours after this

exposure the COHb level remained elevated (4.4 percent versus 0.8 percent prior to exposure) (*80*).

Based on this time lag, prohibiting a worker exposed to methylene chloride from smoking on the job would not be sufficient to protect the worker who smokes after he leaves work from the additive burdens of CO from methylene chloride and tobacco smoke.

Other Chemical Agents

Other chemical agents found in tobacco, or in the combustion of tobacco products, and also potentially found in the workplace include: acetone, acrolein, aldehydes, arsenic, cadmium, formaldehyde, hydrogen sulfide, ketones, lead, methyl nitrite, nicotine, nitrogen dioxide, phenol, and polycyclic compounds (*83*).

Smoking may contribute to an effect comparable to that which can result from exposure to toxic agents found in the workplace, thus causing an additive biological effect.

Coal Dust

Coal dust and cigarette smoking appear to act in an additive fashion to produce obstructive airway disease. Although dust exposure alone plays a significant role in the development of this disease, there is a significantly higher prevalence of obstructive airway disease in smoking miners than in nonsmoking miners with the same dust exposure (*41*). Flow volume curve data suggest that nonsmoking miners with dust-induced chronic obstructive airway disease have decreased flow rates primarily at higher lung volumes, whereas smoking miners have decreased flow rates at all lung volumes (*32*).

Cotton Dust

Many investigators have noted that among cotton workers, cigarette smokers show increased prevalence of byssinosis when compared to nonsmoking cotton workers (*13*, *53*, *54*, *55*). Cotton dust inhalation produces an acute clinical syndrome consisting of chest tightness, cough, and shortness of breath in cotton workers (*34*). This was formerly known as "Monday morning fever" since symptoms develop on the first day of work after an absence. The clinical syndrome may be accompanied by significant reduction in pulmonary function (*52*). The acute clinical and functional abnormalities produced by cotton dust gradually become more frequent as the disease progresses, eventually resulting in chronic obstructive airways disease (*34*).

In the acute phase of the illness there is a significantly greater diminution in pulmonary function in smokers than in nonsmokers (*55*), and the relationship of cotton dust and smoking to pulmonary dysfunction appears to be additive.

In the more severe phase of chronic obstructive airway disease, the relationship between smoking and cotton dust exposure appears to be synergistic (*55*).

Beta-Radiation

In studies in mice when both *beta*-radiation and cigarette tar were applied to produce carcinomas in the skin, cancers appeared 6 to 7 months earlier than when radiation was administered alone. The shortened latent period gave an illusion of synergism which was reported in a preliminary analysis based on tumor yield at 18 months. However, at the conclusion of the experiment, the authors felt there was actually nothing more than an additive biological effect of cigarette tar and *beta*-radiation (*23*).

Chlorine

Exposure to chlorine and cigarette smoke may cause an additive biological effect. Chester, et al. (*20*) examined 139 men in a plant producing chlorine and sodium hydroxide by electrolysis of brine. Of the 139 workers, 55 had been accidentally exposed one or more times to chlorine at high concentrations and had required oxygen therapy at least once during their employment. The maximal mid-expiratory flow (MMF) values of workers with accidental chlorine exposure was compared with those of nonexposed workers for smokers and nonsmokers. A significant difference in MMF was seen when chlorine and smoking were considered as additive toxic agents. MMF values decrease in the sequence from unexposed nonsmokers (4.36) to unexposed smokers (4.13) to exposed nonsmokers (4.10) and to exposed smokers (3.57).

Capodaglio, et al. (*19*) studied the diffusing capacity of the lung in workers employed in a plant for electrolytic production of chlorine and soda. He compared 52 exposed workers to 27 unexposed workers. The diffusing capacity of the lung was significantly lower in exposed smokers than in nonexposed smokers ($P \leq 0.02$), lower in exposed smokers than in exposed nonsmokers, and lower in exposed smokers than in unexposed nonsmokers ($P \leq 0.03$).

These studies show the additive effects of cigarette smoking and chlorine exposure.

Exposure Among Fire Fighters

A study of the prevalence rates of chronic nonspecific respiratory disease among 2,000 Boston fire fighters showed a contribution from both occupation and smoking (*77*). Rates of chronic nonspecific respiratory disease in young fire fighters increased with amount smoked; however, new fire fighters had lower rates for all smoking categories than experienced fire fighters. The experienced fire fighter

who was a light or nonsmoker had more than a threefold higher rate of chronic nonspecific respiratory disease than the new fire fighter in the same smoking category.

Smoking may act synergestically with toxic agents found in the workplace to cause a much more profound effect than that anticipated simply from the separate influences of the agent and smoking added together.

Asbestos

Asbestos provides one of the most dramatic examples of adverse health effects resulting from interaction between the smoking of tobacco products and an agent used in the workplace. Asbestos, the generic term used to describe chain-silicates, was first used in Finland to strengthen clay pottery about 2500 B.C. (*79*). Modern industrial use of asbestos is relatively more recent, dating from 1880 when it was used to make heat- and acid-resistant fabrics (*35*, *72*). From that beginning its usefulness has grown immensely, output having increased over one thousandfold in the past 60 years (*79*).

With increasing industrial importance has come an increasing awareness of the adverse health consequences incurred by working with asbestos. Asbestosis was first reported early in the twentieth century, and subsequent individual observations and epidemiological studies have well defined the association of this nonmalignant respiratory disease with asbestos exposure. In 1935 Lynch and Smith reported a suspected association between asbestosis and lung cancer (*49*). Succeeding epidemiological studies have given significant support to these early reports.

In 1968 a prospective study of insulation workers by Selikoff, et al. (*75*) defined cigarette smoking as an additional hazard to the health of workers exposed to asbestos. In a study of 370 asbestos insulation workers, 1963-1967, Selikoff found that of 87 men with no history of cigarette smoking, none died of bronchogenic carcinoma, while 24 of 283 cigarette smokers did die of that disease. This study suggested that asbestos workers who smoke have 8 times the lung cancer risk of all other smokers and 92 times the risk of nonsmokers not exposed to asbestos. This same group of insulation workers was restudied 5 years later (*31*). At that time 41 of the 283 smokers had died of bronchogenic cancer. In a larger prospective study involving 11,656 insulation workers in the United States and Canada, 134 deaths due to lung cancer were found among 9,591 men with a history of regular cigarette smoking (*31*). Of the 2,066 noncigarette smokers followed over the same 5-year period, only two deaths were due to lung cancer.

Over a 10-year period, Berry, et al. (*14*) studied 1,300 male and 480 female asbestos factory workers in whom a smoking history was known. The male and female groups were then evaluated on whether they had low to moderate or high asbestos exposure. The researchers

found no significant excess deaths from lung cancer in either smoking or nonsmoking groups at low to moderate exposures. However, a highly significant increase in lung cancer deaths was seen in the severely exposed who also smoked.

The above mentioned studies and other similar studies have shown that cigarette smoking and asbestos exposure together are associated with extremely high rates of lung cancer. But what role does each play in this process? Two general hypotheses have been proposed to answer this question (*14*). The additive hypothesis suggests that asbestos exposure and cigarette smoking act independently to produce lung cancer and that the excess risk seen when both are experienced together is due to the sum of their risks. The multiplicative (synergistic) hypothesis contends that each of the involved risk factors has a certain value for its risk and that the product of these two risks (asbestos exposure × cigarette smoking) describes how they work together to bring about a certain result (lung cancer). Selikoff's data suggest a synergistic effect. However, in the study by Berry, et al. (*14*), the male data do not fit either hypothesis while the female data easily support the multiplicative hypothesis. A more recent study by Martischnig, et al. (*50*) of 201 men with confirmed bronchial carcinoma was much less consistent with the multiplicative hypothesis and pointed more closely to the additive hypothesis. However, the smoking histories were obtained retrospectively, smoking-specific estimates were not available, and the data are difficult to interpret. Regardless of whether the action is additive or synergistic, a substantial risk faces smokers who are exposed to asbestos. The extraordinary increase in lung cancer resulting from the interaction of cigarette smoking and asbestos exposure has led the Johns-Manville Corporation to ban smoking in its asbestos plants (*38*).

Other neoplasms have been associated with exposure to asbestos but appear to be independent of smoking habits. Eighty-five to ninety percent of mesothelioma has been attributed to exposure to asbestos (*84*). The relationship of pleural and peritoneal mesothelioma to smoking and asbestos exposure was investigated by Hammond and Selikoff (*31*). Calculations from their studies reveal 0.38 deaths from pleural mesothelioma per 1,000 man years of observation among asbestos-exposed cigarette smokers and 0.39 for exposed nonsmokers. Rates for peritoneal mesothelioma were 0.73 for smokers and 0.83 for nonsmokers (*74*). On the other hand, esophageal cancer rates were significantly increased, but only among smokers. Rates for stomach and colon cancer showed no such restriction (*31, 75*).

In 1971 Weiss (*87*) explored the relationship of asbestosis to cigarette smoking. He examined 100 asbestos textile workers by chest X-ray and questionnaire. Pulmonary fibrosis was found in 40 percent of 75 workers who smoked and 24 percent of 25 nonsmokers. Weiss determined that age, sex, and duration of exposure to asbestos were

not responsible for the difference noted. Seventy-three of the above cigarette smokers were then questioned concerning amount and duration of smoking. The prevalence of fibrosis was 23 percent of 13 workers who smoked less than one pack per day and 43 percent of 60 who smoked one or more packs per day. Of 18 workers who smoked a pack or more per day for less than 20 years and had less than 20 years of asbestos exposure, 28 percent had fibrosis. Of 19 workers who smoked more than 20 years and with more than 20 years of exposure to asbestos, 74 percent had fibrosis. This study suggested that the prevalence of pulmonary fibrosis increases with an increasing amount and duration of cigarette smoking as well as with an increasing duration of exposure to asbestos. Due to the small size of the observed group, Weiss was unable to determine whether cigarette smoking and asbestos exposure were working in an additive or multiplicative manner. A study recently published by Weiss and Theodos indicates that type of asbestos as well as smoking habits are factors in the development of pleuropulmonary disease in asbestos workers (*88*).

In summary, workers exposed to tobacco smoke and asbestos experience far greater levels of lung cancer than would be expected from the contribution of either tobacco smoke or asbestos alone. However, other adverse health effects of occupational exposure to asbestos (for example, mesothelioma) appear to be independent of smoking habits. Thus, smoking varies in its contribution to the development of different adverse health effects resulting from occupational exposure to a particular occupational agent.

Exposures in the Rubber Industry

In a study of rubber workers, Lednar, et al. (*47*) reported that smokers exposed to fumes and dust, particularly talc and carbon black, had a significantly higher risk of developing a pulmonary disability than did nonsmokers. The combination of smoking and occupational exposure significantly elevated the probability of developing an early pulmonary disability. The authors reported that a rubber worker exposed to dust and smoking was associated with 10 to 12 times the risk of pulmonary disability retirement compared to the risk of a nonsmoking, nonoccupationally-exposed rubber worker. This elevated risk was found where there were exposures to respirable particulates and/or solvents. This study suggests that smoking and occupational exposures in the rubber industry are synergistic since the authors report that a rubber worker who smoked and was exposed to talc had an excess relative risk of 3.40, whereas an excess relative risk of 1.77 would be expected if the effects of smoking and work exposure were additive. The mechanism of this interaction is not yet understood.

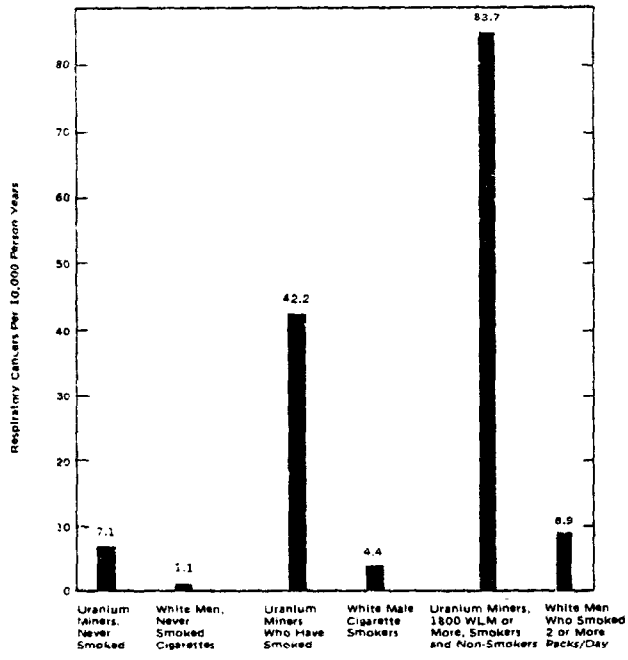

FIGURE 1.—Respiratory cancer rates among uranium miners by cigarette usage and radiation exposure compared with rates among nonminers

SOURCE: Archer, V.E. (*4*).

Radon Daughters

A substantial excess of lung cancer, reduced pulmonary function, and emphysema has been reported among uranium miners (*48*). The excess has been attributed primarily to irradiation of the tracheobronchial epithelium by *alpha* particles emitted during the decay of radon (Rn) and its daughter products. In a study of uranium miners, Archer, et al. (*4*) found that respiratory cancer rates among smoking and nonsmoking uranium miners were six to nine times greater than among nonminers with similar smoking habits. The lung cancer rate for nonsmoking uranium miners was 7.1 per 10,000 person years compared to 1.1 for nonminers who did not smoke. The lung cancer rate for uranium miners who smoked was 42.2 per 10,000 person years compared to 4.4 for nonminers who smoked two or more packs of cigarettes a day (Figure 1). There was also a definite association between the prevalence of emphysema and the cumulative amount of cigarettes smoked, as well as with accumulative radiation exposure.

Exposure in Gold Mining

An epidemiological study of a gold mining community in South Africa suggests that a synergistic interplay between smoking and exposures in the gold mine is responsible for the excess prevalence of chronic bronchitis among smoking miners (*78*). A significantly higher prevalence of chronic bronchitis was observed among smoking miners (50.5 percent) than among smoking nonminers (28.0 percent), nonsmoking miners (8.2 percent), or nonsmoking nonminers (6.7 percent). In addition, evaluation of the data for smokers by age as well as by the amount of tobacco smoked per day showed that chronic bronchitis was significantly more common in miners than in nonminers for every age and smoking category. The gold miners in this study were exposed to relatively low dust levels with high free silica content (50 to 70 percent) in contrast to the high dust levels with low silica content in coal miners.

Smoking may contribute to accidents in the workplace.

In a 9-month study of job accidents, the total accident rate was more than twice as high among smokers as among nonsmokers (*93*). Other authors have suggested that injuries attributable to smoking were caused by loss of attention, preoccupation of the hand for smoking, irritation of the eyes, and cough (*67*).

Smoking can also contribute to fire and explosions in occupational settings where inflammable and explosive chemical agents are used. In many of these areas smoking is prohibited. For example, smoking is not permitted in coal mines and miners are personally fined if found in violation of this provision.

Examples where action between smoking and occupational exposure has been suggested or only hypothesized

Cadmium

Several studies of the effects of occupational exposure to cadmium on smokers and nonsmokers have been conducted (*42*, *45*, *46*, *51*, *70*). Pulmonary function is poorer in smokers than in nonsmokers exposed to cadmium, and smokers also had a higher incidence of proteinuria than did nonsmokers in a cadmium-exposed population in a Swedish battery factory. An additive rather than a potentiating effect seems more likely from the limited data.

Chloromethyl Ether

A group of 129 men in a chemical plant where chloromethyl ether was used were screened by 70 mm chest photofluorograms and questionnaires regarding age, smoking habits, and respiratory symptoms at intervals averaging 8.5 months for 7 years and follow-up for an additional 5 years (*86*). Each job classification was ranked according to

degree of exposure to chloromethyl ether and an exposure index was calculated for each man by cumulating the total exposure.

Chronic cough and expectoration showed a dose-response relationship to chemical exposure. Chronic cough was also related to smoking, but for each smoking category chronic cough was more common for exposed than for unexposed men.

The 10-year incidence of lung cancer was dose-related to chemical exposure but not to cigarette smoking. All cancers were small cell carcinomas, occurred in men younger than 55, and had an induction-latent period of 10 to 24 years. The 10-year mortality rate in this group of workers was 2.7 times that expected, and lung cancer accounted for the excess number of deaths.

Bronchogenic carcinomas linked to cigarette smoking are most often squamous cell in type with long induction-latent periods and, in the absence of occupational agents, tend to occur after the age of 60. The cancers which tend to occur in workers exposed to chloromethyl ether are small cell in type, have short induction-latent periods, and tend to appear before the age of 55. The absence of a relationship between cigarette smoking and lung cancer in this study may be due to the competing effect of chloromethyl ether which results in lung cancer in exposed workers before the long-term carcinogenic effect of cigarette smoking could be demonstrated. However, cough related to cigarette smoking appears earlier in exposed workers, thus demonstrating the action of cigarette smoking with exposure to chloromethyl ether in the development of chronic cough symptoms. This case study also points up the complex issues involved in understanding the actions between smoking and occupational exposures.

Beta-Naphthylamine and Other Aromatic Amines

Doll, et al. found an excess risk of bladder cancer in a series of studies (*24*, *25*) of men employed in coal gas production in England and Wales. Most of the gas workers were smokers. Chemical studies showed that inside the retort houses gas workers inhaled *beta*-naphthylamine and other aromatic amines (known bladder carcinogens). Since aromatic amines are also found in cigarette smoke (*83*), the gas workers who smoked received exposure to bladder carcinogens from two sources. This evidence is difficult to interpret at the present time. There are reports of associations between cigarette smoking and bladder cancer (*30*, *92*); however, occupational exposures were generally not controlled in these studies. There is a need to assess further the action between smoking and exposure to aromatic amines.

Trends in Smoking Habits and in Morbidity and Mortality Rates for Various Occupational Groups

Surveys (*56*) have shown that male blue-collar workers are much more likely to smoke cigarettes than white-collar workers. While in 1970 only 37 percent of white-collar workers were reported to be current smokers, 51 percent of those in blue-collar occupations smoked. Also, more ex-smokers are found among white-collar workers than among blue-collar workers (35 percent and 28 percent respectively). Smoking among white-collar workers dropped from 48 to 37 percent between 1966 and 1970; during the same time period smoking among blue-collar workers dropped from 62 percent to 51 percent.

The pattern among female employees is quite different (*56*). There was little difference in smoking rates between white- and blue-collar female workers, 36 and 38 percent respectively, in 1970. In addition, the smoking rates for 1966 were the same as those for 1970 in both groups of female workers. During the period studied, the increased cessation of smoking among female workers was offset by the increased initiation of smoking in the same group.

In a study by Boucot, et al. (*16*), 121 new lung cancers developed among 6,136 men aged 45 and older who volunteered to report semiannually for chest X-rays and answer questionnaires about symptoms, smoking habits, and so forth, over a 10-year period beginning in 1951. The risk of developing lung cancer increased with increasing age, was higher in nonwhites than in whites, and bore a dose-response relationship to cigarette smoking. The highest lung cancer risk was among asbestos workers, 42.9/1000 man-years (crude rate). The risk was 2.2/1000 man-years (crude rate) for men in occupational categories not thought to be associated with an increased risk of lung cancer. When adjusted for age, race, and smoking, these rates were respectively 23.0/1000 and 1.4/1000 man-years. Occupational categories showing somewhat increased risk were metal workers, cooks, and automobile drivers. A higher percentage of nonwhites (22.6 percent) than whites (13.5 percent) worked in occupations thought to be at increased lung cancer risk. The excess lung cancer rate in nonwhite males could not be attributed to smoking.

The smoking habits in various occupational groups demonstrate ample opportunity for interaction between cigarette smoking and physical and chemical agents in the workplace. In general, those who have the highest smoking rates also have the highest risk for industrial exposures. Both the consumption of tobacco products and exposure to industrial agents increased steadily from 1920 to 1960. This is reflected in certain mortality trends. For example, the United States age-adjusted mortality rate from carcinoma of the pancreas has been reported to have risen from 2.9 to 8.2 per 100,000 population from 1920 to 1965, an increment of 283 percent. The rise was found to be real and threefold in magnitude when adjustments were made for the aging of

the population. A literature review on pancreatic cancer was conducted by Krain to help identify real causes or associations for pancreatic cancer. His report indicated that only the data on industrial carcinogen exposure and cigarette smoking show both the trend and the statistical magnitude of association to consider them as real causes or associations (*43*).

Since 1966 the consumption of tobacco products has decreased in blue-collar workers while the number of industrial exposures has continued to increase (*17, 56*). The increasingly higher rates of lung cancer in nonwhite males, independent of smoking habits, may reflect the late entry of nonwhites into industrial settings and the fact that they have jobs with higher risk for occupational exposure to toxic agents.

Summary and Recommendations

Although precise relationships between smoking and occupational exposures cannot always be quantified, the necessary data are beginning to accumulate.

From 1920 to 1966 tobacco consumption increased as did the introduction into the workplace of chemicals with unstudied biologic effects. Workers with the greatest risk of exposure to industrial agents in many cases had the highest smoking rates. Since 1966 the consumption of tobacco products has decreased in male blue-collar workers while the introduction of new chemicals into the workplace has continued to increase.

At least six different ways have been illustrated by which smoking may act with physical and chemical agents in the workplace to produce or increase adverse health effects. These actions need not be mutually exclusive, and exposure to multiple physical and chemical agents in the workplace can compound these various types of actions.

The examples of the interactions between the smoking of tobacco products and industrial exposures cited in this report indicate that a curtailment of smoking in certain occupational settings would contribute to the reduction of specific disease processes. The National Institute for Occupational Safety and Health has therefore recommended in certain circumstances that workers exposed to particular agents refrain from smoking. However, it is important to note that in some situations (for example, radon daughters and chloromethyl ether) the contribution of occupational exposures to adverse health effects was greater than the contribution of cigarette smoking. Therefore, the curtailment of smoking in the workplace should be accompanied by simultaneous control of occupational exposures to toxic physical and chemical agents. Both are needed!

Recommendations for Research

1. Studies on the health effects of smoking should take occupational exposures into consideration and vice versa. Whenever possible, studies should include data on nonsmoking workers as well as unexposed smoking and nonsmoking controls.

2. The increasing rates of lung cancer in nonwhite males compared to white males should be investigated further with respect to occupational exposures and smoking habits.

3. The change in smoking habits of blue-collar workers over the last decade provides an opportunity to assess more critically the contribution of smoking versus occupational exposure to certain disease states. Cohorts should be identified and followed prospectively for this purpose.

4. Workplace agents which interact with the smoking of tobacco to produce adverse health effects should be identified.

5. Investigation of the mechanisms of synergism between smoking and occupational exposures is needed.

6. The impact of the combination of smoking and workplace exposures upon reproductive experience merits further study.

7. The impact of smoking in the workplace upon accidents merits further study.

8. The lack of information on the effect of sidestream smoke in the development of occupational disease in nonsmoking workers merits attention.

9. The effects of cessation of smoking upon lung cancer risk among those occupationally exposed to toxic workplace agents requires investigation.

Interaction Between Smoking and Occupational Exposures: References

(1) ADAMS, W.G.F. Polymer fume fever due to inhalation of fumes from polytetrafluorethylene. Transactions of the Association of Industrial Medical Officers 13: 20-21, 1963.

(2) ALTSCHUL, A.M., ABRAMS, R., HOGNESS, T.R. Cytochrome c peroxidase. Journal of Biological Chemistry 136(3): 777-794, December 1940.

(3) ANDERSON, E.W., ANDELMAN, R.J., STRAUCH, J.M., FORTUIN, N.J., KNELSON, J.H. Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. Annals of Internal Medicine 79(1): 46-50, July 1973.

(4) ARCHER, V.E., WAGONER, J.K., LUNDIN, F.E., JR. Uranium mining and cigarette smoking effects on man. Journal of Occupational Medicine 15(3): 204-211, March 1973.

(5) ARONOW, W.S., CASSIDY, J., VANGROW, J.S., MARCH, H., KERN, J.C., GOLDSMITH, J.R., KHEMKA, M., PAGANO, J., VAWTER, M. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. Circulation 50(2): 340-347, August 1974.

(6) ARONOW, W.S., GOLDSMITH, J.R., KERN, J.C., JOHNSON, L.L. Effect of smoking cigarettes on cardiovascular hemodynamics. Archives of Environmental Health 28(6): 330-332, June 1974.

(7) ARONOW, W.S., HARRIS, C.N., ISBELL, M.W., ROKAW, S.N., IMPARATO, B. Effect of freeway travel on angina pectoris. Annals of Internal Medicine 77(5): 669-676, November 1972.

(8) ARONOW, W.S., ISBELL, M.W. Carbon monoxide effect on exercise-induced angina pectoris. Annals of Internal Medicine 79(3): 392-395, September 1973.

(9) ARONOW, W.S., STEMMER, E.A., ISBELL, M.W. Effect of carbon monoxide exposure on intermittent claudication. Circulation 49(3): 415-417, March 1974.

(10) ASTRAND, I., OVRUM, P., CARLSSON, A. Exposure to methylene chloride. I. Its concentration in alveolar air and blood during rest and exercise and its metabolism. Scandinavian Journal of Work, Environment and Health 1(2): 78-94, June 1975.

(11) BARLAS, J.A. Polymer fume fever in a printing works. British Medical Journal 1(5539): 567, March 4, 1967.

(12) BARNES, R., JONES, A.T. Polymer-fume fever. Medical Journal of Australia 2(2): 60-61, July 8, 1967.

(13) BERRY, G., MCKERROW, C.B., MOLYNEUX, M.K.B., ROSSITER, C.E., TOMBLESON, J.B.L. A study of the acute and chronic changes in ventilatory capacity of workers in Lancashire cotton mills. British Journal of Industrial Medicine 30(1): 25-36, January 1973.

(14) BERRY, G., NEWHOUSE, M.L., TUROK, M. Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. Lancet 2(7775): 476-479, September 2, 1972.

(15) BINKLEY, F. On the nature of serine dehydrase and cysteine desulfurase. Journal of Biological Chemistry 150(1): 261-262, September 1943.

(16) BOUCOT, K.R., WEISS, W., SEIDMAN, H., CARNAHAN, W.J., COOPER, D.A. The Philadelphia pulmonary neoplasm research project: Basic risk factors of lung cancer in older men. American Journal of Epidemiology 95(1): 4-16, 1972.

(17) BRIDBORD, K., FRENCH, J.G., FINKLEA, J.F. Toxic materials — Respiratory pathways. Proceedings, International Conference on Cybernetics and Society, September 19-21, 1977. New York, The Institute of Electrical and Electronics Engineers, Inc., 1977, pp. 80-81.

(18) BRUTON, D.M. Polymer fume fever. British Medical Journal 1(5542): 757, March 25, 1967.

(19) CAPODAGLIO, E., PEZZAGNO, G., BOBBIO, G.C., CAZZOLI, F. Indagine sulla funzionalita' respiratoria di lavoratori addetti a produzione elettrolitica di cloro e soda (A study of the respiratory function in workers engaged in the electrolytic production of chlorine and soda). Medicina del Lavoro 60(3): 192-202, 1969.

(20) CHESTER, E.H., GILLESPIE, D.G., KRAUSE, F.D. The prevalence of chronic obstructive pulmonary disease in chlorine gas workers. American Review of Respiratory Disease 99(3): 365-373, 1969.

(21) CHEVALIER, R.B., KRUMHOLZ, R.A., ROSS, J.C. Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. Journal of the American Medical Association 198(10): 1061-1064, December 5, 1966.

(22) CLAYTON, J.W., JR. Fluorocarbon toxicity and biological action. Fluorine Chemistry Reviews 1(2): 197-252, 1967.

(23) COWDRY, E.V., CRONINGER, A., SOLARIC, S., SUNTZEFF, V. Combined action of cigarette tar and beta radiation on mice. Cancer 14(2): 344-352, March/April 1961.

(24) DOLL, R., FISHER, R.E.W., GAMMON, E.J., GUNN, W., HUGHES, G.O., TYRER, F.H., WILSON, W. Mortality of gasworkers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. British Journal of Industrial Medicine 22(1): 1-12, 1965.

(25) DOLL, R., VESSEY, M.P., BEASLEY, R.W.R., BUCKLEY, A.R., FEAR, E.C., FISHER, R.E.W., GAMMON, E.J., GUNN, W., HUGHES, G.O., LEE, K., NORMAN-SMITH, B. Mortality of gasworkers—final report of a prospective study. British Journal of Industrial Medicine 29(4): 394-406, 1972.

(26) EVANS, E.A. Pulmonary edema after inhalation of fumes from polytetrafluoroethylene (PTFE). Journal of Occupational Medicine 15(7): 599-601, July 1973.

(27) FASSETT, D.W. Cyanides and nitriles. In: Patty, F.A. (Editor). Industrial Hygiene and Toxicology, Second Revised Edition, Volume II. New York, John Wiley and Sons, Inc., 1963, pp. 1991-2036.

(28) FODOR, G.G., PRAJSNAR, D., SCHLIPKOETER, H.-W. Endogene CO-Bildung durch inkorporierte Halogenkohlenwasserstoffe der Methanreihe (Endogenous CO formation by encorporated halogenated hydrocarbons of the methane series). *Staub Reinhaltung der Luft*, 33(6): 258-259, June 1973.

(29) GOLDSMITH, J.R., TERZAGHI, J., HACKNEY, J.D. Evaluation of fluctuating carbon monoxide exposures. Theoretical approach and a preliminary test of methods for studying effects on human populations of fluctuating exposures from multiple sources. Archives of Environmental Health 7(6): 647-663, December 1963.

(30) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenzel, W. Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(31) HAMMOND, E.C., SELIKOFF, I.J. Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States. In: Bogovski, P., Gilson, J.C., Timbrell, V., Wagner, J.C., Davis, W. (Editors). Biological Effects of Asbestos. International Agency for Research on Cancer, Scientific Publication No. 8, Lyon, France, International Agency for Research on Cancer, 1973, pp. 312-317.

(32) HANKINSON, J.L., REGER, R.B., MORGAN, W.K.C. Maximal expiratory flows in coal miners. American Review of Respiratory Disease 116(2): 175-180, 1977.

(33) HARRIS, D.K. Polymer-fume fever. Lancet 261(6692): 1008-1011, December 1, 1951.

(34) HARRIS, T.R., MERCHANT, J.A., KILBURN, K.H., HAMILTON, J.D. Byssinosis and respiratory diseases of cotton mill workers. Journal of Occupational Medicine 14(3): 199-206, March 1972.

(35) HENDRY, N.W. The geology, occurrences, and major uses of asbestos. Annals of The New York Academy of Sciences, 132(1): 12-22, December 31, 1965.

(36) HORVAT, M., YOSHIDA, S., PRAKASH, R., MARCUS, H.S., SWAN, H.J.C., GANZ, W. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. Circulation 45(4): 837-844, April 1972.

(37) HOSEY, A.D. Priorities in developing criteria for "breathing air" standards. Journal of Occupational Medicine 12(2): 43-46, February 1970.

(38) JOHNS-MANVILLE. President's Bulletin No. 640-1. Denver, Johns-Manville Corporation, January 1, 1978, 20 pp.

(39) JONES, J.G., WALTERS, D.H. A study of carboxyhaemoglobin levels in employees at an integrated steelworks. Annals of Occupational Hygiene 5: 221-230, 1962.

(40) JUDD, H.J. Levels of carbon monoxide recorded on aircraft flight decks. Aerospace Medicine 42(3): 344-348, March 1971.

(41) KIBELSTIS, J.A., MORGAN, E.J., REGER, R., LAPP, N.L., SEATON, A., MORGAN, W.K.C. Prevalence of bronchitis and airway obstruction in American bituminous coal miners. American Review of Respiratory Disease 108(4): 886-893, 1973.

(42) KJELLSTROM, T., EVRIN, P.-E., RAHNSTER, B. Dose-response analysis of cadmium-induced tubular proteinuria. A study of urinary β_2-microglobulin excretion among workers in a battery factory. Environmental Research 13(2): 303-317, April 1977.

(43) KRAIN, L.S. The rising incidence of carcinoma of the pancreas—Real or apparent? Journal of Surgical Oncology 2(2): 115-124, 1970.

(44) KUNTZ, W.D., MCCORD, C.P. Polymer-fume fever. Journal of Occupational Medicine 16(7): 480-482, July 1974.

(45) LAUWERYS, R. BUCHET, J.P., ROELS, H. Une etude de la fonction pulmonaire et renale de travailleurs exposes au cadmium (A study of pulmonary and renal function in workers exposed to cadmium). The 18th International Congress on Occupational Health, Brighton, England, September 14-19, 1975, pp. 279-280. (Abstract)

(46) LAUWERYS, R.R., BUCHET, J.P., ROELS, H.A., BROUWERS, J., STANESCU, D. Epidemiological survey of workers exposed to cadmium. Effect on lung, kidney, and several biological indices. Archives of Environmental Health 28(3): 145-148, March 1974.

(47) LEDNAR, W.M., TYROLER, H.A., MCMICHAEL, A.J., SHY, C.M. The occupational determinants of chronic disabling pulmonary disease in rubber workers. Journal of Occupational Medicine 19(4): 263-268, April 1977.

(48) LUNDIN, F.E., JR., WAGONER, J.K., ARCHER, V.E. Radon Daughter Exposure and Respiratory Cancer. Quantitative and Temporal Aspects. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health. National Institute of Environmental Health Science. Joint Monograph No. 1, June 1971, 175 pp.

(49) LYNCH, K.M., SMITH, W.A. Pulmonary asbestosis III: Carcinoma of lung in asbesto-silicosis. American Journal of Cancer 24(1): 56-64, May 1935.

(50) MARTISCHNIG, K.M., NEWELL, D.J., BARNSLEY, W.C., COWAN, W.K., FEINMANN, E.L., OLIVER, E. Unsuspected exposure to asbestos and bronchogenic carcinoma. British Medical Journal 1(6063): 746-749, March 19, 1977.

(51) MATERNE, D., LAUWERYS, R., BUCHET, J.P., ROELS, H., BROUWERS, J., STANESCU, D. Investigations sur les risques resultant de l'exposition au cadmium dans deux entreprises de production et deux entreprises d'utilisation du cadmium (Investigations on the risk resulting from exposure to cadmium in two production plants and two plants using cadmium). Cahiers de Medecine du Travail 12(1 and 2): 5-76, March-June 1975.

(52) MERCHANT, J.A., HALPRIN, G.M., HUDSON, A.R., KILBURN, K.H., MCKENZIE, W.N., JR., HURST, D.J., BERMAZOHN, P. Responses to cotton dust. Archives of Environmental Health 30(5): 222-229, May 1975.

(53) MERCHANT, J.A., KILBURN, K.H., O'FALLON, W.M., HAMILTON, J.D., LUMSDEN, J.C. Byssinosis and chronic bronchitis among cotton textile workers. Annals of Internal Medicine 76(3): 423-433, March 1972.

(54) MERCHANT, J.A., LUMSDEN, J.C., KILBURN, K.H., O'FALLON W.M., UJDA, J.R., GERMINO, V.H., JR., HAMILTON, J.D. Dose response studies in cotton textile workers. Journal of Occupational Medicine 15(3): 222-230, March 1973.

(55) MERCHANT, J.A., LUMSDEN, J.C., KILBURN, K.H., O'FALLON, W.M., UJDA, J.R., GERMINO, V.H., JR., HAMILTON, J.D. An industrial study of the biological effects of cotton dust and cigarette smoke exposure. Journal of Occupational Medicine 15(3): 212-221, March 1973.

(56) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1973, 137 pp.

(57) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard ...Occupational Exposure to Boron Trifluoride. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-122, December 1976, 83 pp.

(58) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Carbaryl. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-107, September 1976, 192 pp.

(59) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Decomposition Products of Fluorocarbon Polymers. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-193, September 1976, 112 pp.

(60) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Dinitro-Ortho-Cresol. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 78-131, February 1978, 147 pp.

(61) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Formaldehyde. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-126, December 1976, 165 pp.

(62) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Hydrogen Cyanide and Cyanide Salts (NzCN, KCN, and $Ca(CN)_2$). U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-108, October 1976, 191 pp.

(63) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Inorganic Fluorides. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HEW Publication No. (NIOSH) 76-103, 1975, 191 pp.

(64) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Inorganic Mercury. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, HSM 73-11024, 1973, 129 pp.

(65) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Methyl Parathion. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-106, September 1976, 177 pp.

(66) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Organotin Compounds. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-115, November 1976, 187 pp.

(67) NAUS, A., ENGLER, V., HETYCHOVA, M., VAVRECKOVA, O. Work injuries and smoking. Industrial Medicine and Surgery 35(10): 880-881, October 1966.

(68) OSBORNE, J.S., ADAMEK, S., HOBBS, M.E. Some components of gas phase of cigarette smoke. Analytical Chemistry 28(2): 211-215, February 1956.

(69) PETTIGREW, A.R., FELL, G.S. Simplified colorimetric determination of thiocyanate in biological fluids, and its application to investigation of the toxic amblyopias. Clinical Chemistry, 18(9): 996-1000, September 1972.

(70) PISCATOR, M., ADAMSON, E., ELINDER, C.-G., PETTERSSON, B., STENINGER, P. Studies on cadmium exposed women. Eighteenth International Congress on Occupational Health, Brighton, England, September 14-19, 1975, pp. 281-282. (Abstract)

(71) RADOJICIC, B. Odredivanje rodanida u mokraci u radnika izlozenih cijanidima (Determination of thiocyanates in urine of workers occupationally exposed to cyanides). Arhiv za Higijenu Rada i Toksikologiju 24: 227-232, 1973.

(72) RENTCHNICK, P. (Editor). Recent results in cancer research 3. In: Hueper, W.C. Occupational and Environmental Cancers of the Respiratory System. Berlin, Springer-Verlap, 1966, pp. 38-56, 166-170.

(73) ROBBINS, J.J., WARE, R.L. Pulmonary edema from teflon fumes. Report of a case. New England Journal of Medicine 271(7): 360-361, August 13, 1964.

(74) SELIKOFF, I.J. Cancer risk of asbestos exposure. In: Hiatt, H.H., Watson, J.D., Winston, J.A. (Editors). Origins of Human Cancer. New York, Cold Spring Harbor Laboratory, 1977, pp. 1765-1783.

(75) SELIKOFF, I.J., HAMMOND, E.C., CHURG, J. Asbestos exposure, smoking, and neoplasia. Journal of the American Medical Association 204(2): 106-112, April 8, 1968.

(76) SHERWOOD, R.J. The hazards of fluon. Transactions of the Association of Industrial Medical Officers 5: 10-12, 1955.

(77) SIDOR, R., PETERS, J.M. Prevalence rates of chronic non-specific respiratory disease in fire fighters. American Review of Respiratory Disease 109(2): 255-261, February 1974.

(78) SLUIS-CREMER, G.K., WALTERS, L.G., SICHEL, H.S. Chronic bronchitis in miners and non-miners: An epidemiological survey of a community in the gold-mining area in the Transvaal. British Journal of Industrial Medicine 24(1): 1-12, January 1967.

(79) STELL, P.M., MCGILL, T. Exposure to asbestos and laryngeal carcinoma. Journal of Larynogology and Otology 89(5): 513-517, May 1975.

(80) STEWART, R.D., HAKE, C.L. Paint-remover hazard. Journal of the American Medical Association 235(4): 398-401, January 26, 1976.

(81) TOLA, S., NORDMAN, C.H. Smoking and blood lead concentrations in lead-exposed workers and an unexposed population. Environmental Research 13: 250-255, 1977.

(82) TOUEY, G.P., MUMPOWER, R.C., II. Measurement of the combustion-zone temperature of cigarettes. Tobacco 144(8): 18-22, February 22, 1957.

(83) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.

(84) WAGNER, J.C., GILSON, J.C., BERRY, G., TIMBRELL, V. Epidemiology of asbestos cancers. British Medical Bulletin 27(1): 71-76, 1971.

(85) WEGMAN, D.H., PETERS, J.M. Polymer fume fever and cigarette smoking. Annals of Internal Medicine 81(1): 55-57, July 1974.

(86) WEISS, W. Chloromethyl ethers, cigarettes, cough and cancer. Journal of Occupational Medicine 18(3): 194-199, March 1976.

(87) WEISS, W. Cigarette smoking, asbestos, and pulmonary fibrosis. American Review of Respiratory Disease 104(2): 223-227, August 1971.

(88) WEISS, W., THEODOS, P.A. Pleuropulmonary disease among asbestos workers in relation to smoking and type of exposure. Journal of Occupational Medicine 20(5): 341-345, May 1978.

(89) WILLIAMS, N., ATKINSON, G.W., PATCHEFSKY, A.S. Polymer-fume fever: Not so benign. Journal of Occupational Medicine 16(8): 519-522, August 1974.

(90) WILLIAMS, N., SMITH, F.K. Polymer-fume fever. An elusive diagnosis. Journal of the American Medical Association 219(12): 1587-1589, March 20, 1972.

(91) WOOD, J.L. Biochemistry. In: Wood, J.L. (Editor). Chemistry and Biochemistry of Thiocyanic Acid and its Derivatives. New York, Academic Press Inc., 1975, pp. 156-221.

(92) WYNDER, E.L., GOLDSMITH, R. The epidemiology of bladder cancer. A second look. Cancer 40(3): 1246-1268, September 1977.

(93) YUSTE, P.C., DE GUEVARA, M.L. Influencia del fumar en los accidentes laborales. Encuesta estadistica (The influence of smoking on industrial accidents. A statistical study). Medicina y Seguridad del Trabajo 21(84): 38-46, October/December 1973.

(94) ZIELHUIS, R.L., STUIK, E.J., HERBER, R.F.M., SALLE, H.J.A., VERBERK, M.M., POSMA, F.D., JAGER, J.H. Smoking habits and levels of lead and cadmium in blood in urban women. International Archives of Occupational and Environmental Health 39: 53-58, 1977.

8. PREGNANCY AND INFANT HEALTH.

National Institute of Child Health and Human Development

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Introduction

Biomedical Aspects of Smoking

Data accumulating in the scientific literature during the past decade strongly corroborate findings reported in the 1960's that cigarette smoking during pregnancy has a significant and adverse effect upon the well-being of the fetus, the health of the newborn baby, and the future development of the infant and child. Adverse effects on pregnancy range from increased risk for reproductive loss, fetal mortality, preterm birth, and neonatal death, to retardation in fetal growth as reflected in birth measurements of lower mean body weight, shortened body length, and smaller head circumference, as well as to a number of problems of adaptation in the neonatal period. In addition, there is suggestive evidence of long-term impairments in physical growth, diminished intellectual function, and deficiencies in behavioral development for those babies who survive the first 4 weeks of life. It appears that children of smoking mothers do not catch up with the offspring of nonsmoking mothers in various phases of development.

The present chapter highlights previously reported and recent studies on the relationships between cigarette smoking and pregnancy outcome, including sections on historical considerations, birth weight and fetal growth, fetal and infant mortality, lactation and breast feeding, and physiologic-experimental studies. The concluding section of this chapter, entitled Research Issues, identifies questions and areas of concern that need clarification and further investigation.

Historical Considerations

In 1957, Simpson (*172*) reported that infants born to women who smoked during their pregnancies were of significantly lower birth weight relative to babies born to nonsmokers. During the intervening 20 years, there has been increasing concern, coupled with the conduct of a large number of related studies, about the effect of smoking during pregnancy upon the well-being of the developing fetus and infant.

Concern about the effects of exposure to tobacco and cigarette smoking during pregnancy upon reproductive loss, maternal health, pregnancy outcome, and infant well-being dates back a century. In 1902, Ballantyne (*9*) questioned what might be the effect of tobacco poisoning upon antenatal life. While he did not specifically mention maternal smoking during pregnancy, he summarized the opinions of a number of authors writing during the latter part of the 19th century about the risks of spontaneous abortion for women who worked in tobacco factories. He referred specifically to an 1879 paper by Decaisne from France and to an 1868 report by Kostial from Austria about female tobacco workers. Ballantyne wrote that both of these authors "were quite convinced that abortion was very frequent in women

workers in tobacco [factories]...." Ballantyne concluded by stating, "While there is much doubt, therefore, regarding the evil effect of nicotism in cutting short antenatal life, there seems to be no shadow of doubt that there is a very large infantile mortality in postnatal life among the offspring of women workers in tobacco. Possibly this may be due in part to the influence of the milk, but it is more probable that it is on account of congenital debility."

Discussion of the problem of smoking during pregnancy at the turn of the century appears to have been based on empirical evidence and anecdotal reports. Until the end of the 1920's, there was a sparsity of reports on this topic in the scientific literature. Thereafter, several articles were published reporting the results of animal studies and clinical investigations pertinent to the effects of nicotine and smoking during pregnancy upon reproductive loss, maternal health, and pregnancy outcome.

In 1935, Sontag and Wallace (*175*) investigated the effects of cigarette smoking during pregnancy upon fetal heart rate. Their observations were made during the last 2 months of pregnancy on eight mothers and their fetuses. Their data revealed that the smoking of one cigarette by the pregnant woman generally produced an increase in the rate of the fetal heart beat, and sometimes a decrease. They concluded that there was "a definite and real" increase in the fetal heart rate after the mother began to smoke a cigarette and that this was probably due to transplacental transfer of nicotine into the fetal circulation.

In 1935 and again in 1936, Campbell (*23*, *24*) reported that heavy cigarette smoking was prejudicial to efficient childbearing as a result of chronic nicotine poisoning. Campbell warned that excessive smoking in certain cases was detrimental to maternal health. He noted that, in general, a woman who smoked during pregnancy was likely to have more difficulty during the course of pregnancy, parturition, and lactation than a woman who did not smoke.

In 1940, Essenberg and associates (*46*), in a well-designed study, investigated the effects of nicotine and cigarette smoke on pregnant female albino rats and their offspring. The three groups of subjects included a group of animals that received intraperitoneal or subcutaneous injections of solutions of chemically pure nicotine, a second group of animals that were exposed to tobacco smoke that approximated human smoking of one pack of cigarettes a day, and a third group of animals that were untreated.

The immediate effects on the animals in the two treated groups were similar, although more severe in the injected group. It was reported that:

1. Two-thirds of all the young of treated mothers were underweight; the young from nicotine-injected mothers were more underweight than those from mothers exposed to tobacco smoke.

2. The underweight group remained underweight during the entire period of observation; many of the young of this group were undersized and died early.
3. Of the females injected, 63.0 percent lost one or more young before weaning, and 33.3 percent lost all of their young.
4. Of the mothers exposed to tobacco smoke, 28 percent lost one or more of their young before weaning, and 25 percent were underweight.
5. Of the mothers exposed to smoke prior to mating, 23.3 percent lost one or more of their young before weaning, and 25 percent were underweight.
6. In both groups of treated mothers, temporary sterility, resorption of young *in utero*, and abortions were noted.
7. Alteration of maternal behavior was observed, consisting of cannibalism and neglect of the young as to care and feeding.

The findings of Essenberg, et al. (*46*), reported in 1940, raised important questions regarding the effects of smoking on pregnancy outcome that were not investigated in depth until some 20 years later when Simpson reported her findings (*172*).

Results of epidemiological surveys and experimental studies appearing in the literature over the past two decades owe much to improvements in research technology which contributed to more accurate and reproducible measurements in the laboratory. For example, nicotine concentrations in minute amounts can be determined with gas chromatography, and the degree of carbon monoxide displacement of oxygen from hemoglobin can be assessed with considerable precision by biophysical methodology. Use of new technology has often permitted scientists to confirm earlier impressions obtained with the use of crude but ingenious bioassays. Such confirmation is a tribute to the perception and the dedication of these pioneering investigators and astute clinicians.

Smoking, Birth Weight, and Fetal Growth

Birth Weight

Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable women who do not smoke. Since 1957, when Simpson reported this finding from her original study (*172*), it has been confirmed by over 45 studies of more than half a million births (*1, 2, 7, 20, 22, 29-31, 37, 41, 47, 54, 61, 62, 71, 72, 86, 89, 90, 101-103, 115, 118, 119, 123-127, 137, 141-143, 145, 147, 151, 155-157, 161, 163-166, 168, 169, 185, 188, 189, 190-192, 208, 212*). Results of these studies are expressed as mean birth weights of smokers' and nonsmokers' babies, or alternatively, as the percentage of babies who weigh less than a specified amount, usually 2,500 grams. The methods and results of 28 studies carried out between 1957 and 1970 were

summarized in the chapter on smoking and pregnancy in *The Health Consequences of Smoking, A Report of the Surgeon General: 1971*, which concluded: "Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight alone" (*190*). The same conclusion has been drawn from subsequent studies.

In the chapter on pregnancy in *The Health Consequences of Smoking* in 1973, a detailed, critical review is given of studies published to that date. The chapter summary of the evidence that the association between maternal smoking and reduced birth weight is one of cause and effect includes the following (*192*):

1. Results are consistent in all studies, retrospective and prospective, from many different countries, races, cultures, and geographic settings (*2, 7, 20, 22, 30, 31, 41, 47, 54, 62, 72, 81, 86, 89, 109, 115, 118, 119, 125–127, 137, 141–143, 147, 151, 152, 157, 161, 163, 164, 166, 169, 172, 185, 189, 192, 193, 206, 212*).

2. The relationship between smoking and reduced birth weight is independent of all other factors that influence birth weight, such as race, parity, maternal size, socioeconomic status, sex of child, and other factors that have been studied (*1, 2, 7, 20, 22, 31, 47, 54, 71, 101, 102, 115, 118, 119, 142, 143, 152, 157, 164, 169, 192, 193*). It is also independent of gestational age (*2, 19, 20, 22, 54, 72, 115, 141, 157, 163, 166, 169, 192, 206*).

3. The more the woman smokes during pregnancy, the greater the reduction in birth weight; this is a dose-response relationship (*2, 22, 31, 47, 54, 89, 101, 102, 103, 115, 118, 119, 137, 142, 143, 169, 189, 192, 193, 206*).

4. If a woman gives up smoking during pregnancy, her risk of delivering a low-birth-weight baby is similar to that of a nonsmoker (*22, 54, 101, 103, 206*).

To illustrate typical results of studies showing the association between maternal smoking and an increased proportion of low-birth-weight infants, five published studies with an aggregated total of almost 113,000 births in Wales, the United States, and Canada are summarized in Table 1. In these populations, 34 to 54 percent of the mothers smoked during pregnancy and on the average had twice as many low-birth-weight babies as the nonsmokers. Under these conditions, from 21 to 39 percent of the low-birth-weight incidence in the total population could be attributed to maternal smoking (*2, 20, 47, 115, 137, 142, 143*).

An outstanding feature of the relationship between maternal smoking and birth weight is its dependence on the level of maternal smoking and its independence of the large variety of other factors that influence birth weight, such as maternal size, maternal weight gain, age, parity, socioeconomic status, and sex of child (*1, 2, 20, 22, 31, 47,*

TABLE 1.—Birth weight under 2,500 grams by maternal smoking habit, relative and attributable risks derived from published studies

Study	Nonsmokers (No.)	Smokers		Births <2,500 gm(%)		Relative risk smoker: nonsmoker	Attributable risk* (%)
		No.	Proportion	Nonsmoker	Smoker		
Cardiff	7,176	6,238	.465	4.1	8.1	1.98	31
US Collaborative							
White	8,466	9,781	.536	4.3	9.5	2.21	39
Black	11,252	7,777	.409	10.7	17.5	1.64	21
California, Kaiser Permanente							
White	3,189	2,145	.402	3.5	6.4	1.83	25
Black	934	479	.338	6.4	13.4	2.09	27
Montreal	3,954	3,004	.432	5.2	11.4	2.19	34
Ontario	27,316	21,062	.435	4.5	9.1	2.02	31

*Percentage of total birth weights <2,500 gm attributable to maternal smoking. Attributable risk in population = b(r-1) divided by b(r-1) +1 where b = proportion of mothers who smoke and r = relative risk of low birth-weight = smoker rate/nonsmoker rate

SOURCE: Meyer, M.B. (*115*).

71, 101, 102, 115, 118, 119, 137, 152, 157, 163, 164, 169, 192, 193). This feature is illustrated in Tables 2 and 3. Table 2 shows mean birth weights for babies of smokers and nonsmokers in selected subdivisions by biologic and socioeconomic factors, using data from the approximately 10,000 white births studied from 1960 to 1967 by the Berkeley Child Health and Development Studies whose subjects were members of the Kaiser Foundation Health Plan. Mean birth weights vary with maternal age, parity, height, weight, and socioeconomic status, from a low of 2,912 grams for babies of smoking mothers who had given birth to previous low-birth-weight infants, to a high of 3,573 grams for babies of nonsmoking mothers of high parity. Nevertheless, within each subgroup the effect of maternal smoking on mean birth weight is clearly seen, with smokers' infants weighing from 193 to 286 grams less than nonsmokers' infants in the subgroups shown (*193*). Table 3, using data from the 50,097 births of the Ontario Perinatal Mortality Study, shows the incidence of low birth weight (percent under 2,500 grams) for three levels of maternal smoking and for subcategories of hospital pay status, mother's height and weight, and the sex of the child. Despite percentages of births under 2,500 grams that vary from 2.7 percent for nonsmokers who were 68 inches or taller to 15.8 percent for smokers of more than a pack per day who weighed less than 120 pounds before pregnancy, the increased risk of having a baby weighing less than 2,500 grams is remarkably stable—about 70 percent for women who smoke less than a pack of cigarettes per day and about 160 percent for smokers of a pack or more per day—compared with the risk for nonsmokers (*119*).

The picture that emerges from these findings is that birth weight is affected by maternal smoking independently and to a uniform extent, regardless of other determinants of birth weight. Comparisons of the percentage distributions of birth weights for smokers' and nonsmokers' babies show a downward shift of the whole set of weights of smokers' babies by about 200 grams, as illustrated in Figure 1 (*103*). In other words, the data displayed in Figure 1 corroborate the impression that all births are affected similarly by maternal smoking and negate the possibility that changes in mean birth weight are due to extreme effects in a few cases with other cases unchanged.

Placental Ratios

Authors of a few earlier studies in which placental weights were analyzed by maternal smoking habits noted that these weights were either not affected or were less affected by maternal smoking than were birth weights (*81, 89, 125, 141, 202*). As a result, because of the dose-related reduction in birth weights with increasing number of cigarettes smoked, the ratio of placental weight to birth weight, or placental ratio, tended to be larger for smokers than for nonsmokers.

TABLE 2.—Mean birth weight of infants of smoking and nonsmoking mothers, by other biologic and socioeconomic factors

Prepregnancy factors	Mean birth weight (gm)	Mean difference Nonsmokers-Smokers(gm)
Gravida's age <20 years		
Smokers	3,219	193
Nonsmokers	3,412	
Parity > 4 previous pregnancies		
Smokers	3,287	286
Nonsmokers	3,573	
Previous birth <2,500 grams		
Smokers	2,912	208
Nonsmokers	3,120	
Gravida's height <60 inches		
Smokers	3,058	201
Nonsmokers	3,259	
Gravida's prepregnancy weight <100 lbs.		
Smokers	2,918	246
Nonsmokers	3,164	
Gravida's education: less than high school graduate		
Smokers	3,196	253
Nonsmokers	3,446	
Husband's education: less than high school graduate		
Smokers	3,196	256
Nonsmokers	3,452	
Husband's occupation: unskilled laborer, service worker		
Smokers	3,224	247
Nonsmokers	3,471	

SOURCE: van den Berg, B.J. (*193*).

Kullander and Kaellen reported placental ratios of 0.171, 0.175, 0.178, and 0.188, respectively, for nonsmokers, smokers of less than 10 cigarettes a day, those smoking 10 to 20 a day, and those smoking more than 20 cigarettes per day, based on a prospective study of 6,376 pregnancies in Malmo, Sweden (*89*). Wilson compared the ratios of untrimmed, fresh placenta weights to birth weights for 1,895 deliveries in Sheffield, England, finding a significantly higher ratio for babies born to smokers than to nonsmokers. He suggested that the increase might signify a response by the placenta to chronic hypoxia in the fetus (*202*).

Wingerd, et al. have now published a definitive study of this relationship, using data from a prospective study of 7,000 pregnancies among members of the Kaiser Foundation Health Plan in Oakland,

TABLE 3.—Birth weight under 2,500 grams by maternal smoking and other factors (Ontario data)

Factor and class	Births under 2,500 grams (per hundred total births) Maternal smoking: packs per day			Smoker: nonsmoker Relative risk Packs per day	
	0	<1	1+	<1	1+
Hospital status					
Private	4.4	7.1	10.6	1.6	2.4
Public	5.8	10.3	16.5	1.8	2.8
Mother's height					
< 62 inches	5.9	10.8	15.1	1.8	2.6
62–64 inches	4.7	7.9	12.8	1.7	2.7
65–67 inches	3.9	6.2	10.1	1.6	2.6
68+ inches	2.7	6.0	9.3	2.2	3.5
Prepregnant weight					
< 120 pounds	6.1	10.2	15.8	1.7	2.6
120–134 pounds	4.2	6.3	9.5	1.5	2.2
135+ pounds	3.3	5.1	8.7	1.5	2.6
Sex of child					
Male	4.2	7.3	11.5	1.7	2.7
Female	5.2	8.3	12.7	1.6	2.4

SOURCE: Meyer, M.B. (*115*).

California (*203*). At an interview early in pregnancy, information was obtained about numerous factors related to the pregnancy, including the woman's smoking habits. Placentas were weighed by specially trained personnel after the cord and attached membranes had been trimmed off according to Benirschke's protocol, an extremely important procedure to reduce variability of measurement. The study was confined to black or white women who delivered single, live infants without severe anomalies between 37 and 43 weeks' gestation and for whom at least one hemoglobin value during gestation had been reported. Because placental ratios change with gestational age, it is important to compare values specific for weeks of gestation at the time of delivery. Results of this study are shown in Figure 2. At each gestational age from 37 through 43 weeks, the more the mother smoked during pregnancy the higher is the placental ratio. Comparison of the observed mean weights by smoking level showed that, as expected, birth weights decreased as smoking level increased. Furthermore, mean placental weights were the same or slightly lower for light smokers and slightly higher for heavy smokers (over 20 cigarettes per day) than for nonsmokers. Ratios were higher for black than for white women and tended to increase as maternal hemoglobin level decreased. This trend was most marked in black women who smoked (*203*).

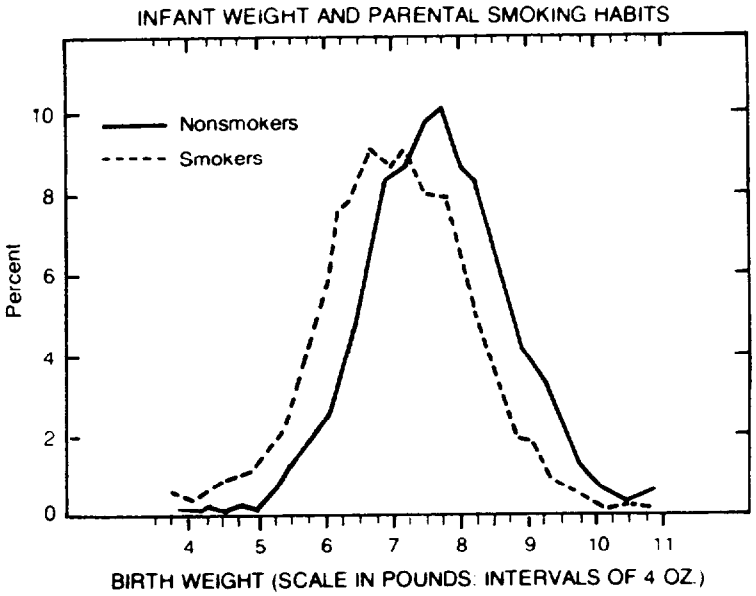

FIGURE 1.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked one pack or more of cigarettes per day
SOURCE: MacMahon, B. (*103*).

As described in another section of this chapter, the carbon monoxide present in cigarette smoke combines with maternal and fetal hemoglobin and results in a reduced carrying capacity of the blood for oxygen and also a reduction of the pressure at which oxygen is delivered to the fetal tissues. Somewhat similar reductions of oxygen availability for the fetus occur at high altitude and in cases of maternal anemia. Under these conditions, increases in placental ratios have also been observed that are in proportion to the elevation or to the degree of anemia (*14, 88, 108*). The possibility that these changes may represent physiological responses to relative fetal hypoxia, with increased oxygen delivery by a larger placenta and decreased oxygen demand by a smaller fetus, has been considered (*14, 88, 108, 202, 203*). If this is the case, it is important to know whether a mechanism that might increase the possibility of survival at a lower birth weight is accompanied by any long-term costs in later growth and development.

Gestation

The consistent finding that mean birth weights were lower and the frequency of low-weight babies higher for women who smoked during pregnancy than for similar nonsmokers raised the obvious question of

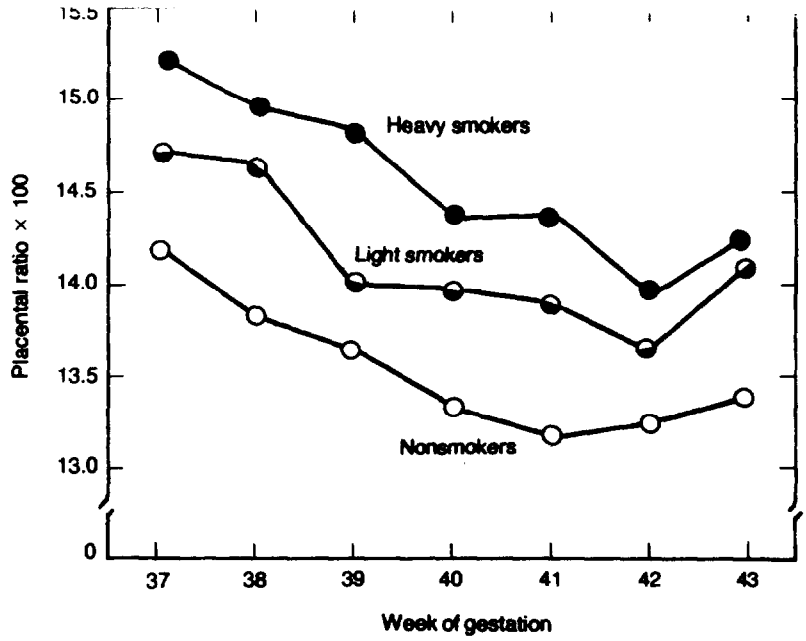

FIGURE 2.—Ratio of placental weight to birth weight by length of gestation and maternal smoking category
SOURCE: Wingerd, J. (*205*).

whether this might be due to a corresponding reduction in the duration of gestation if the mother smoked. In his study of 2,042 women in Birmingham, England, published in 1959, Lowe noted that the infants of smoking mothers were delivered only 1.4 days earlier on the average than those of nonsmokers, not enough to account for the mean birth weight reduction of 170 grams (*101*). Subsequent studies of mean gestation have shown similarly small differences between mean durations of pregnancy for smokers and nonsmokers (*2, 19, 20, 67, 72, 141, 157, 166, 206*). For example, Buncher, in an analysis of the 49,897 births to U.S. Navy wives studied by Underwood, et al. (*189*), found that the mean duration of pregnancy was only 0.25 weeks shorter for male babies and 0.18 weeks shorter for female babies if the mother smoked during pregnancy (*19*).

The finding that maternal smoking does not cause an overall downward shift in the distribution of gestational ages, such as was shown for birth weights, leads to the conclusion that the lower birth weight of smokers' infants must be due to a direct retardation of fetal growth. In other words, these infants are small-for-dates rather than preterm. The truth of this conclusion has been demonstrated by studies in which mean birth weights or percentages of low-birth-weight babies

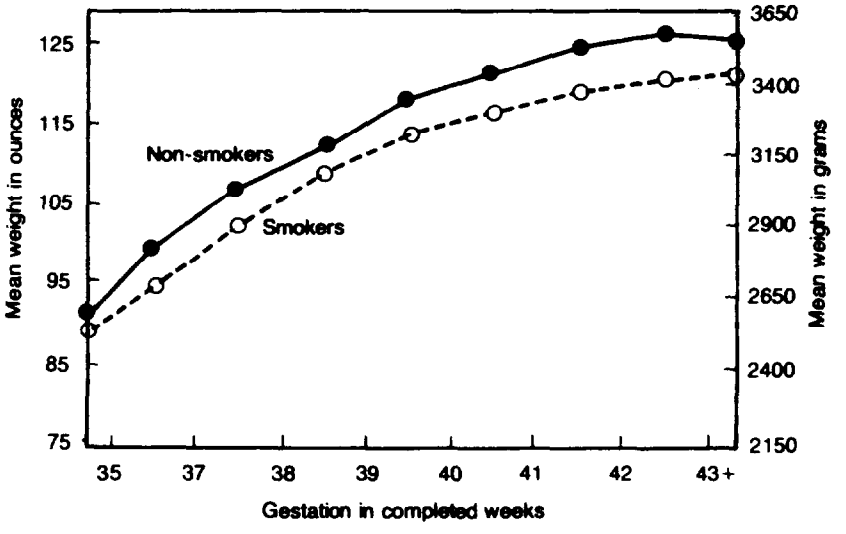

FIGURE 3.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons
SOURCE: Butler, N.R. (*20*).

were compared within units of gestational age. Butler and Alberman, in an analysis of data from the British Perinatal Mortality Study of 17,000 births in Great Britain in March, 1958, found lower mean birth weights for smokers' than for nonsmokers' babies at each week of gestation from 36 through 43, as shown in Figure 3 (*20*). Evidence of the same birth weight relationship is presented in Figure 4 (*113*), taken from Meyer's analysis of data from the Ontario Perinatal Mortality Study (*142, 143*). This Figure shows that, as one would expect, the proportion of births under 2,500 grams decreases as gestation increases. It also shows, within each gestational age group, the effect of maternal smoking on birth weight, as the frequency of low-weight births increases directly with smoking level for term births of early, average, and late time of delivery.

Fetal Growth

As the low birth weight associated with maternal smoking is independent of gestational age and is not due to a significant reduction in mean gestation, it must therefore be due to a reduction in the rate of fetal growth. In several studies the relationship between maternal smoking and other body measurements besides birth weight has been examined. Kullander and Kaellen, in a prospective study of 6,376 births in Malmo, Sweden, found that, as the level of maternal smoking increased, the body length, head circumference, and shoulder circumference decreased consistently for both male and female babies (*89*).

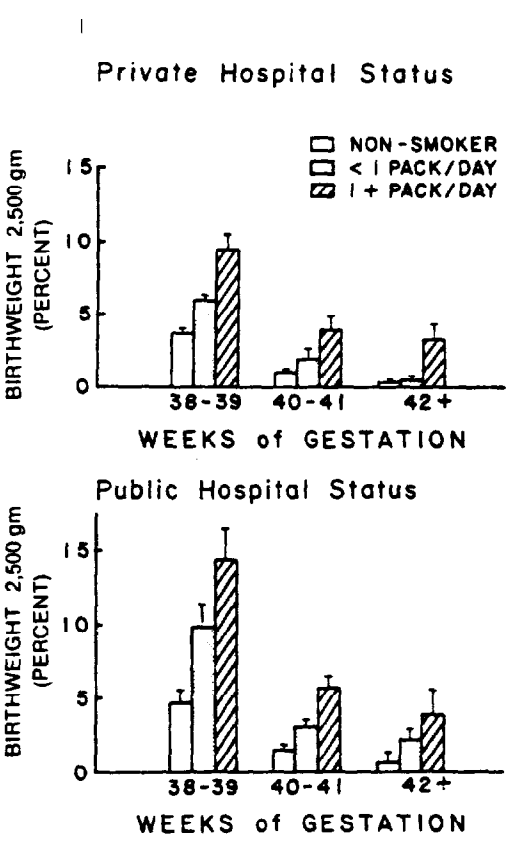

FIGURE 4.—Percentage of birth weights under 2,500 grams by maternal smoking level for early, average, and late-term births. Private hospital status and public hospital status (Bars show 95 percent confidence intervals)
SOURCE: Meyer, M.B. (*115*).

Other studies have corroborated these findings (*34, 67, 81, 141*). Hardy and Mellits compared the birth measurements and subsequent growth of 88 pairs of neonates from the population of the Collaborative Perinatal Study of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (*137*). Women who reported smoking 10 or more cigarettes a day and whose children had survived and been examined at age 7 were matched by race, age, educational background, sex of child, and delivery date with women who did not smoke any cigarettes during pregnancy and whose children were examined at age 7. At birth, the smokers' babies weighed an average of 250 grams less ($p \leq 0.001$), were 1.34 centimeters shorter ($p < 0.001$), and had head circumferences 0.32 centimeters smaller than babies of nonsmoking mothers (*67*). In a study of 1,159 infants whose mothers' smoking habits were ascertained early in pregnancy, Davies

and coworkers found the familiar gradient of decreasing mean birth weights with increasing smoking level. When these infants were measured at 7 to 14 days of age, a similar gradient was found for body length and head circumference of both male and female babies (*34*). These and other studies (*33, 67, 204*) indicate that maternal smoking leads to an overall retardation of fetal growth.

Miller, Hassanein, and coworkers have described two types of fetal growth retardation in term babies. One is characterized by an abnormally low ratio of birth weight to crown-heel length, the thin baby with a low ponderal index but with normal length. The other is characterized by abnormally short crown-heel length for fetal age, the baby who is generally smaller than expected in all measurements (*118*). A study of 1,112 uncomplicated term pregnancies indicated that mothers who smoked cigarettes during pregnancy were more likely to have infants with short body lengths for dates, whereas mothers who had abnormally low weight gain in the last two trimesters were more likely to have babies with low ponderal indices (*119*).

Long-Term Growth and Development

Whether or not there are long-term consequences of the fetal growth retardation associated with maternal smoking during pregnancy is of much greater concern than are measurements at the time of birth. There is evidence that children of smoking mothers have measurable deficiencies in physical growth, intellectual development, and emotional development that are independent of other known predisposing factors.

The matched-pair study of Hardy and Mellits compared physical measurements and intellectual function in children of smokers and nonsmokers through age 7. Among 88 pairs, although the babies of smokers were 250 grams lighter and 1 to 2 cm shorter at birth and still shorter than their counterparts at one year, the authors reported that there was no significant difference in either physical measurements or intellectual function at 4 and 7 years (*67*). It should be noted, however, that to achieve statistical significance from such numbers of cases, the difference between them must be very strong. In Hardy and Mellits' study of the 88 pairs of children matched for race, date of delivery, maternal age and education, and sex of child, mean values for the children of nonsmokers were larger than those of smokers at all ages for all measurements through age 7, including body weight, body length, and head circumference. At age 1 year, 96 percent of nonsmokers' babies and 90 percent of smokers' babies had normal neurological status. At age 4, nonsmokers' babies had slightly higher scores on the Stanford-Binet intelligence test, and at age 7 they tested higher on all of the tests reported except for the Wide Range Achievement Test subtest for arithmetic. An additional set of 55 pairs of children of smokers and nonsmokers who were matched on birth

weight as well as on the other factors listed also showed fewer smokers' children with normal neurological status and lower scores for smokers' children on 6 out of 8 tests of intellectual function. The fact that few of these differences reached "statistical significance" does not rule out the possibility that harmful long-term effects may exist (*38*, *43*).

In the California study by Wingerd and Schoen (*204*), the net effect of various factors on length at birth and height at 5 years was determined in 3,707 single-born, white, California children. Children of smoking mothers were found to be shorter ($p<0.001$) at birth and at 5 years than children of nonsmoking mothers. (Intellectual development was not measured in this study.)

In a prospective study of children of low birth weight, Dunn and coworkers analyzed growth with respect to maternal smoking habits of 81 who were "small-for-dates," 99 "truly premature," and 146 controls of full birth weight. At $6\frac{1}{2}$ years of age, the children of nonsmoking mothers had a slightly greater mean height and weight in all three categories. The mean social class of the smoking mothers was lower than that of the nonsmokers, but within the two lowest social classes, IV and V (77 percent of all subjects), the nonsmokers' children had a greater mean height and weight than their counterparts whose mothers smoked. Statistically significant differences in favor of nonsmokers' children were demonstrable with regard to weight gain and growth in length/weight at 1 to 4 years and with regard to actual height at 4 and $6\frac{1}{2}$ years and weight at $6\frac{1}{2}$ years in the full birth weight controls (*43*). There was no evidence that the children of smoking women "caught up" in growth with the nonsmokers' children, a concept postulated by Russell, et al. (*164*) but not corroborated by other studies.

Dunn also evaluated the neurological, intellectual, and behavioral status of these children at age 7 and analyzed the results according to the mothers' smoking habits during pregnancy. Neurological abnormalities, including minimal cerebral dysfunction and abnormal or borderline encephalograms, were slightly more common among children of smoking women, although this difference was not quite statistically significant. In a battery of psychological tests, the mean scores of children of nonsmoking mothers were better than those of smokers' children in 45 out of 48 correlations, and the difference was significant in 14 of these. Factorial analysis of variance suggested that these differences could be only partially attributed to the slightly lower social status of smokers' children. Some significant differences in favor of nonsmokers' children were also demonstrated with respect to behavior ratings and school placement (*44*). These results are very similar to those of Hardy and Mellits in that the direction of the differences is almost always in favor of the nonsmokers' child. Perhaps more attention should be paid to these patterns and less to the question

of "statistical significance," which is difficult to achieve with such small numbers. Dunn concludes that "some slight direct damaging effect on foetal brain development and subsequent intelligence and behaviour cannot be excluded" (*44*).

Small numbers and population selection factors are not a problem in the longitudinal follow-up of the population originally included in the British Perinatal Mortality Study, comprising approximately 17,000 births, an estimated 98 percent of all births in England, Scotland, and Wales during the week of March 3 to 9, 1958. These children have been traced and studied again at age 7 and at age 11, to describe their behavior, their health, their physical development, their educational standards, and their home environment. At ages 7 and 11 years, physical and mental retardation due to smoking in pregnancy were found, and this deficit increased with the number of cigarettes smoked during pregnancy. Children whose mothers smoked 10 or more cigarettes a day during pregnancy were on average 1.0 centimeters shorter and between 3 to 5 months retarded in reading, mathematics, and general ability, as compared with the offspring of nonsmokers. After allowing for associated social and biological factors, all of these differences are highly significant ($p<0.001$)(*33*, *38*, *43*, *204*).

Recently an association has been reported between maternal smoking and hyperkinesis in children. Denson and colleagues matched each of 20 consecutive methyl-phenidate-sensitive cases with a nonhyperkinetic dyslexic child and also with a normal control by sex, age within six months, and social class. Mean birth weights were similar for the three groups. Mothers of hyperkinetic children tended to be younger, and significantly more of their children were first-born. Outstanding and highly significant differences were found in maternal cigarette consumption. Mothers of hyperkinetic children consumed more cigarettes during the study pregnancy ($p<0.05$), had higher maximum consumption during that pregnancy ($p<0.01$), and consumed more at the time of questioning ($p<0.001$). The present mean consumption by mothers of hyperkinetic children was 23.3 cigarettes per day, more than three times the average for the two control groups. Only four mothers of hyperkinetic children had not smoked during pregnancy, and all of these reported complicated deliveries. Of smokers, 11 with complicated pregnancies had a mean consumption of 13.4 cigarettes daily, and 5 with various complications smoked an average of 28 cigarettes daily throughout pregnancy. The role of anoxia as a possible cause of hyperkinetic disease and the hypoxic effects of carbon monoxide and of smoking-related complications of pregnancy and labor are discussed in the study. The authors conclude: "These findings are consistent with the hypothesis that smoking during pregnancy is an important cause of the hyperkinetic syndrome" (*36*).

These studies suggest unfavorable effects of maternal smoking during pregnancy on the child's long-term growth, intellectual development, and behavioral characteristics. Although these changes are difficult to study because of the vast complexity of possible antecedent and confounding variables, high priority should be given to obtaining conclusive answers about the role of fetal exposure to maternal smoking in these conditions. The fact that the direction of observed differences in a variety of different studies is the same adds to the urgency of this question.

Role of Maternal Weight Gain

In the search for mechanisms through which maternal smoking reduces birth weight, the question has been asked whether it might be an indirect result of reduced appetite, less intake of food, and lower maternal weight gain. Several early studies reported no differences between smoking and nonsmoking women in intake of food or in weight gain and concluded that the effect of maternal smoking on birth weight was not mediated in this way (*8, 54, 76, 101, 141, 212*). Recently the question has been raised again by Rush in a study of births to 160 women of whom 41 smoked throughout pregnancy. His evidence showed that the mean weekly weight gain was reflected in the infant's weight at birth (*162*). In a subsequent study, Davies, et al. examined the interrelationships of cigarette smoking in pregnancy, maternal weight gain, and fetal growth. By analysis of covariance of 480 mother-infant pairs from the total of 1,159 included in the study, these authors stated: "Correction of birth weights within smoking groups to a common mean maternal weight gain appears to remove most of the differences between infants of nonsmokers and heavy smokers, although technically these corrected means are still statistically heterogeneous." That is, the effect of smoking on birth weight was still observed although diminished by these procedures. From this the authors concluded that "a large part of the effect of maternal smoking is mediated through maternal weight gain with only a very small additional direct effect on the fetus. This suggests that increasing weight gain in smoking mothers might prevent some of the harmful effects of smoking on fetal growth." However, the alternative explanation that lower maternal weight gain and fetal growth retardation are both independently related to cigarette smoking in pregnancy is also mentioned (*34*).

Other studies have not corroborated these findings. Mau reports results of the German prospective study in which 6,200 pregnant women were examined every month from the first trimester to delivery and the children followed for up to three years. Smoking was classified as none, 1 to 5, 6 to 10, or more than 10 cigarettes per day. No significant association was found between smoking habit and weight gain. On the other hand, there was a close correlation between the

number of small-for-dates babies and the smoking habit in a subgroup of women with normal weight gain (10 to 15 kg). The proportions of babies below the tenth percentile were 7.7 percent for nonsmokers, 8.4 percent at 1 to 5 cigarettes, 12.5 percent at 6 to 10, and 17.6 percent at over 10 cigarettes per day. These babies had a general retardation of weight, length, and head circumference rather than appearing malnourished (*107*). These findings are in agreement with the studies of Miller and Hassanein, who found that the effects of smoking on fetal growth did not appear to be related to poor maternal nutrition. Mean weight gains during the last two trimesters of pregnancy were not significantly different in smoking and nonsmoking mothers and were above the mean weight gains recommended by the National Research Council (*118*).

Meyer investigated the relationship of maternal smoking to maternal weight gain and to birth weight, using data from the 31,788 births to English-speaking Canadian-born women included in the Ontario Perinatal Mortality Study (*113, 142, 143*). As expected, birth weight distributions shifted downward as maternal smoking level increased. Maternal weight-gain distributions, on the other hand, were the same for smokers and nonsmokers. Furthermore, the proportion of infants weighing less than 2,500 grams increased with each level of smoking (none, less than a pack, and more than 1 pack per day) within each maternal weight-gain group from less than 5 pounds to more than 40 pounds. This evidence supports a direct effect of maternal smoking on birth weight rather than one mediated through eating. Evaluation of Rush's study (*162*) is difficult because of small numbers and because of population-selection factors that led to large differences between smokers and nonsmokers in age, parity, marital status, and education. The study population of Davies, et al. (*34*) is more homogeneous and contains 450 smokers, but both studies share a common problem in interpretation. Meyer points out that an inevitable correlation exists between maternal weight gain and birth weight insofar as both increase with gestational age, necessitating careful control of this factor. Furthermore, the fact that fetal weight is an increasingly important component of maternal weight gain towards term (51 percent between 30 and 40 weeks) and accounts for a larger proportion of a low-weight gain than of a high-weight gain ensures a considerable degree of correlation between the two values. The same baby is weighed twice, once while growing *in utero* and contributing to maternal weight gain, and again at birth. In this way the mother gains weight because the baby is growing, and not vice versa. Meyer concludes that efforts to prevent or reduce smoking during pregnancy should have greater benefits for mother and child than would efforts to increase food intake among women who smoke (*113*).

Evidence for Indirect Associations Between Smoking and Birth Weight

Yerushalmy has suggested that smoking is an index to a particular type of reproductive outcome and does not play a causal role in the production of small-for-dates infants (*206-208*). The line of reasoning and evidence presented by Yerushalmy and the responses to it are discussed in detail in the 1973 report on *The Health Consequences of Smoking* (*192*). The problems inherent in Yerushalmy's study, in which he found a higher percentage of low birth weights among 210 nonsmokers who later became smokers than among nonsmokers who did not take it up, have been described. The most serious of these problems is the bias introduced by the study design resulting in significantly younger ages for the "future smoker" group (mean age 19.70 ± 0.15) than for his nonsmokers (22.10 ± 0.04); the doubly retrospective nature of the information gathered (women being asked about smoking habits at the time of previous pregnancies); and lack of control for other important factors influencing birth weight, such as primiparity and sex of child.

Silverman addressed the question of whether the smoker rather than the smoking was responsible for increased frequency of low birth weight by comparing pairs of births to the same woman, using data from the 1963 private census of the population of Washington County, Maryland (*28*). In this census all members of the household were listed with birth dates, and all members were asked whether and how much they smoked and when they had started. Using these data, Silverman constructed a population of pairs of births that occurred during the 17-year period prior to the census date of July 15, 1963. Assuming that the mothers did not stop smoking during pregnancy and that the age of starting was accurately reported, she was able to compare birth weights in first and second births of 143 women who smoked during the second pregnancy, but not during the first, with corresponding birth weights from 382 women who smoked during neither pregnancy and 491 women who smoked during both pregnancies. The many problems inherent in this study were faced, and adjustments were made insofar as possible. For example, as in Yerushalmy's study, significantly more of the future smokers (44.8 percent) were under 20 years of age at the time of the first study birth, compared with 24.5 percent of the continuing nonsmokers. Young, primiparous mothers are known to have lighter babies than older mothers with higher parity. When weights were compared specific for maternal age and sex of child, the mean birth weight for the first member of the birth pair was lower in four out of six comparisons and higher in two. With simultaneous adjustment for the effects of infant sex, maternal age, and birth order, there were no significant differences in mean birth weight difference among pairs in which the mother smoked during both pregnancies and pairs in which the mother smoked during the

second pregnancy of the pair, but not the first. Comparison of the mean birth weights for the first infants in each pair showed that future smokers had babies who weighed less than those of women who did not take up smoking and more than those of women who were already smokers and continued to smoke. Silverman concluded: "These findings neither confirm nor deny the hypothesis that the smoker rather than the smoking per se causes a reduction in birthweight" (*171*).

Evidence for a direct effect of maternal smoking on fetal growth as presented in this chapter is extremely strong. Furthermore, the biological effects of carbon monoxide, nicotine, and other known components of cigarette smoke are compatible with the findings from epidemiologic studies. Therefore, there seems little value in arguing that this direct effect does not exist. On the other hand, smokers are to some extent self-selected, and comparisons of "smokers" and "nonsmokers" in a population reveal differences between them. These may be related to calendar time trends, peer group influence, cultural and ethnic background, social class, or personality type. Because the relationship between maternal smoking and birth weight is so strong, these differences do not obscure it. More problems arise from lack of adjustment for differences between smokers and nonsmokers in the distribution of such factors as age, parity, socioeconomic status, and race when the relationship of maternal smoking to perinatal mortality is under study; these issues are discussed in detail in another section of this chapter. In addition, attention should be paid to the possibility that psychological makeup and strength of addiction to cigarette smoking may have an independent influence on some of the outcomes being studied. Future studies should not only adjust for independent factors that influence whether or not a woman becomes a smoker and smokes during pregnancy but should also distinguish between the effects of a personality type that adopts smoking and the physical effects of the smoke on mother, placenta, and fetus.

Summary

1. Babies born to women who smoke during pregnancy are on the average 200 grams lighter than babies born to comparable women who do not smoke. The whole distribution of birth weights of smokers' babies is shifted downward, and twice as many of these babies weigh less than 2,500 grams compared with babies of nonsmokers. There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight.

2. Birth weight is affected by maternal smoking independently and to a uniform extent, regardless of other determinants of birth weight. The more the mother smokes, the greater the reduction in birth weight of the baby.

3. The ratio of placenta weight to birth weight increases with increasing levels of maternal smoking. This increase may signify a response to reduced oxygen availability due to carbon monoxide and may have some survival value for the fetus.

4. There is no overall reduction in the duration of gestation with maternal smoking, indicating that the lower birth weight of smokers' infants is due to retardation of fetal growth.

5. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions: body length, chest circumference, and head circumference are smaller if the mother smokes. Smokers' babies are short for dates as well as light and do not exhibit reduction in ponderal index.

6. Studies of long-term growth and development give evidence that smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11.

7. Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate directly, that fetal growth rate is not due to characteristics of the smoker rather than to the smoking nor mediated by reduced maternal appetite, eating, and weight gain.

Cigarette Smoking and Fetal and Infant Mortality

Overview

In contrast with the strong, consistent relationship of maternal smoking to reduced birth weight, the relationship of maternal smoking to perinatal mortality has been marked by variation in the level of increased risk for women who smoke. This has led to controversy as to whether there truly are lethal effects for the fetus or neonate caused by maternal smoking.

Earlier epidemiological studies of the association between maternal cigarette smoking and perinatal mortality (fetal deaths, neonatal deaths, or perinatal deaths) were reviewed in the 1971, 1972, and 1973 reports on *The Health Consequences of Smoking* (*190–192*). The 1971 report gave details of 12 studies of maternal smoking and the incidence of spontaneous abortion, stillbirth, and neonatal death (*20, 41, 54, 87, 101, 141, 151, 164, 166, 188, 206, 212*). The increased risk of loss among smokers varied from study to study. Inconsistencies between studies were described, and it was noted that both smoking habits and perinatal loss were influenced by such factors as social class, maternal age, and parity. Rush and Kass reviewed the English language literature in 1972 and found reports of 12,388 perinatal deaths and abortions with a mean excess perinatal loss for smokers of 34.4 percent. Where reported, excess loss was higher among the poor and among blacks. Their study of black and white women in Boston showed excess

mortality risks of 86 percent for black smokers and 11 percent for white smokers (*163*).

The 1973 report (*192*) summarized studies that were published up to that date and contained a critical analysis of known reasons for variability in the strength of the association between maternal smoking and increased perinatal loss. Much of the controversy about whether maternal smoking did or did not cause fetal or neonatal loss centered around the basically irrelevant issues of whether studies were "prospective" or "retrospective" (usually referring to the time at which smoking information was obtained rather than to whether the study was based on a cohort of births or on a set of cases and controls), and on whether or not the differences were "statistically significant." Classification of the studies reviewed in the 1973 report according to statistical significance revealed that studies in which the higher rates of mortality for the infants of smokers compared with nonsmokers reached a significant level (usually $p \leq 0.05$ or smaller) (*20, 22, 30, 54, 86, 89, 124, 142, 143, 165, 180*) had mortality ratios (smoker rate: nonsmoker rate) that ranged from 1.38 to 1.78, whereas studies in which significant levels were not reached (*41, 141, 151, 155, 166, 189, 207*) had mortality ratios that ranged from 1.01 to 1.06. Both groups contained retrospective and prospective studies of comparable size. Statistical significance obviously depended upon the combined effects of the risk ratio and the size of the study. A further source of controversy in this matter was the fact that when one compares neonatal death rates for low-birth-weight babies only, the low-weight babies of smokers have lower death rates than those of nonsmokers. This apparently paradoxical relationship is partly due to the relatively greater maturity of the under-2,500-gram smokers' babies. It is also due to the fact that maternal smoking affects birth weight more strongly than it does neonatal mortality. Because the denominators of these rates include only babies under 2,500 grams, the downward shift of birth weight with maternal smoking inflates the denominators and lowers neonatal mortality rates for smokers. Numerators include a majority of low-birth weight babies, whether or not the mother smokes. This matter is discussed more fully in the 1973 report (*192*) and in the commentary by Meyer and Comstock (*114*).

In the 1973 report, analysis of reasons for variability between studies included two important points. First was the observation that other important variables might influence the results if they were unequally distributed in comparison groups of smokers and nonsmokers. A logistic transformation analysis of variance applied to data from the British Perinatal Mortality Study demonstrated that in addition to maternal smoking, maternal height, age, parity, social class, and severe preeclampsia had significant independent effects on late fetal and neonatal mortality (Figure 5). Meyer and Comstock (*114*) provided examples of how the differential distribution of smoking and other

factors could bias data. For example, as reported in the data from the Collaborative Perinatal Study of the NINCDS (1959–1966), U.S. mortality rates were higher for black than for white babies, while white women were more often smokers and smoked more cigarettes than black women (*137*). Selection of births on the basis of smoking alone would tend to include more nonsmokers who were black and at high risk and more smokers who were white and at basically low risk, thereby minimizing the apparent effects of maternal smoking on perinatal loss. In three reported studies in which adjustment for other factors was carried out, a significant independent association between cigarette smoking and infant mortality persisted (*20, 22, 30, 169*). Of the studies that revealed no significant increase in mortality risks for smokers' infants, one (*207*) controlled for race alone. "Hence, at least part of the discrepancy in results between the two groups of studies may be explained by a lack of control of variables other than smoking" (*192*).

The second important point presented in the 1973 report was the suggestion that cigarette smoking might be more harmful to the fetuses of certain women than of others. Analysis of data by socioeconomic status (*2, 22, 29*), race (*137, 163, 188, 206, 207*), previous obstetrical experience (*22, 151, 169*), and maternal age (*20*) indicated that the increased perinatal mortality risk associated with maternal smoking varied considerably with these other factors (*192*).

Spontaneous Abortion

The results of several past studies have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (*74, 89, 141, 147, 188, 212*). Data from some of these studies have documented a strong dose-response relationship between the number of cigarettes smoked and the incidence of spontaneous abortion (*147, 188, 212*). Spontaneous abortions are difficult to study because of problems in ascertainment. The most complete ascertainment is possible when the mother's history of past spontaneous abortions is used, despite problems of recall. Differences in rates between smokers and nonsmokers are largest when this method is used (*141, 212*). In prospective studies, many early spontaneous abortions will be missed, and bias will occur if one group tends to register earlier than the other. Nevertheless, higher rates of spontaneous abortion are also reported among smoking mothers in prospective studies (*89*). The study by Kullander and Kaellen counted spontaneous abortions through the eighth month of gestation and noted that the largest increase was among smoking women whose pregnancies were unwanted. Although this was a prospective study, with smoking data collected repeatedly during prenatal care, the method of analysis was retrospective. Rearrangement of their table to

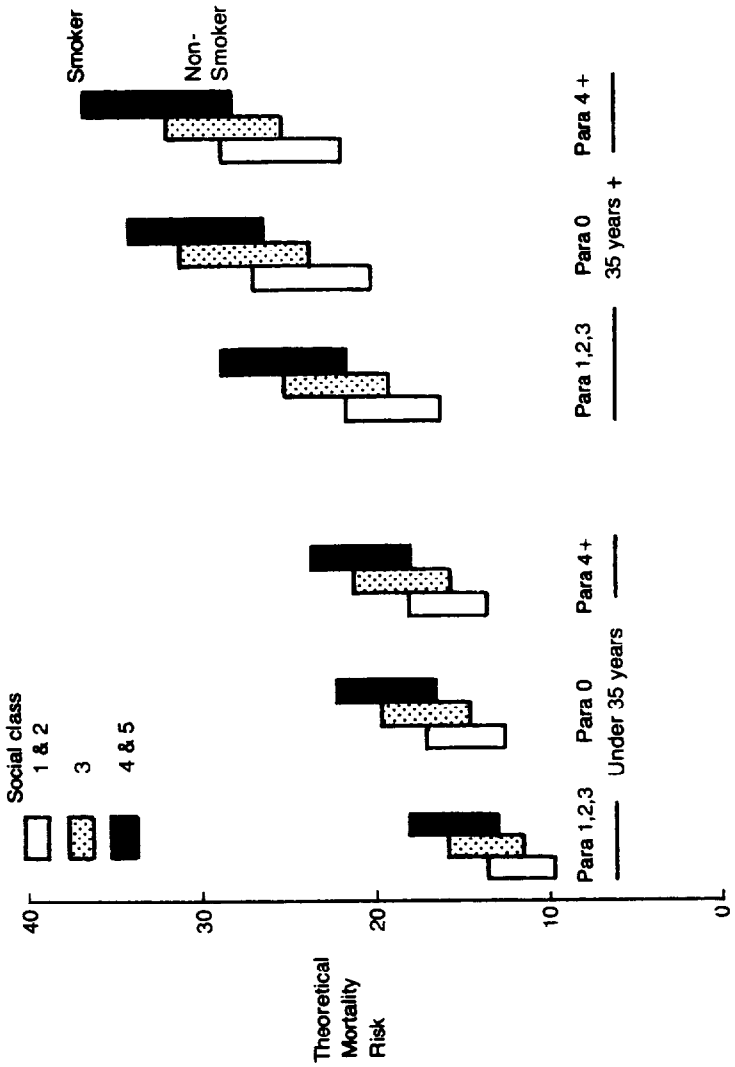

FIGURE 5.—Theoretical cumulative mortality risk according to smoking habit, in mothers of different age, parity, and social class groups

SOURCE: Butler, N.R. (*20*).

obtain incidence rates of spontaneous abortion for subgroups of smokers and nonsmokers gives rates and relative risks of spontaneous abortion by desideration of pregnancy (Table 4). More of the smokers' than nonsmokers' pregnancies were unwanted (19 percent versus 13

TABLE 4.—Spontaneous abortions by maternal smoking habit and desideration of pregnancy

	Spontaneous abortions per 100 pregnancies		Smoker: nonsmoker Relative risk
	Smokers	Nonsmokers	
Total spontaneous abortions	9.4	7.2	1.31
Pregnancy wanted	7.8	6.5	1.20
Pregnancy unwanted	16.0	11.9	1.34

SOURCE: Kullander, S. (*89*).

percent), but the increased risk of spontaneous abortion was seen among smokers whether or not the pregnancy was wanted (*89*).

The method for studying spontaneous abortions that may be the least subject to error if carefully done is the traditional, retrospective, case-control approach, used recently by Kline and coworkers (*87*). In their study a log-linear analysis was used to test the hypothesis that maternal smoking is associated with spontaneous abortion, controlling for confounding variables such as age, number of previous spontaneous abortions, induced abortions, and live births. Of the cases of spontaneous abortion, 41 percent were smokers compared with 28 percent of the controls, giving an odds ratio of 1.8. This leads to the conclusion that smoking during pregnancy is a risk factor for spontaneous abortion.

Perinatal Mortality

Most of the epidemiological studies about which questions of causality have arisen have used perinatal death (late fetal and early neonatal), neonatal death, or combinations of these as their outcome variable. Ascertainment and recordkeeping may start at 20 weeks, at 28 weeks, or at the time of registration. These differences in definition and design affect the study results but are not fundamental to the basic questions raised in the 1973 report and by other authors.

Progress toward resolving these questions has been made since the 1973 report through new studies and analyses in which attention is paid not only to differences in the number of cigarettes smoked but also to other characteristics of the study populations. A table from Fabia's study of a 10 percent random sample of registered births in Quebec in 1970-71 illustrates this approach (Table 5). Within subgroups of the population by maternal age, parity, and years of school, the relative perinatal mortality risk for smoking versus nonsmoking mothers varies from 1.00 to 1.81 for categories with at least 10 deaths (*47*). Table 6 (*117*) shows examples of a number of studies in which

TABLE 5.—Perinatal mortality rates per 1,000 live births to smoking and nonsmoking mothers, and relative risks for infants of smokers by maternal age, parity, and years of school (10 % random sample of medical certificates of births in Quebec in 1970–71)

Maternal characteristics	Total births	Perinatal deaths per 1,000 live births		Smoker: nonsmoker Relative risk
		Nonsmokers	Smokers	
Age				
< 25	3,143,	12.1	16.1	1.33
25-34	3,717	12.6	13.2	1.05
35+	757	23.0	41.7	1.81
Parity				
0	2,798	14.2	18.7	1.32
1-3	3,959	11.2	11.2	1.00
4+	860	21.8	36.1	1.66
Years of school				
< 8	1,600	14.5	18.8	1.30
8-11	3,043	12.8	19.7	1.54
12+	1,170	13.5	(8.9)	(0.66)

Excludes births weighing less than 1,001 grams.
Rates in parentheses based on fewer than 10 deaths.
SOURCE: Fabia, J. (*47*).

perinatal mortality rates by maternal smoking are shown within categories of other relevant factors. These studies show that perinatal mortality rates vary with maternal smoking level and also with the other factors shown. The general statement can be made that the detrimental effect of maternal smoking on fetal survival is greater in groups of women who already have a higher risk of perinatal loss for other reasons. Women characterized by low social class, low level of education, less than optimum maternal age, or being black have higher risks of perinatal mortality than their counterparts, and their relative increase in risk due to maternal smoking is enhanced. Studies in which the population, by design or by chance, includes mainly or only women without other reproductive risk factors show the smallest differences between the risks of smokers and nonsmokers (*22, 30, 47, 137, 155, 163, 206*).

A series of articles by Meyer, et al. reports analyses of data from the Ontario Perinatal Mortality Study of all single births in 10 Ontario teaching hospitals in 1960-61, including 51,490 births, 701 fetal deaths, and 655 neonatal deaths (*115, 116, 117*). For the Ontario study, sponsored and supported by the Maternal and Child Health Branch of the Ontario Department of Health (*142, 143*), detailed data were

TABLE 6.—Examples of perinatal mortality by maternal smoking status related to other subgroup characteristics

Study population	No. of births		Category	Perinatal or neonatal deaths/1,000 births		Relative risk*
	Non-smokers	Smokers		Non-smokers	Smokers	
British Perinatal Mortality Survey, England, all births	11,145	4,660	Social class			
			1,2 (high)	25.8	26.3	1.02
			3–5	33.5	46.6	1.39
Washington Co. Maryland, white	7.646	4.641	Father's education			
			9+ years	14.4†	16.1†	1.12
			≤8 years	17.6†	38.0†	2.16
Northern Finland, white	8.898	2.346		23.2	23.4	1.01
California, middle to upper middle class			Race			
	6,067	3,726	White	11.0†	11.3†	1.03
	2,219	1,071	Black	17.1†	21.5†	1.26
Boston City Hospital, Prenatal Clinic			Race			
	513	892	White	29.2	31.4	1.08
	1,225	636	Black	28.6	54.1	1.89
Collaborative Perinatal Study, 12 U.S. centers			Race and cigarettes/day			
	8,521	11,369	White	31.4		
			1–10		31.5	1.00
			11+		38.2	1.22
	9,862	8,160	Black	38.5		
			1–10		41.5	1.08
			11+		57.4	1.49
Quebec, 10% sample of registered births	3,912	2,967	Maternal age			
			<25	12.1	16.1	1.33
			25–34	12.6	13.2	1.05
			35+	23.0	41.7	1.81

*Ratio of mortality rate for smokers' to nonsmokers' babies.
†Neonatal only.
SOURCE: Meyer, M.B. (*117*).

collected from routine records, and from interviews with mothers, anesthetists, and attending physicians, and from autopsy records. Results related perinatal mortality to social, demographic, and physical maternal factors, prenatal care, histories of prior pregnancies, complications of pregnancy, details of anesthesia, delivery, hospital course, and survival of the infant up to 8 days. The interviews of

mothers included questions on the maximum amount smoked during pregnancy, expressed as packages per day (*142, 143*). The large size of this study and the richness of its available information provided a valuable resource for sorting out complex interrelationships between maternal smoking, other factors, and perinatal loss. In the first article of the series, the differential risk of smoking based on maternal characteristics was demonstrated by extensive cross-tabulation of perinatal mortality rates for 3 levels of smoking (none, less than a pack, 1 pack or more per day) within 52 subgroups of other maternal variables. Risk ratios for light smokers compared with nonsmokers showed excess death risks of less than 10 percent for women of young age, low parity, and normal hemoglobin. At the other extreme, mothers of high parity, public hospital status, with previous premature infants, or with hemoglobin under 11 grams and who were heavy smokers (one pack or more per day) had increased perinatal mortality risks of 70 to 100 percent. Risks for light smokers who had other antecedent risk factors and for heavy smokers with otherwise good prognosis fell between these extremes when compared with nonsmokers. These relationships show how selection of a study population from one end or the other of this spectrum of smoking-associated risk levels would influence the relative risk found for smoking when no adjustment is made for these other factors (*117*). Other studies in which similar cross-tabulations have been made between maternal smoking level and socioeconomic level, maternal age, parity, previous pregnancy history, and other such factors have corroborated these findings (*2, 22, 29, 47, 102, 169*).

Because of possible interactions between maternal smoking and the other independent variables, Meyer, et al. undertook further analysis of the Ontario data to define and measure the independent effect of maternal smoking on the risk of perinatal mortality. For this a multiple regression analysis was used to compare the relative importance of smoking and other factors in their influence on perinatal mortality and on the frequency of low birthweight, of preterm delivery, and of placental complications (*115*). When the rates of perinatal mortality by smoking were adjusted for the effects of all other factors, perinatal mortality rates per thousand births were 23.5 for nonsmokers, 28.2 for smokers of less than a pack per day, and 31.8 for smokers of a pack or more per day. In other words, light smoking increased the risk by 20 percent and heavy smoking increased it by 35 percent. This is a highly significant, dose-related, independent effect, but it is less strong than the relationship to perinatal mortality of hospital pay status (a 55 percent increase for public status mothers), age-parity differences, or a history of previous pregnancy loss (190 percent greater risk if there is a previous loss compared with primiparity or with a previous pregnancy with no fetal or neonatal loss) (*115*).

TABLE 7.—Cause of stillbirth related to smoking habit

Cause of stillbirth	Percentage incidence	
	Nonsmokers	Smokers
Maternal disease	0.01	—
Maternal hypertension	0.19	0.17
Difficult labour	0.09	0.05
Antepartum hemorrhage	0.11	0.39
Congenital malformation	0.32	0.27
Haemolytic disease	—	0.13
Infection	0.01	—
Anoxia (without obvious cause)	0.24	0.23
Other cause stillbirth	—	0.02
Macerated stillbirth (without obvious cause)	0.29	0.23
Total stillbirths	1.30	1.54

SOURCE: Andrews, J. (2).

Cause of Death

The weight of evidence presented in this chapter clearly indicates that maternal smoking does increase the risk of spontaneous abortion, early and late fetal death, and early neonatal death. This being so, it is appropriate to attempt to identify mechanisms of action and intermediate pathways between the cigarette smoke and the fatal event. Clues to these mechanisms might be found if certain causes of death showed an excess among the infants of smoking mothers. Several authors have reported cause-specific mortality rates for the infants of smokers and nonsmokers. Andrews and McGarry (*2*) reported stillbirth rates of 1.30 per 100 births for nonsmokers and 1.54 per 100 for smokers, among which 0.11 and 0.39 were due to antepartum hemorrhage for nonsmokers and smokers respectively. For neonatal deaths, causes showing excess rates for infants of smoking mothers were "immaturity (no other cause)," "respiratory distress syndrome," and "pneumonia," with overall rates of 1.10 and 1.40 for nonsmokers, and smokers, respectively (Tables 7 and 8). Comstock, et al. (*30*) compared observed neonatal deaths of smokers' babies with numbers of deaths expected at nonsmoker rates. Out of 100 total observed deaths, smokers' infants had excesses of 17 due to immaturity, 15 due to asphyxia and atelectasis, and 7 due to birth injuries, with deficiencies of -7 due to congenital defects and -4 due to "other," leaving a net excess of +28. In the prospective study of 9,169 pregnancies carried out by Goujard, et al. (*63*), causes of stillbirth that increased significantly with maternal smoking were "abruptio placentae" ($p = .005$) and "unknown cause" ($p = 0.0005$). Overall differences in stillbirth rates showed an excess for smokers at a significance level of $p = 0.0001$ (Table 9).

TABLE 8.—Cause of neonatal death related to smoking habit

Cause of neonatal death	Percentage incidence	
	Nonsmokers	Smokers
Immaturity (no other cause)	0.25	0.36
Congenital malformation	0.33	0.31
Pneumonia	0.06	0.19
Asphyxia-atalectasis	0.17	0.12
Birth injury	0.03	0.09
Infection	0.03	—
Haemolytic disease	0.01	0.03
Respiratory distress syndrome	0.09	0.16
Other	0.11	0.12
Total neonatal deaths	1.10	1.40

SOURCE: Andrews, J. (*2*).

TABLE 9.—Stillbirths according to cause in relation to maternal smoking during pregnancy

Stillbirths	Number of deliveries	% of smokers	Comparison with live births †
Cause of death:			
Vascular	8	25%	
Abruptio placentae	13	46%	p=0.005
Mechanical cause	13	15%	
Miscellaneous (syphilis, Rh, *malformations*)	24	13%	
Unknown cause	37	35%	p=0.0005
Detailed records not available	5	—	
Total	100	26%	p=0.0001
Livebirths	9069	12%	

†When p is not given, the difference is not significant.
SOURCE: Goujard, J. (*63*).

Meyer and Tonascia (*116*) have analyzed fetal and neonatal deaths from the Ontario Perinatal Mortality Study (*142, 143*) to identify causes of death that show an excess if the mother smokes and to examine the relationship of these deaths to complications of pregnancy and labor. Fetal and neonatal deaths by coded cause and maternal smoking habit are shown in Table 10. For each cause the observed numbers for smokers were compared with the number expected at nonsmoker rates. The differences between observed and expected numbers indicate the number of deaths in each category attributable to maternal smoking. Significance levels of the differences between smoker and nonsmoker rates, based on the null hypothesis of no difference, are shown for p values of 0.06 or less.

TABLE 10.—Fetal and neonatal deaths by coded cause and maternal smoking habit (English speaking mothers)

Coded cause	Observed		Expected smoker*	Observed-expected difference	*P* value†
	Nonsmoker	Smoker			
Fetal deaths					
Unknown	75	125	81.4	43.6	0.003
Malformations	32	24	34.7	-10.7	N.S.
Hemolytic disease	11	15	11.9	3.1	N.S.
Anoxia	16	29	17.4	11.6	N.S.
Maternal cause	31	45	33.7	11.3	N.S.
All others	8	13	8.7	4.3	N.S.
Total	173	251	187.9	63.1	0.003
Neonatal deaths					
Unknown	52	51	56.5	-5.5	N.S.
Malformations	22	24	23.9	0.1	N.S.
Hemolytic disease	7	8	7.6	0.4	N.S.
Respiratory difficulty	46	63	50.0	13.0	N.S.
Prematurity alone	33	65	35.8	29.2	0.005
Maternal cause	2	6	2.2	3.8	N.S.
All others	16	16	17.4	-1.4	N.S.
Total	178	233	193.3	39.6	0.06
Total births	15,240	16,549			

N.S. = Not significant.
*Based on nonsmoker rate.
†P value derived from chi square based on a null hypothesis of no difference between smokers and nonsmokers.
SOURCE: Meyer, M.B. (*116*).

For fetal deaths, the largest category of coded cause was "unknown," and by far the largest and most significant smoking-related difference fell in this category ($p=0.003$). Smokers also showed more than expected fetal deaths due to anoxia and maternal causes and fewer deaths than expected due to malformations. In other categories only minor mortality rate differences were found between the two groups. For neonatal deaths the largest cause of death category was "unknown," but here there was no excess for smokers' infants. Most of the smoking-related excess of neonatal deaths was among those attributable to prematurity alone ($p=0.005$), with additional numbers in the related category of "respiratory difficulty." Differences between observed and expected deaths in other categories were negligible.

The tentative conclusion to be drawn from these findings is that many of the excess fetal deaths associated with maternal smoking do not have any recognizable pathology but occur from otherwise unknown causes. A significant excess also occurs as a result of antepartum hemorrhage or abruptio placentae. The excess neonatal deaths among the infants of smokers appeared to be due to prematurity and to related respiratory problems. In other words, these

deaths occurred in babies who were born preterm, but were without other pathology. There is no convincing evidence that maternal smoking increases the incidence of congenital malformations. Results of published studies, reviewed in the 1973 report, show relative risks for smokers versus nonsmokers ranging from 0.31 to 1.55 (*192*).

Complications of Pregnancy and Labor

Observations from the Ontario study and other data showed that women who smoked during pregnancy had excess fetal deaths either unexplained or attributed to anoxia and excess neonatal deaths due to premature delivery. These findings suggested that maternal smoking might increase the risk of certain pregnancy complications that were related, in turn, to these causes of perinatal loss. A direct relationship between maternal smoking level and the incidence of placenta previa, abruptio placentae, bleeding during pregnancy, and premature rupture of membranes had been reported previously (*2, 31, 63, 115, 189*). Underwood, et al., found higher rates for smokers than for nonsmokers of bleeding, abruptio placentae, and placenta previa combined, and of premature rupture of membranes in three groups of women with different socioeconomic and racial backgrounds (*188*). In a large study of births to U.S. Navy wives, the same complications increased with maternal smoking. In the latter study, the incidence of premature rupture of membranes increased within four levels of maternal smoking from none to 31+ cigarettes per day (*189*). Kullander and Kaellen found a significant increase in the frequency of abruptio placentae among children dying before the age of 1 week (*89*). Andrews and McGarry found increased incidence of abruptio placentae and other forms of accidental antepartum hemorrhage to be associated with maternal smoking. They stated that this was thought to be the cause of premature delivery in 1.2 percent of smokers compared with only 0.5 percent of nonsmokers. The incidence of accidental hemorrhage specific for parity was higher for smokers than for nonsmokers at all parities, rising to 3.16 percent of smokers who were para 4 or more (*2*). Similarly, Russell, et al. found an increase in vaginal bleeding during early pregnancy among women who smoked (*165*). In the study by Goujard, et al., as previously noted, a large proportion of the increase in stillbirths among smokers was caused by abruptio placentae (*63*). Naeye reviewed the clinical and postmortem material from the 3,897 fetal and infant deaths in the Collaborative Perinatal Project of the NINCDS (*137*) and reported an association between perinatal mortality rates caused by abruptio placentae and number of cigarettes smoked by the mother (*131*). Abruptio placentae was the underlying cause identified in 11 percent of all the deaths in this large study (*129*).

The Ontario data corroborated these findings, as shown in Table 11. Increasing levels of smoking resulted in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding, and

TABLE 11.—Perinatal mortality and selected pregnancy complications by maternal smoking levels

Outcome	Smoking level (packs per day) (rates per 1,000 total births)			
	0 (28,358 births)	<1 (15,328 births)	1+ (6,381 births)	Chi square*
Perinatal mortality	23.3	28.0	33.4	27.8†
Abruptio placentae	16.1	20.6	28.9	47.3†
Placenta previa	6.4	8.2	13.1	28.6†
Bleeding during pregnancy	116.5	141.6	180.1	201.9†
Rupture of membranes >48 hours	15.8	23.3	35.8	109.9†
Rupture of membranes only at admission	30.3	39.3	45.0	45.7†

*Cochran's chi square for trends.
†$p<0.00001$.
SOURCE: Meyer, M.B. (*116*).

prolonged rupture of membranes—all of which carry high risks of perinatal loss. Fetal and neonatal deaths from the Ontario study were analyzed (*116*) to look for smoking-related excesses of various complications of pregnancy and labor among those coded by the original Ontario Perinatal Mortality Study (*142*). Results are shown in Table 12. Most diagnoses showed no association with excess mortality for smokers' babies, but a few stood out as highly significant. As shown in Table 10, the net excess of fetal deaths for smoking mothers was 63. Table 12 shows that these deaths were strongly associated with bleeding during pregnancy, either before ($p=0.01$) or after ($p=0.0005$) 20 weeks' gestation, with 88 percent of the total excess falling in these categories. In other coded categories, a significant excess of fetal deaths occurred among smoking mothers with abruptio placentae ($p=0.001$) or other obstetrical problems. Analysis of coded complications of labor showed an excess of 32 fetal deaths coded as abruptio placentae and 8 coded as placenta previa. Fourteen more than expected had prolonged rupture of membranes.

Similar comparisons were made for neonatal deaths (Table 8). For these, the net excess among smoking mothers was 40. Among women who had vaginal bleeding before 20 weeks' gestation, there were 41 more neonatal deaths observed than expected, accounting for the total difference ($p=0.0001$). Other categories that showed significant increases of smoking-associated neonatal deaths are the admission status of rupture of membranes only, other obstetric complications, and duration of rupture of membranes over 48 hours, with 19 more neonatal deaths than expected in the latter group (*116*).

TABLE 12.—Fetal and neonatal deaths by maternal smoking and other coded conditions (Ontario Perinatal Mortality Study data. Canadian-born, English-speaking women, N = 31,789 births, 411 perinatal deaths)

Coded condition	Deaths of smokers' babies Observed-expected differences*			
	Fetal	P†	Neonatal	P†
Admission status				
True labor	15.3	N.S.	26.3	N.S.
Toxemia	-0.9	N.S.	0.7	N.S.
Abruptio placentae	48.5	0.001	2.5	N.S.
Elective cesarean section	-2.3	N.S.	-5.9	N.S.
Induction	-4.9	N.S.	-4.8	N.S.
Rupture of membranes only	0.4	N.S.	13.9	0.04
Other obstetric abnormality	16.8	0.06	6.0	0.01
Duration of rupture of membranes				
< 24 hours	32.2	N.S.	13.7	N.S.
24-48 hours	2.3	N.S.	3.3	N.S.
48+ hours	14.3	N.S.	19.4	0.01
In caul	8.5	0.02	1.7	N.S.
Unknown	5.8	N.S.	1.7	N.S.
Bleeding during pregnancy				
None	2.6	N.S.	-5.4	N.S.
Before 20 weeks	23.7	0.01	41.3	0.0001
After 20 weeks	32.2	0.0005	3.3	N.S.
Complications of labor				
None	19.2	N.S.	22.2	N.S.
Placenta previa	7.6	N.S.	6.6	N.S.
Abruptio placentae	32.3	0.002	6.2	N.S.
Abnormal uterine action	0.7	N.S.	4.9	N.S.
Cephalopelvic disproportion, dystocia	-2.4	N.S.	1.8	N.S.
Tumultuous labor	8.4	N.S.	7.1	N.S.
Postpartum hemorrhage	-4.6	N.S.	-8.0	0.06

N.S. = Not significant.
*Based on nonsmoker rate.
†P value derived from chi square based on a null hypothesis of no difference between smokers and nonsmokers.
SOURCE: Derived from Meyer, M.B. (*116*).

The conclusion may be drawn that maternal smoking increases the risk of fetal and neonatal death at least partly by increasing the incidence of these complications. The mechanisms of action of various components of cigarette smoke in bringing about these events are discussed in another section of this chapter.

Preeclampsia

It has been a consistent finding in almost all published studies that the incidence of preeclampsia and toxemia, however defined, is negatively associated with maternal smoking (*2, 10, 31, 42, 74, 89, 101, 146, 164,*

189, 212). Some of these studies have shown an inverse dose-response relationship, the incidence of preeclampsia declining as the number of cigarettes smoked increased (*146, 189*). Data from the British Perinatal Mortality Study were cross-tabulated by parity, severity of preeclampsia, and maternal smoking status. Smokers had lower rates of all grades of preeclampsia than nonsmokers, whether they were primiparae or multiparae (*20*). Andrews and McGarry showed that the negative relationship between cigarette smoking and preeclamptic toxemia was independent of social class, maternal weight before pregnancy, and maternal weight gain during pregnancy (*2*). Despite the favorable effect of smoking on the incidence of hypertension in pregnancy, there is a greatly increased risk of perinatal mortality if preeclampsia or hypertension does develop in a smoker (*2, 42, 164*). Several authors have suggested that this negative association may be due to the hypotensive effect of thiocyanate, which is derived from the cyanide present in cigarette smoke and regularly found in the blood of smokers (*2, 146*).

Preterm Delivery

Previous sections of this chapter have indicated that the downward shift of the distribution of birth weights with maternal smoking is not accompanied by a similar downward shift of gestational ages. On the other hand, abundant evidence has been presented that a smoking-related increase in preterm delivery plays an important role in the increased risk of neonatal death for the infants of smokers. Explanation of this apparent paradox is found by examination of the distribution by gestational age of births to nonsmokers, light smokers, and heavy smokers as shown in Figure 6, plotted on a semilogarithmic scale to emphasize relative differences in the early weeks. There is little difference between the means of these curves because the great majority of births occur around term in all groups. There is, however, a significant and dose-related increase in the proportions of preterm babies born to women who smoke. These preterm deliveries account for a small proportion of total births but for a large proportion of the deaths (*112*).

Published studies in which the percent of births occurring before term has been related to maternal smoking have consistently shown higher rates for smokers than for nonsmokers. Some examples are shown in Table 13. In four studies where all births and perinatal deaths were included, the risk of early delivery increased from 36 to 47 percent if the mother smoked, and 11 to 14 percent of all preterm births could be attributed to maternal smoking (*2, 20, 47, 207*). The lower relative and attributable risks found in Yerushalmy's study (*207*) may have resulted from selection of particular births to be studied and from the exclusion of fetal deaths. Analysis of the Ontario Study data

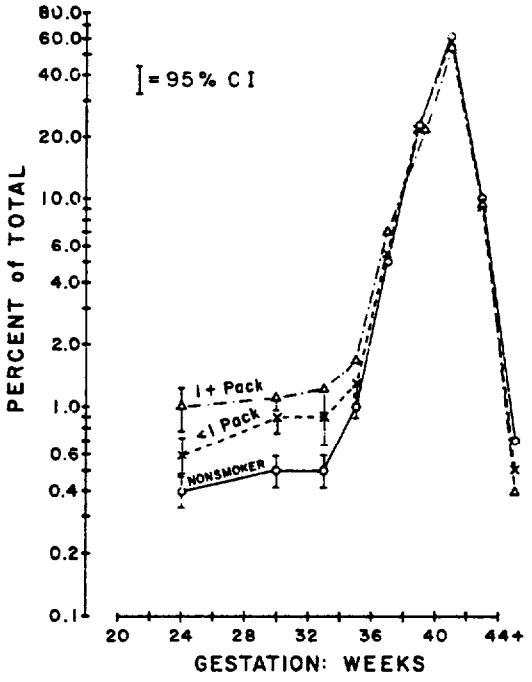

FIGURE 6.—Percentage distribution by weeks of gestation of births to nonsmokers, smokers of less than one pack per day, and smokers of one pack per day or more

SOURCE: Meyer, M.B. (*112*).

showed rates of delivery before 38 weeks of 77 per 1,000 births for nonsmokers, 92 per 1,000 for light smokers, and 116 per 1,000 for heavy smokers, after adjustment for the effects of other maternal factors (*115*).

Pregnancy Complications and Perinatal Mortality by Gestation

Meyer and Tonascia (*116*) have related the excess fetal and neonatal mortality of smokers' infants and the excess incidence of pregnancy complications among women who smoke to the gestational age of occurrence, using a life-table approach. A starting population of all pregnancies *in utero* at 20 weeks was used to calculate the probabilities of fetal death, live delivery followed by survival or death, or the occurrence of a complication followed by fetal death or delivery. At 28 weeks (the next point defined by the data), the population at risk included those remaining *in utero* at that point. Figure 7 shows the risk of perinatal death during each period of gestational age starting at 20 weeks. Risks for smokers' infants were significantly greater in the

TABLE 13.—Preterm births by maternal smoking habit, relative and attributable risks, derived from published studies

Study	Smokers (proportion)	Preterm births* per 100 total births		Relative risk: Smokers/Non-smokers	Attributable risk** %
		Nonsmokers	Smokers		
Cardiff (2)	.465	6.7	9.2	1.36	14
Great Britain (20)	.274	4.7	6.9	1.47	11
Montreal (47)	.432	7.7	10.6	1.38	14
Ontario***	.435	7.4	10.1	1.36	4
California (207)					
White	.402	5.9	6.9	1.10	4
Black	.338	13.4	16.7	1.25	8

*Cardiff and Ontario data are for < 38 weeks. All others are for < 37 weeks.
**Failure of totals to agree is due to omission of unknowns.
***Unpublished, derived from original data.

earlier weeks, remaining higher until term. Separate calculations for fetal and neonatal deaths (not shown) indicated a fetal death pattern very similar to the one shown for perinatal deaths. Neonatal deaths appeared to be due solely to an increased risk of early delivery among smokers' babies, rather than to differences in survival between smokers' and nonsmokers' babies of the same gestational age.

A similar approach was applied to the risk of abruptio placentae, placenta previa, and premature rupture of membranes for smokers and nonsmokers, as shown in Figure 8. All of these complications are more frequent in smokers than in nonsmokers throughout gestation, but again the biggest differences occur in the weeks of pregnancy from 20 to 32 or 34 weeks (*116*). The relationships between maternal smoking, these complications, early fetal death, and preterm delivery accompanied by neonatal death are apparent from the statistical associations between them and from the similar time patterns they share.

Sudden Infant Death Syndrome

Maternal smoking habits have been ascertained in several studies of the sudden infant death syndrome (SIDS). In all of these, a positive association has been found between maternal smoking during pregnancy and the incidence of sudden infant death. Steele and Langworth, in a study of 80 cases, each with two matched controls, which were traced back to the Ontario Perinatal Mortality Study population of 1960-61, found that sudden infant deaths were strongly associated with the frequency of maternal smoking during pregnancy ($p<0.001$) and also with the level of maternal smoking. Thirty-nine percent of the cases were nonsmokers versus 60 percent of controls; 36 percent of the

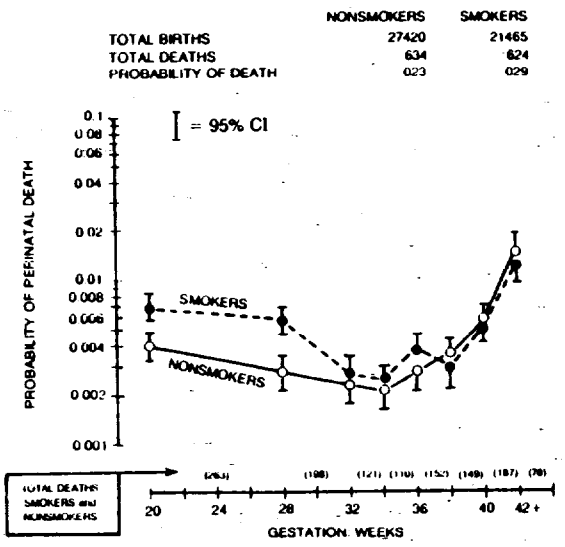

FIGURE 7.—Probability of perinatal death for smoking and nonsmoking mothers, by period of gestational age. Bars show 95 percent confidence intervals

SOURCE: Meyer, M.B. (*116*).

cases and 27 percent of the controls smoked less than a pack per day; 24 percent of the cases and 10 percent of the controls smoked a pack per day or more. The habits of the remaining 1 to 2 percent of mothers were unknown (*180*). Bergman and Wiesner noted the effects of exposure to cigarette smoke (passive smoking) on infants, including the increased frequency of respiratory infections in the infants of smoking mothers, and stated their impression that the amount of smoking seemed unusually heavy at meetings of parents who had lost children to SIDS. The authors studied 56 families who lost babies to the sudden infant death syndrome and 86 control families. They reported that a higher proportion of SIDS mothers smoked during pregnancy than controls (61 percent versus 42 percent), more smoked after pregnancy (59 percent versus 42 percent), and SIDS mothers smoked a significantly greater number of cigarettes than controls. These authors indicate that exposure to cigarette smoke (passive smoking) appears to enhance the risk for SIDS for reasons not yet known (*15*). However, whether prenatal or postnatal exposure is more important cannot be determined. Naeye, et al., in their analysis of 125 SIDS victims from the population of the Collaborative Perinatal Project of the NINCDS, stated: "The gestations that produced the SIDS victims were characterized by a greater frequency of mothers who smoked cigarettes and had anemia" than was true for the whole population of 53,721 infants or for a set of 375 controls matched on important factors

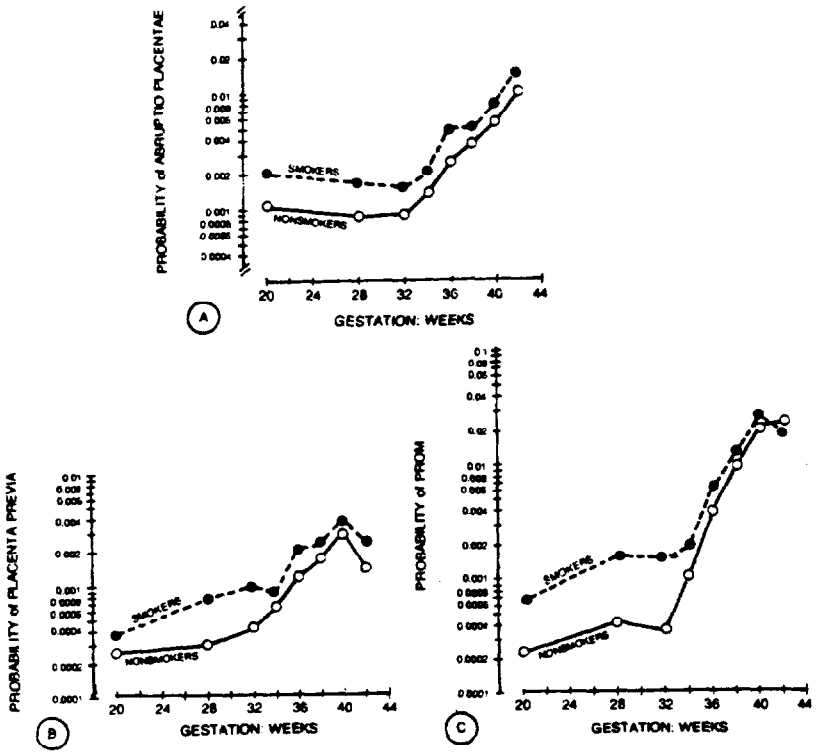

FIGURE 8.—Risks of selected pregnancy complications for smoking and nonsmoking mothers, by period of gestational age at delivery. A—abruptio placentae; B—placenta previa; C—admission diagnosis, rupture of membranes only

SOURCE: Meyer, M.B. (*116*).

(*130*). Rhead, commenting on studies published to date which demonstrate an increased incidence of maternal cigarette smoking in SIDS, states: "It is now...clear that maternal cigarette smoking contributes to an infant's risk of dying from SIDS" (*159*).

Summary

1. The risk of spontaneous abortion, of fetal death, and of neonatal death increases directly with increasing levels of maternal smoking during pregnancy.

2. Published studies of smoking during pregnancy show a range of perinatal mortality risk ratios (smokers versus nonsmokers) from a low of 1.01 to a high of 2.42.

3. Causes of variability between risk ratios in different study populations have been explained by recent analyses. They include:

(a) Lack of comparability between smokers and nonsmokers with respect to other important variables that influence perinatal mortality, such as race, socioeconomic status, age, parity, and others.

(b) Interaction between the effects of maternal smoking and these other variables, which makes maternal smoking more dangerous for the fetus in some pregnancies than in others.

4. Studies failing to take account of these other variables may show unusually high or unusually low risk ratios.

5. In one large study, the perinatal mortality risk increased by 20 percent for the infants of smokers of less than a pack per day and by 35 percent for smokers of a pack per day or more, compared with nonsmokers, after simultaneous adjustment to balance the effects of variables other than smoking. These increases are similar to those of other large studies with appropriate control of other variables.

6. Excess deaths of smokers' infants are found mainly in the coded cause categories of "unknown" and "anoxia" for fetal deaths, and in the categories of "prematurity alone" and "respiratory difficulty" for neonatal deaths. This finding indicates that the excess deaths result not from abnormalities of the fetus or neonate, but from problems related to the pregnancy.

7. Increasing levels of maternal smoking result in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery—all of which carry high risks of perinatal loss.

8. Although there is little effect of maternal smoking on mean gestation, the proportion of fetal deaths and live births that occur before term increases directly with maternal smoking level. Up to 14 percent of all preterm deliveries in the United States may be attributable to maternal smoking.

9. According to the results of one large study, the most significant difference between smokers' and nonsmokers' risk of perinatal mortality and pregnancy complications occurs at the gestational ages from 20 weeks to 32 or 36 weeks.

10. These findings lead to the conclusion that maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes.

Lactation and Breast Feeding

Introduction

In 1902, Ballantyne (*9*) suggested the possibility of detrimental effects of breast feeding on babies whose mothers worked in tobacco factories. In the intervening years, questions have been raised concerning the interaction between cigarette smoking and lactation, as well as the relationship of cigarette smoking to the quantity of milk produced, to the presence of constituents of cigarette smoke within the milk, and to effects upon the nursing infant mediated through changes in either the quantity of milk available or the substances within the milk.

Epidemiological Studies

Underwood, et al. (*188*), in a study of 2,000 women from various social and economic strata, observed a trend, though statistically insignificant, toward more frequent inadequacy of breast milk production among those smoking mothers who attempted to nurse, as compared to nonsmokers. They concluded that smoking does not interfere with breast feeding to any significant degree. However, this study, based on interviews of puerperal women, was not designed to analyze the effect of smoking on breast feeding and presents only percentile results. No data are provided to permit a reanalysis to determine the validity of their conclusions.

Perlman, et al. (*149*) also present anecdotal data. They found that in their postpartum population practically all smoking women started to consume cigarettes within two days after delivery. Although they collected milk between the fourth and ninth postpartum days to determine nicotine content, they do not report and compare actual amounts of milk secreted by both smokers and nonsmokers. They noted that of the 55 smoking, lactating mothers, 11 failed to have enough breast milk for the needs of their babies. No comparative study was done in a nonsmoking but otherwise equivalent population.

Mills (*120*) studied the nursing patterns of 520 women giving birth to their first live-born infant. Among the mothers nursing their babies for a minimum of 2 months and beyond, the mean nursing period was significantly shorter for smokers than for nonsmokers. Moreover, among the 24 mothers who had given up smoking during at least the final 3 months of their pregnancies, the average length of nursing was identical to that of the nonsmokers. There was no significant difference between smokers and nonsmokers with regard to complete inability to nurse their offspring. This study is difficult to interpret because the author did not determine the reason(s) for the discontinuation of nursing among the women.

Surveys of larger populations of women, smokers and nonsmokers, are needed to determine accurately the effect of smoking on milk

production and to correlate amount and pattern of smoking with the concentration of nicotine in milk throughout the lactating cycle.

Experimental Studies

Studies in Animals

Nicotine

Influence on the Lactation Process. Blake and Sawyer (*17*) studied the influence of subcutaneously injected nicotine (4 mg total over a 5-minute period) upon lactation in the rat. They found that nicotine inhibited the suckling-induced rise in prolactin. No effect of injected nicotine was demonstrated for oxytocin secretion since milk release was not blocked. In essence, these findings suggest that nicotine can cause a malfunction in milk production but not in its release mechanism. This phenomenon was examined by Terkel, et al. (*184*) in terms of pups' survival. Most of those pups born to females given a high dose of nicotine throughout pregnancy and lactation died of starvation before weaning. Their mothers' mammary glands contained very little milk, and plasma prolactin levels were very low. The mechanism by which nicotine may affect prolactin release is not yet clarified.

Hatcher and Crosby (*68*) found that injection of 4.0 mg/kg nicotine into nursing cats suppressed lactation for several hours. This was also observed in a cow.

Wilson (*202*) examined the effects of nicotine supplied through drinking water (0.5, 1.0, and 2.0 mg daily) on the weight gain of nursing rats. Apparently, the nicotine had been available throughout gestation as well, because the author commented on a reduction in litter size among the experimental groups, more or less proportionate to the dose of nicotine; hence, a prenatal effect could not have been distinguished from a postnatal one. Average birth weight was similar for experimental and control groups. No difference in weight gain was seen for any of the groups. The lack of impact on birth weight suggests that the dose was lower than that used in other studies. Indeed, Becker and Martin (*13*) observed a significant decrease in weight in the offspring of rats receiving 3.0 mg/kg twice daily during gestation. If the treatment continued throughout the nursing period, the young had a poorer survival chance than when exposed only *in utero* or when subjected daily to hypoxic stress in a special environmental chamber.

Presence of Nicotine in the Milk and its Effect Upon the Nursing Offspring. Hatcher and Crosby (*68*), using a frog bioassay, reported traces of nicotine in cow's milk 24 hours after the intramuscular injection of 5.0 mg/kg. They also reported that 0.5 mg/kg nicotine injected into nursing cats had no apparent harmful effect upon the kittens. Kittens fed the milk from the cow that had been injected with 5.0 mg/kg nicotine were apparently unaffected.

Nitrosamines. Mohr and Althoff (*121*) found that diethylnitrosamine and dibutylnitrosamine, when administered to lactating hamsters, were associated with the development of typical tracheal papillary tumors in the young, suggesting passage of those compounds in the milk. Although diethylnitrosamine and dibutylnitrosamine have not been identified in cigarette smoke, many N-nitrosamines are potent carcinogens, and some of them are present in cigarette smoke (*82, 160*).

Studies in Humans

Nicotine and Tobacco Smoke

Influence on the Lactation Process. Emanuel (*45*) noted no reduction in milk production among 10 wet nurses who were encouraged to smoke 7 to 15 cigarettes daily; some were observed to inhale the smoke. Hatcher and Crosby (*68*) noted that after a mother smoked seven cigarettes within 2 hours, it was difficult to obtain a specimen of breast milk. Perlman, et al. (*149*) found that, of 55 women smokers with an adequate milk supply at the beginning of his study, 11 (20 percent) had an inadequate supply at the time of discharge from the hospital. No relationship was reported between the number of cigarettes smoked and the likelihood of developing an inadequate milk supply. The authors' impression was that there was no greater proportion with an inadequate milk supply among smokers than among nonsmokers, but no corroborating data were supplied. Thompson (*186*) relates the fact that a young primipara who consumed 14 cigarettes secreted only 35 cc of milk obtained at two pumpings. He states that although the evidence is minimal, he has yet to observe a patient averaging eight or more cigarettes daily whose lactation was adequate at 3 months postpartum.

Presence of Nicotine in the Milk. Using a frog bioassay, Hatcher and Crosby (*68*) found that the milk of a woman collected after she had smoked seven cigarettes in 2 hours contained approximately 0.6 mg/liter nicotine. Emanuel (*45*), using a leech bioassay, studied excretion of nicotine in the milk of wet nurses who were encouraged to smoke for the experiment. After the subjects had smoked 6 to 15 cigarettes over a 1- to 2-hour period, the author found nicotine in their milk 4 to 5 hours after smoking, with a maximum concentration of 0.03 mg/liter. Bisdom (*16*) demonstrated nicotine in the milk of a mother who smoked 20 cigarettes a day. Thompson (*186*) found approximately 0.1 mg/liter of nicotine in the milk of a mother who smoked nine cigarettes a day and attempted three "pipesful." Perlman, et al. (*149*), using a Daphnia bioassay, demonstrated nicotine in the milk of all women in their study who smoked. Moreover, they found a direct dose-relationship between concentrations of nicotine and the number of cigarettes smoked. No comment was made by the authors on the possible inaccuracy introduced by examining only the residual milk

following nursing, but it is well known that the composition of the fore milk and the hind milk is different, and perhaps the concentration of nicotine also differs.

These ingenious bioassay methods have now been replaced by modern technology. Ferguson, et al. (*50*) measured by gas chromatography nicotine in a total of 34 samples of human milk from 15 donors. No nicotine peaks were found in the chromotograms of the six donors who were nonsmokers. The average nicotine content for the other samples was 91 parts per billion (ppb), ranging from 20 to 512 ppb. Because the sampling was done randomly, the authors could not correlate the amount of smoking with the concentration of nicotine in milk. A well-planned pharmacokinetic study is needed to determine the rate of nicotine secretion and modifying factors.

Evidence for a Clinical Effect Upon the Offspring. Emanuel (*45*) noted that, among the infants in his study, loose stools were observed only in the one infant whose wet nurse had smoked 20 cigarettes in the previous 4 hours. Bisdom (*16*) observed a case of "nicotine poisoning" in a 6-week-old infant whose mother smoked 20 cigarettes a day. The symptoms included restlessness, vomiting, diarrhea, and tachycardia. Nicotine was demonstrated in the milk, and the symptoms abated when smoking was stopped. Greiner (*64*) also described a case of possible nicotine poisoning in a 3-week-old nursling whose mother smoked 35 to 40 cigarettes a day. The symptoms gradually abated over a 3-day period. Perlman, et al. (*149*) noted no effect of smoking on the weight gain of the infants of the smokers in their study. Furthermore, no untoward symptoms were observed. They therefore doubted an effect of smoking on lactation. They noted that the dose received by the infants was beneath the toxic level as computed from adult experience, and this was in accord with their clinical observations. The fact that they studied only women with an apparently adequate milk supply may have affected their results. The authors suggested that perhaps the lack of effect of smoking upon lactation might represent the development of tolerance to nicotine, as both the mother and the offspring had been exposed throughout the pregnancy. Ferguson, et al. (*50*) noted that all infants observed in their study were asymptomatic, with normal feeding habits and behavior. While all authors refer to the presence or absence of immediate toxic effects, no evaluation of subtle effects has been done. Such effects may develop as a consequence of the infant's double exposure, through milk ingestion and inhalation from a "smoking" environment.

DDT. Bradt and Herrenkohl (*18*) measured DDT content in human milk samples from 10 donors and found that the results were correlated with the number of cigarettes smoked per day. This suggests either that cigarette smoke may be a source of the human body burden of DDT or that it may cause more DDT to be excreted in

the milk. The study was preliminary, however, and further data are needed to evaluate the implications for the health of infants.

Vitamin C. Venulet and Danysz (*195, 196*) demonstrated in a series of studies that the level of vitamin C was reduced in the milk of smoking mothers as compared with nonsmokers. The clinical significance of this observation has not been evaluated.

Physiologic-Experimental Studies

Studies in Animals

Tobacco Smoke

Several investigators have demonstrated that exposure of pregnant rats or rabbits to tobacco smoke leads to a reduction of birth weight in the offspring, as compared to controls (*47, 168, 211*). Apparently Essenberg, et al. (*46*) were the first to study the effects of cigarette smoke on pregnant animals. These authors reported that in female rats exposed to smoke from cigarettes the incidence of sterility, reabsorption of the young *in utero,* abortions, and newborn deaths prior to weaning increased significantly as compared to controls. Wagner, et al. (*197*) reported that, in albino mice exposed to tobacco smoke, maternal weight gain during pregnancy was significantly less than in control animals. Shoeneck (*168*) exposed rabbits to tobacco smoke for several generations. The original doe weighed 3.5 kg. A female of the first generation weighed 2.8 kg, that from the second generation weighed only 1.5 kg, and all attempts to breed the doe were either totally unsuccessful or resulted in stillbirths or neonatal deaths.

Of course, factors other than carbon monoxide in tobacco smoke may also cause fetal growth retardation. Younoszai, et al. (*211*) reported data from studies in rats which indicated that some agent present in cigarette smoke other than nicotine was responsible for the reduction in birth weight observed. These workers exposed rats to several types of smoke, including the smoke of tobacco leaf, smoke from lettuce leaves plus nicotine, and smoke from lettuce leaves alone. The body weight of rat fetuses exposed to lettuce leaf smoke decreased 9 percent, body weight of the fetuses exposed to lettuce leaf smoke plus nicotine decreased about 12 percent, and body weight of fetuses exposed to tobacco smoke decreased about 17 percent. The reported carboxyhemoglobin concentrations varied from 2 to 8 percent in all animals, but the data were not given. Although the authors suggested that carbon monoxide might not be responsible for the retardation of fetal growth, the evidence presented was inadequate to support a firm conclusion.

In an attempt to determine whether the decrease in fetal weights of smoking mothers results from smoking per se or from decreased food intake, Haworth and Ford (*69*) compared fetal body and organ weights

in pregnant rats exposed to tobacco smoke for 6 to 8 minutes, five times a day, from days 3 to 20 of gestation. These rats were compared with another group whose food intake was restricted to the amount actually consumed by the tobacco-exposed rats, and both were compared to a well-fed control group. The animals in both experiments were killed on the 21st day of gestation, and weights of the entire body, the liver, and the kidney of each fetus were recorded. The total average fetal weight of the group exposed to tobacco smoke was significantly lower than that of both the food-restricted and control groups. The fetal weights of the latter two groups were quite similar. Protein and DNA analyses were performed separately on the entire forebrains and hindbrains of the fetuses and on the entire carcass. Both DNA and protein were significantly and proportionately reduced in the carcass and hindbrains of the animals exposed to tobacco smoke. This implies that cell number was reduced and cell size was normal, suggesting that the exposure to tobacco smoke either inhibited cellular proliferation or accelerated cellular destruction.

Another study of smoking in animals that is quoted for its relatively negative results is that of Kirschbaum, et al. (*85*). These researchers attempted to simulate maternal smoking in 12 near-term pregnant sheep by having the ewe inspire cigarette smoke periodically so that 8 to 9 cigarettes were consumed in one hour. The authors reported only minor changes in maternal and fetal blood pressures, heart rates, and blood gases. However, on the basis of the blood carbon monoxide contents (and assuming a normal blood hemoglobin concentration), one can calculate that the maternal blood carboxyhemoglobin concentration during smoking equaled only 0.6 percent, a concentration not significantly greater than that obtained under normal control conditions in most reports (*99*). Thus, one must conclude that in fact the carboxyhemoglobin concentrations did not approach those levels seen even in one-pack-a-day smokers.

In one of the few studies on simulated marijuana smoking in animals, Singer, et al. (*173*) reported that in guinea pigs exposed to marijuana smoke the maternal heart rate increased during the "smoking" period, and the maternal electroencephalogram changed to a pattern of low-frequency and high-amplitude activity. The fetal electroencephalogram changed to a low-frequency, high-voltage activity pattern during the smoking period; after cessation of maternal smoking, it changed to a lower-voltage and higher-frequency activity.

Nicotine

Following the studies of Essenberg, et al. (*46*), several workers have demonstrated that chronic injections of large doses of nicotine into pregnant rats result in a reduction of birth weight of the offspring (*11-13, 46, 84, 122*). For example, Becker, et al. (*12*) demonstrated that the fetuses of mothers who received nicotine not only weighed less for

their age, but had a shorter crown-rump length, a smaller transverse head diameter, less ossification of forelimb bones, shorter vibrassae, and shorter claw length in relation to fetal age. Nishimura and Nakai (*136*) reported numerous malformations, particularly of the skeletal system of fetal mice (strain S) whose mothers received injections of nicotine. These developmental anomalies included delayed osteogenesis and malformation of major joints, polydactyly, syndactyly, spinal curvature, etc. The critical period for producing these abnormalities was longer than for many other drugs tested, extending from the 6th through the 14th day of gestation. In a subsequent study, Geller (*57*) showed that doses of nicotine, about 15 percent of that used by Nishimura and Nakai, resulted in no fetal abnormalities. Landauer (*91*) also noted multiple congenital abnormalities in white leghorn chicks in which the eggs were injected with varying concentrations of nicotine sulfate at several stages of incubation. The predominant lesion noted was shortening and twisting of the neck, secondary to abnormal development of the cervical spine.

Several groups have shown that nicotine administration to pregnant rats resulted in prolonged gestation (*11, 13, 75, 79*). For instance, in Sprague-Dawley rats receiving daily injections of 3 mg of nicotine per kg of body weight throughout the 21 days of gestation, the onset of labor was delayed 1 day in 40 percent, delayed 2 days in another 40 percent, and the remainder delivered on the third day (*13*). Maternal weight gain in nicotine-treated rats is also significantly less (*12, 78, 79*). Damage to the placental capillaries of nicotine-treated dogs was reported by Fischer (*52*).

That nicotine definitely crosses the placenta into the fetus has been demonstrated by a number of workers (*66, 187*). Nicotine and its metabolic product, cotinine, are also found in amniotic fluid (*194*). The question of the rate at which nicotine and its metabolites cross the placenta is of some interest. Tjalve, et al. (*187*) showed that, following maternal injection of C^{14}-labeled nicotine, radioactivity appeared rather quickly in the placenta and fetal tissues, reaching a peak in both in about 30 minutes. In studies of rhesus monkeys with catheters in maternal and fetal blood vessels and amniotic fluid, Suzuki, et al. (*182*) measured nicotine levels following a single injection of 0.5 to 1.0 mg ^{3}H-nicotine into the maternal circulation. The decrease in maternal nicotine concentration was a double exponential process. Initially there was a rapid decrease as nicotine became distributed in various maternal body compartments. Then there was a slow decrease due to the metabolism of nicotine and its crossing the placenta. Fetal nicotine concentration increased rapidly; then a plateau developed, followed by a slow decrease as nicotine was metabolized and re-entered the maternal circulation. It was noted that the fetal adrenal glands, heart, and kidneys tended to accumulate the nicotine.

While the fetal liver metabolizes nicotine (presumably in the microsomal fraction), it is less efficient than maternal liver (*187*). Stalhandske, et al. (*179*) quantitated this relation by measuring the formation of labeled cotinine after incubation of C^{14}-labeled nicotine with liver slices from fetal and newborn mice. These workers showed an almost linear increase in the rate of metabolism of nicotine from about 1 day prior to birth, which is normally 19 days in the strain of mice used, until a week following birth.

The effects of nicotine on the fetal circulation may vary somewhat. Nicotine is similar to acetylcholine in its action on both sympathetic and parasympathetic ganglia, on skeletal muscles, as well as on the central nervous system. It acts at all three sites, first stimulating, then depressing them. Minute doses of nicotine stimulate the chemoreceptors of the carotid and aortic bodies, causing reflex hypertension, cardiac acceleration, and increased respiratory rate. Nicotine also releases epinephrine from the adrenal medulla, thereby producing cardiovascular changes. Thus, nicotine can produce widely differing effects, depending on the dosage and the particular site that is most sensitive to stimulation or depression.

Suzuki, et al. (*181*) studied the effects of nicotine injection on heart rate and arterial blood pressure in rhesus monkeys. Following infusion of nicotine into the mother for 20 minutes (at a rate of 100 mg/kg for a total maternal dose of 2 mg/kg), maternal arterial pressure rose and heart rate fell by about 15 percent. Changes in blood pressure and heart rate of the fetus were less marked and more variable than those of the mother. There was relatively slight hypotension and an irregular delayed tachycardia. Mature fetuses (greater than 120 days gestation) also developed significant acidosis, hypercarbia, and hypoxia. On the other hand, Kirschbaum, et al. (*85*) showed no significant changes in fetal blood pressure or umbilical blood flow following injection of 3 mg/kg nicotine tartrate into a pregnant sheep. However, these negative findings may have resulted from the ewes being anesthetized with the fetuses exteriorized, an experimental condition resulting in altered cardiovascular responses. Suzuki, et al. (*181*) also administered nicotine directly to the fetus *in utero*. The fetal blood pressure immediately rose and heart rate decreased, both values returning to control values within 10 minutes. The fetal responses showed a significant age dependency. The changes were more marked in the older fetuses in contrast to the younger fetuses, despite a larger dose for the latter. These differences in response of the fetuses as a function of gestational age imply differences in the development of the autonomic nervous system, with the more mature fetuses being more sensitive than less mature ones.

In a preliminary study, Resnik, et al. (*158*) report that injection of 1 to 1.5 mg/min of nicotine reduced uterine blood flow 40 percent in pregnant sheep. This decreased flow was associated with a twofold

increase in blood epinephrine and norepinephrine concentrations, compared with preinjection values. The authors concluded that the uterine vascular response to nicotine was mediated by the release of catecholamines within the maternal circulation.

Several investigators have studied nicotine effects on the fetal and newborn central nervous system. Hudson, et al. (*77*) injected 3 mg of nicotine per kg body weight twice daily in rats during the course of a 21-day pregnancy and attempted to assess nicotine effects on the developing brain from behavioral responses. They compared seizure activity between the offspring of nicotine-treated and untreated animals. Such electrophysiological data have been shown to provide useful information on brain maturation patterns. Although convulsive seizures represent a fundamentally pathologic phenomenon, when used experimentally they offer a measure of interaction occurring between inhibitory and excitatory systems of the central nervous system that manifests as overt motor activity. The researchers utilized the electroshock seizure threshold as a specific index of subcortical brain maturation, showing it to be markedly effected in nicotine-treated animals. In control newborn rats, the electroshock seizure threshold decreased slowly from day 10 to day 18 and remained at this level until day 24, the last day of testing. On the other hand, in the offspring from nicotine-treated mothers, the electroshock seizure threshold increased from days 10 to 14, then dropped below control values on day 16 and continued to decrease until day 24. The differences in electroshock seizure thresholds indicate that nicotine induced a transitory effect on the development of seizure activity, most likely involving subcortical inhibitory and excitatory pathways.

Hudson, et al. (*77*) also utilized maximal electroshock seizure patterns as a specific index of the whole brain maturation and cortical development. They showed that on day 26, the duration of flexion was shorter and the duration of extension longer in offspring of nicotine-treated rats than in their corresponding controls. These responses returned to control levels within 33 days. The responses indicate increased brain excitability, which at this age may indicate immaturity or other disturbances of central nervous system maturation. Thus, nicotine administration during gestation prolonged the normal maturational timetable for excitatory and inhibitory systems, either by delaying the development of excitation or accelerating the development of inhibition. Although these specific electroconvulsive responses normalize with increasing age, even transient abnormalities occurring during critical maturational periods may have functional repercussions because of the complexity of events taking place during central nervous system development. Indeed, these authors point out that continuing studies on the effects of endogenous and exogenous factors on central nervous system development reveal that alterations at critical periods of prenatal and postnatal brain maturation, though not

always immediately observable, are frequently manifest in the onset of specific functions or when a specialized demand is placed on the organism.

Nicotine administration during gestation also may affect newborn psychomotor function. Martin and Becker (*106*) noted that young rats so treated performed less well than control animals on fixed-ratio, variable discrimination, and discrimination reversal.

Carbon Monoxide

Classically, it has been held that carbon monoxide exposure resulting in significant biologic effects on the human organism is produced mainly by poisoning with relatively high concentrations of blood carboxyhemoglobin. During the past decade, it has been appreciated that even relatively low carboxyhemoglobin concentrations, for example, 4 to 5 percent, can result in demonstrable disturbances of mental, visual, and other functions (*26*). Longo (*93*) recently has reviewed numerous aspects of carbon monoxide exposure in the pregnant mother, the fetus, and the newborn infant. Those studies derived from animal experiments may be considered from the standpoint of the rate of buildup or elimination of carbon monoxide from the pregnant mother and fetus, fetal to maternal carboxyhemoglobin concentrations under steady-state conditions, and the effects of carbon monoxide on the fetus *in utero*. For obvious ethical and technical reasons, studies of maternal and fetal carbon monoxide exchange are impossible in human beings, and much of our knowledge of these relations are based on animal studies.

Blood carboxyhemoglobin concentration [HbCO] usually is expressed as percent saturation:

$$\left[\text{HbCO}\right] = \frac{\text{blood CO content}}{\text{blood CO capacity}} \times 100$$

The terms "percent saturation" and "carboxyhemoglobin concentration" are used interchangeably. Both imply the percentage of hemoglobin combined with carbon monoxide. Douglas, et al. (*39*) first showed that the amount of blood carboxyhemoglobin concentration in relation to oxyhemoglobin concentration resulted not only from the ratio of the partial pressure of carbon monoxide, P_{CO}, to the partial pressure of oxygen, P_{O_2}, but in addition, from the relative affinity of hemoglobin for carbon monoxide as compared with oxygen, a factor expressed by the symbol M.

$$\frac{[\text{HbCO}]}{[\text{HbO}_2]} = \frac{P_{CO} \times M}{P_{O_2}}$$

Tc determine the rate at which blood carboxyhemoglobin concentrations in the mother and the fetus change in response to exposure to a given concentration of carbon monoxide in the air, Longo and Hill (*97*) exposed pregnant sheep with catheters chronically implanted in maternal and fetal blood vessels to inspired CO concentrations of 30 to 300 ppm. Figure 9 summarizes the results for changes in maternal and fetal carboxyhemoglobin concentrations. It also compares the experimental results with predictions made using a mathematical model. At all levels of carbon monoxide exposure, the maternal carboxyhemoglobin concentration increased relatively rapidly during the first 2 to 3 hours. It then continued to increase more slowly over the next few hours, reaching a relatively constant level in 7 to 8 hours. The change in maternal carboxyhemoglobin concentration resembled a simple exponential process with a half-time of 2.5 hours.

The increase in fetal carboxyhemoglobin concentrations lagged behind maternal concentrations (*97*). During the first hour of exposure, fetal carboxyhemoglobin concentrations showed little change. During the following 4 to 5 hours they increased, but at a relatively slow rate as compared with the rate of the early carboxyhemoglobin rise in the mother. By 5 to 6 hours, fetal carboxyhemoglobin equaled maternal concentrations, after which the values continued to increase slowly for 24 hours or more. Only after 36 to 48 hours did the fetal blood attain final steady-state carboxyhemoglobin concentrations. The time for fetal carboxyhemoglobin concentration to reach half its final value was about 7 hours. At equilibrium, fetal carboxyhemoglobin concentration exceeded the maternal concentration by about 58 percent. Hill, et al. (*73*) then used a mathematical model to calculate the theoretical relations of fetal-to-maternal carboxyhemoglobin concentrations in humans. Although slightly different in some details, the predicted uptake and elimination curves in pregnant women after exposure to several inspired carbon monoxide concentrations were strikingly similar to the experimental results in animals.

The mechanism by which carbon monoxide crosses the placenta from maternal to fetal blood clearly is by diffusion. Longo, et al. (*99*) showed in sheep and dogs that the half-time for carbon monoxide to diffuse across the placenta is about 2 hours. These workers (*98*) also demonstrated that the resistance to diffusion in the placenta is due equally to the placental membranes per se and to the relative resistance afforded by the chemical combination of carbon monoxide with hemoglobin.

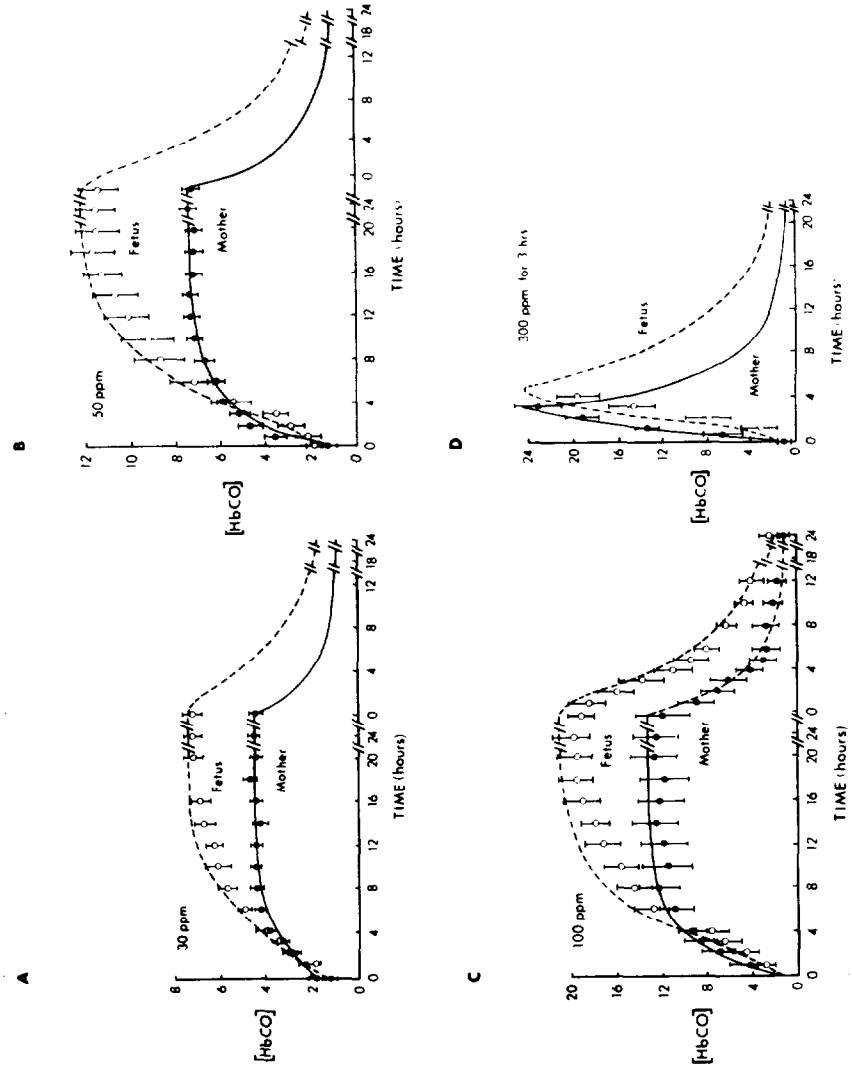

FIGURE 9.—Time course of carbon monoxide uptake in maternal and fetal sheep exposed to varying carbon monoxide concentrations. The experimental results for the ewe (●) and fetal lamb (○) are the mean values (± SEM) of 9 to 11 studies at each inspired carbon monoxide level, except in the case of 300 ppm, at which only three studies were performed. The theoretical predictions of the changes in maternal and fetal carboxyhemoglobin levels for the ewe and lamb are shown by the solid and interrupted lines, respectively

SOURCE: Longo, L.D. (97).

Effects on Fetal Growth and Development

Only a few studies have reported the effects of carbon monoxide on fetal growth and development. Wells (*200*) exposed pregnant rats to 1.5 percent (15,000 ppm) CO for 5 to 8 minutes 10 times on alternate days during the 21-day pregnancy. This resulted in maternal unconsciousness and abortion or absorption of most fetuses. The surviving newborns failed to grow normally. Similar exposure to 5,900 ppm affected only a small percentage of animals. This brief report lacks quantitative data on the number of experimental animals and number and weight of the fetuses. Williams and Smith (*201*) exposed rats to 0.34 percent (3,400 ppm) carbon monoxide for 1 hour daily for 3 months. Peak carboxyhemoglobin concentrations in these animals varied from 60 to 70 percent. Among seven female animals, only one-half the control number of known pregnancies occurred. The number of young per litter was reduced and only 2 out of 13 newborns survived to weaning age. No pregnancies resulted in five females exposed for 150 days.

Astrup, et al. (*5*) reported quantitative data on fetal weights following exposure of pregnant rabbits to carbon monoxide continuously for 30 days. Exposure to 90 ppm resulted in maternal carboxyhemoglobin concentrations of 9 to 10 percent. Birth weights decreased 11 percent from 57.7 to 51.0 g, and neonatal mortality increased to 10.0 percent from a control value of 4.5 percent. Mortality of the young rabbits during the following 21 days increased to 25 percent from a control value of 13 percent. Following exposure to 180 ppm CO, with resulting maternal carboxyhemoglobin concentrations of 16 to 18 percent, birth weights decreased 20 percent from 53.7 to 44.7 g, and neonatal mortality was 35 percent compared with 1 percent for the controls. Three of seventeen newborns in this group had limb deformities. Mortality during the following 21 days was 27 percent, the same value as for the controls.

Fechter and Annau (*48*) exposed pregnant Long-Evans rats to 150 ppm CO throughout gestation. The newborns of the CO exposed rats weighed slightly less at birth than controls (5.55 [$\pm$0.05 SEM]g versus 5.74 [$\pm$0.06]g). During the newborn period this difference increased. By day 21, the weights were about 42 ($\pm$ 1) and 46 ($\pm$ 1)g, respectively. Behavioral tests disclosed less spontaneous and L-dopa-stimulated activity as compared with controls. Garvey and Longo (*56*) exposed pregnant Long-Evans rats to 30 or 90 ppm CO throughout gestation. Although fetal total body weight was unaffected by these concentrations, the brain weights increased 14 percent and lung weight decreased 24 percent in those fetuses exposed to 90 ppm CO. This brain enlargement was attributed to an increased water content as the concentrations of brain protein, DNA, norepinephrine, and serotonin were decreased, as was the brain wet-dry weight ratio. Schwetz, et al. (*170*) reported that mice and rabbit fetuses exposed to 250 ppm CO

from days 6 to 15 of pregnancy (mice) and days 6 to 18 of pregnancy (rabbits) developed minor skeletal alterations.

Carbon Monoxide Effects on Tissue Oxygenation

Several mechanisms probably account for the effects of carbon monoxide on developing tissue. Undoubtedly the most important of these is the interference with tissue oxygenation (*10, 53*). Claude Bernard in 1857 first observed that carbon monoxide decreases the capacity of blood to transport oxygen by competing with it for hemoglobin. Carbon monoxide binding to hemoglobin increases the oxygen affinity of the remaining hemoglobin (Figures 10 and 11). This shift of the oxyhemoglobin saturation curve to the left means that the oxygen tension of blood must decrease to lower than normal values before a given amount of oxygen will release from hemoglobin. This effect may be particularly significant for the fetus because the oxygen partial pressure in its arterial blood is normally relatively low, about 20 to 30 torr as compared to adult values of about 100 torr. Carbon monoxide also interferes with oxygen transport by displacing oxygen from the hemoglobin in arterial blood, thus decreasing the blood oxygen transport capacity. To the pregnant woman these effects on blood oxygenation pose a special threat. Not only is her oxygen consumption increased 15 to 25 percent during pregnancy (*150*), but her blood oxygen capacity is decreased 20 to 30 percent or more because of the decreased concentration of hemoglobin. The woman with a significant anemia faces an even more severe compromise of her oxygen delivery.

Aerobic metabolic processes depend upon the maintenance of tissue oxygen partial pressure above some critical level, which varies among different tissues. Intracellular gas tensions are difficult, if not impossible, to measure directly. However, changes in capillary P_{O_2} values reflect tissue oxygen tensions, other things being equal. In the absence of arteriovenous shunts, the P_{O_2} of venous blood draining a tissue equals the P_{O_2} at the venous end of its capillaries. Thus, venous P_{O_2} roughly indicates the adequacy of tissue oxygenation.

Longo (*94*) and Longo and Hill (*97*) have examined the changes in maternal and fetal oxygen tension in response to various carboxyhemoglobin concentrations in sheep with catheters chronically implanted in maternal and fetal vessels. Figure 12 shows the decreasing oxygen partial pressures in the fetal descending aorta and inferior vena cava below the ductus venosus as the concentration of carboxyhemoglobin increases (*97*). In contrast to the adult, whose arterial oxygen tension remains relatively unaffected by changes in carboxyhemoglobin concentrations, the fetus has arterial oxygen tensions which are particularly sensitive to increases in maternal or fetal carboxyhemoglobin concentrations. In the illustration, the oxygen partial pressure

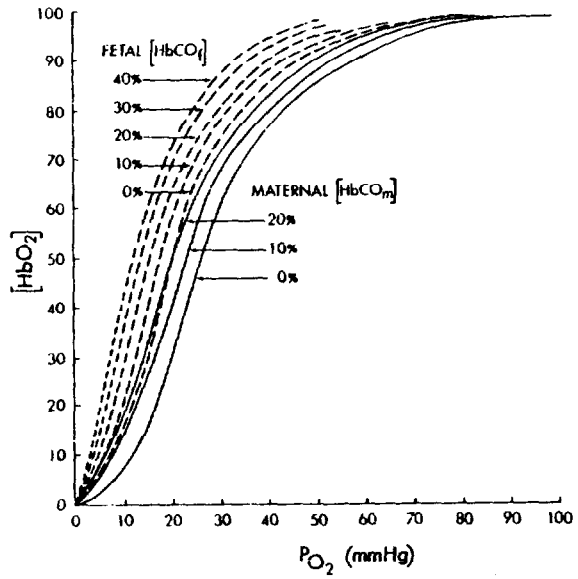

FIGURE 10.—Human maternal and fetal oxyhemoglobin saturation curves showing carbon monoxide effect. The effect of varying concentrations of carboxyhemoglobin [HbCO] is calculated by the method of Roughton and Darling (1944). The oxyhemoglobin saturation [HbO_2] is that percentage of hemoglobin not bound as carboxyhemoglobin

SOURCE: Longo, L.D. (*93*).

in the fetal descending aorta decreased from a control value of about 20.0 torr to 15.5 torr at 10 percent fetal carboxyhemoglobin concentration. (The regression equation for this relation was $P_{O2}=20.1-0.4$ [$HbCO_f$], ($R=-0.094$).) This figure also shows the relation of oxygen tension of the inferior vena cava below the ductus venosus to carboxyhemoglobin concentration in the fetus. At 10 percent carboxyhemoglobin concentration, inferior vena cava oxygen tension decreased from a control value of about 16.0 to 12.5 torr. (The regression equation for this relation was $P_{O2}=-0.3$ [$HbCO_f$], ($R=-.096$).)

As noted above, the fetus, which normally has a relatively low oxygen tension in relation to that of the adult, is particularly vulnerable to these decrements in blood oxygen tension with increased carboxyhemoglobin concentration. In the above-mentioned study (*97*), 57 percent of the fetuses died when fetal carboxyhemoglobin values increased above 15 percent for 30 minutes or longer (5 of 11 died at 100 ppm, and 3 of 3 died at 300 ppm). These deaths presumably resulted from hypoxia of vital tissues. Probably two major reasons account for

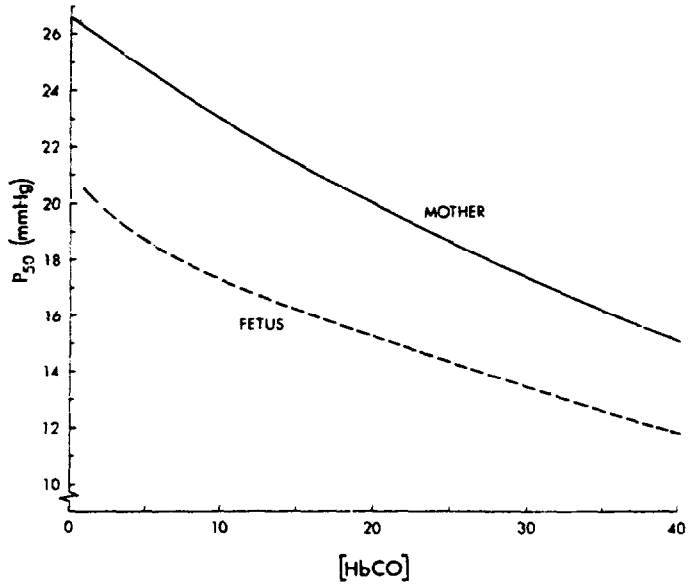

FIGURE 11.—The partial pressure at which the oxyhemoglobin saturation is 50 percent, P50, for human maternal and fetal blood as a function of blood carboxyhemoglobin concentration
SOURCE: Longo, L.D. (*93*).

this. First, in the adult, elevation of carboxyhemoglobin concentration to 15 to 20 percent results in a 6 to 10 torr decrease in venous P_{O2} values. Although this decrease is substantial, the resultant oxygen partial pressures probably remain well above critical values for maintaining tissue oxygen delivery (*178*). In contrast, the fetus with normal arterial and venous P_{O2} values probably close to the critical levels would develop tissue hypoxia or anoxia with substantial decreases in oxygen tension. Furthermore, adult subjects and animals subjected to carbon monoxide hypoxia show increases in cardiac output (*6*) and presumably coronary and tissue blood flow. Apparently such compensatory adjustments are not available to the fetus to any great extent. The decreases in blood oxygen tension measured experimentally followed those predicted, assuming no increase in tissue blood flow. In addition, the fetus probably cannot increase its cardiac output significantly, as the output normally is about two to three times that of the adult on a per weight basis (*154*). Thus, the fetus probably normally operates near the peak of its cardiac function curve.

In an attempt to determine to what extent the fetus *in utero* responds to carbon monoxide hypoxia as compared with hypoxia induced by the mother breathing air or gas with a low oxygen content,

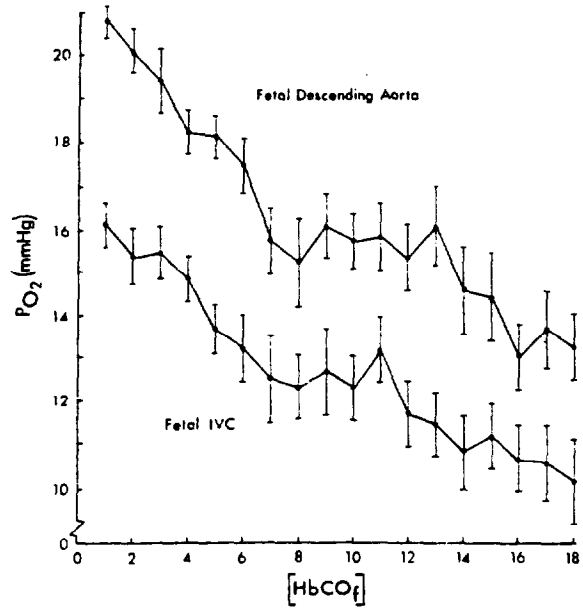

FIGURE 12.—Fetal values of oxygen partial pressure as a function of carboxyhemoglobin concentrations during quasi-steady-state conditions. Fetal inferior vena caval oxygen tension is a function of both maternal and fetal carboxyhemoglobin concentrations. The oxygen partial pressure of fetal arterial blood is chiefly a function of maternal carboxyhemoglobin concentrations. During steady-state conditions, however, it will also be related to the fetal carboxyhemoglobin concentration level. Each point represents the mean ±SEM (vertical bars) of 6 to 20 determinations at each level of blood carboxyhemoglobin

SOURCE: Longo, L.D. (97).

Longo, et al. (*100*) measured the cardiac output and distribution of blood flows to various organs of the fetus. These investigators used chronically-catheterized fetal lambs in near-term pregnant sheep and measured blood flow using radioactive-labeled microspheres. They found that the fetal response to carbon monoxide induced hypoxia was indistinguishable from its response to so-called hypoxic hypoxia. Under both sets of conditions, the output of the fetal heart showed no significant increase during hypoxia, a compensatory adjustment that occurs in adults in an attempt to maintain adequate tissue oxygenation. On the other hand, the fetus demonstrated a redistribution of its peripheral circulation such that blood flow increased somewhat to the brain, heart, and adrenal glands. Presumably this increased flow

occurred in an effort to maintain oxygenation of these "survival" organs.

Ginsberg and Myers (*59*, *60*) studied the effects of CO exposure on near-term pregnant monkeys and their fetuses. When they exposed acutely-anesthetized animals to 0.1 to 0.3 percent carbon monoxide, resulting maternal carboxyhemoglobin concentrations were about 60 percent. During the 1- to 3-hour studies, fetal blood O_2 content decreased to less than 2 ml/100 ml blood, from control values of 9 to 15 ml/100 ml blood. Fetal heart rates decreased in proportion to the blood oxygen values. These fetuses also developed severe acidosis (pH less than 7.05), hypercarbia (P_{CO2}=70 torr or greater), hypotension, and electrocardiographic changes, such as T-wave flattening and inversion (*60*).

Effects on Newborn Animals

The effect of CO on newborn survival has been studied by several groups. Smith, et al. (*174*) exposed rats to mixtures of illuminating gas in air with carbon monoxide concentrations equaling 0.43 percent. For 22 newborn rats, 12 to 48 hours old, exposed to carbon monoxide, the average survival time was about 195 minutes, in contrast to an average survival time of about 36 minutes in mature animals. McGrath and Jaeger (*111*) noted that 50 percent of newly hatched chicks could withstand exposure to 1 percent (10,000 ppm) carbon monoxide for about 32 minutes. This initial resistance to carbon monoxide decreased rapidly. By day 1, mean survival time decreased to about 10 minutes, by day 4 it was 6 minutes, and by day 8 it was 4 minutes, where it remained for all ages tested up to 21 days. Subsequently Jaeger and McGrath (*80*) showed that decreasing the body temperature increased the time to last gasp from a mean value of 9.8 ± 0.5 min at 40°C to 20.7 ± 0.1 at 30°C. They noted that hypothermia caused markedly reduced heart and respiratory rates and suggested that its major benefit was a reduction in energy-requiring functions.

In an attempt to develop an animal model for hyperkinesis, Culver and Norton (*32*) and Norton, et al. (*139*) exposed 5-day-old Sprague-Dawley rats to 1 percent (10,000 ppm) CO until breathing ceased for 20 seconds. This required about 2 hours. Hyperactivity was present when the rats were tested at 4 to 8 weeks of age, but not when they were tested at 3 to 5 months of age. Incidentally, a similar type of hyperactive behavior developed following X-irradiation and bilateral stereotaxic lesions of the globus pallidus (*139*).

Polycyclic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) such as benzo(*a*)pyrene (B*a*P) are constituents of cigarette smoke which have been implicated in the generation of cancers in many animal species (*200*). No studies

presently available relate benzo(*a*)pyrene to a reduction in birth weight of exposed offspring. Evidence suggests, however, that BaP does reach and cross the placenta. Aryl hydrocarbon hydroxylase (AHH) is a part of the cytochrome P-450-containing microsomal enzyme system present in many tissues of different species. This enzyme system is induced to hydroxylate polycyclic aromatic hydrocarbons after exposure of cells to PAH. Several investigators have utilized the inducibility of the enzyme system to demonstrate indirectly that benzo(*a*)pyrene and other polycyclic hydrocarbons reach the placenta and fetus.

Welch, et al. (*199*) extended this work by administering the polycyclic hydrocarbon, 3-methylcholanthrene (3-MC) to rats during late gestation. The metabolism of benzo(*a*)pyrene was studied *in vivo*, using tritium-labeled benzo(*a*)pyrene, and *in vitro*. AHH activity was increased in fetal livers to adult levels by pretreatment with 3-MC. Since a relatively high dose of polycyclic hydrocarbon was required to stimulate enzyme activity in the fetus, compared to the dose which stimulated placental enzyme activity, the authors suggested that the placenta may protect the fetus from exposure to polycyclic hydrocarbons. However, immaturity of the fetal enzyme system might also account for its apparent relative insensitivity to polycyclic hydrocarbons. Therefore, an exposure of the fetus to levels of polycyclic hydrocarbon similar to those experienced by the mother cannot be ruled out by the available data. Nebert, et al. (*133*) and Pelkonen, et al. (*148*) also correlated the activity of this enzyme, which was readily induced in placental tissue with maternal smoking.

Schlede and Merker (*167*) have studied the effect of benzo(*a*)pyrene administration on aryl hydrocarbon hydroxylase activity in the maternal liver, placenta, and fetus of the rat during the latter half of gestation. The pregnant animals were treated with large oral doses of benzo(*a*)pyrene 34 hours prior to sacrifice. Control rats had no detectable levels of aryl hydrocarbon hydroxylase in their placentas. Treatment with benzo(*a*)pyrene resulted in barely detectable placental levels at gestation day 13, but steadily rising values until day 15, and then constant levels thereafter. No activity was detected in the fetuses of untreated controls. In the treated animals, the fetal enzyme activity rose steadily from the 13th to the 18th day of gestation. The authors concluded that the stimulatory effect of benzo(*a*)pyrene treatment on aryl hydrocarbon hydroxylase activity in the fetus demonstrates that benzo(*a*)pyrene readily crosses the rat placenta. The placenta is involved in complex hormonal interrelations between mother and fetus, and oxidative enzyme pathways in the placenta are important in maintaining hormonal balance for normal fetal development. The hydroxylation of polycyclic hydrocarbons and the active transport of various compounds by trophoblast cells may share common enzyme

systems. Thus, the induction of various enzymes by maternal smoking may interfere with the transport systems.

The effect of maternal administration of benzo(*a*)pyrene as a carcinogenic risk for progeny was examined by Nikonova (*135*). Pregnant mice (strains A and C 57 BL) were injected with a single dose of either 4 or 6 mg benzo(*a*)pyrene on the 18th or 19th day of gestation. In both strains, the offspring, when examined 1 year later, showed a markedly higher incidence of neoplasms of the lungs, liver, and mammary glands.

Studies in Humans

Tobacco Smoke

Sontag and Wallace (*175*) first reported an increase in fetal heart rate during maternal smoking. These authors concluded that the response was secondary to the passage of nicotine across the placenta, although this was not demonstrated. Hellman, et al. (*70*) studied several factors affecting the fetal heart rate. These workers asked habitual smokers not to smoke for 24 hours, then to smoke one to two cigarettes. Typically, a gradually increasing maternal tachycardia developed within 3 minutes of the onset of smoking. Fetal tachycardia with a flattening of the normal beat-to-beat variation occurred in about 3.5 minutes. In contrast, a similar response to maternal atropine injection did not occur for about 12 minutes. The authors reported short bursts of fetal tachycardia during the time that the mother was being given the cigarette, but before the lighting of the cigarette. They called this an "anticipatory response" and concluded that it probably resulted from some vasomotor change in the uterine placental vessels. Cloeren, et al. (*25*) reported that in 22 pregnant women studied during the last half of pregnancy fetal tachycardia usually followed maternal smoking, and in two-thirds of the cases the fetal heart rate showed a loss of beat-to-beat variability.

Recent reports indicate that "breathing" movements by the fetus are a normal component of intrauterine development. Both the proportion of time the fetus makes breathing movements and the character of these movements appear to reflect fetal condition. In women with normal pregnancies, cigarette smoking abruptly and significantly decreased the proportion of time that the fetus made breathing movements to 50 percent from a control value of 65 percent (*58, 105*). These acute changes may not result from nicotine or carbon monoxide, however, since marked decreases in breathing failed to occur in the fetuses of women who smoked non-nicotine cigarettes (*104*).

These changes in fetal heart rate and breathing movements can result directly from effects on the fetus per se, or indirectly from effects on the placental circulation, or both. Haberman (see Longo (*96*)) used thermography to assess utero-placental blood flow. In this

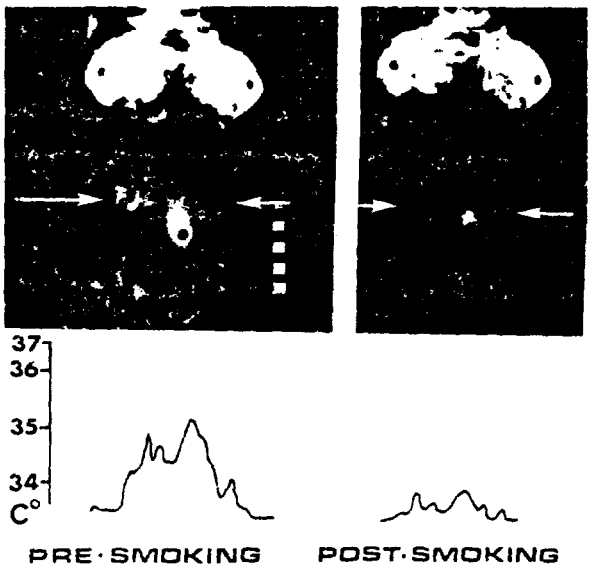

FIGURE 13.—Thermogram from a near-term pregnant patient before and after smoking. The normal thermal imprint of the placenta is shown on the left as a white area between the arrows. The right panel shows decreased heat emission after the mother smoked a single cigarette for 8 minutes. Below are the temperature profiles across the abdomen at the level of the arrows. The small squares in the left panel are the temperature calibrations (Courtesy of Dr. JoAnn D. Haberman)

SOURCE: Longo, L.D. (*96*).

technique, infrared sensors record the heat distribution from a given area of the body. Figure 13 shows a thermogram from a near-term pregnant patient before and after smoking and inhaling from a single cigarette for 8 minutes. The thermal imprint of the placenta (white area between arrows) in the panel on the left markedly decreased following smoking (panel on right). While there is a question as to whether this technique measures blood flow or blood volume in a given area, it is evident that maternal smoking results in changes in heat emission from the pregnant uterus. Cloeren, et al. (*25*) have reported that the utero-placental blood pool, as measured with radioactive Indium, increased during maternal smoking; however, these investigators failed to present any quantitative data.

An additional consideration is the effect of maternal smoking on placental metabolism. Tanaka (*183*) used a Warburg apparatus to measure oxygen consumption of placental slices from nonsmoking and smoking mothers. The oxygen consumption of placental tissue from

normal nonsmoking mothers equaled 1.9 microliters (μl) per mg of placenta per hour. The rate of oxygen consumption from the placentae of smoking mothers decreased in proportion to the carboxyhemoglobin concentration in maternal blood. For instance, it decreased about 30 percent to 1.3 μl/mg/hr at 8 percent maternal carboxyhemoglobin concentration. By energy-dependent processes, placental cells play an important role in metabolizing hormones and other compounds and in actively transporting amino acids, vitamins, and other substances. The components of tobacco smoke may adversely affect fetal development by interfering with these metabolic and transport functions.

Asmussen and Kjeldsen (*4*) used the human umbilical artery as a model to evaluate vascular damage caused by tobacco smoking. In comparison with the vessels from babies of nonsmoking mothers, the umbilical arteries from 13 smoking mothers showed marked changes of the vascular intima. Scanning electronmicroscopy disclosed swollen and irregular endothelial cells with a peculiar cobblestone appearance and cytoplasmic protrusions or blebs on their surface. Transmission electronmicroscopy showed degenerative changes, including endothelial swelling, dilation of the rough endoplasmic reticulum, lysosomes abnormal in appearance, and extensive subendothelial edema. In addition, the basement membrane was markedly thickened, a change probably indicating reparative change. Finally, the vessels showed focal opening of intercellular junctions and loss of collagen fibers. This study underscores the probable vulnerability of the fetus to the effects of smoking by the mother. Subsequently, Asmussen (*3*) noted that in comparison with the placentae of nonsmoking mothers, the placentae of four mothers who smoked disclosed changes similar to those seen in the umbilical arteries; namely, broadening of the basement membrane of the placental villi, increased collagen content of the villi, decreased vascularization, and intimal changes of the villous capillaries and arterioles with pronounced intimal edema. Loehr, et al. (*92*) reported similar changes in placental morphology. In addition, Spira, et al. (*177*) observed that the placentae of smoking mothers show a higher frequency of abnormal trophoblast cells and clumping of the nuclei of the syncytiotrophoblast.

Heron (*71*) reported a delayed onset of crying immediately after birth in the infants of smoking mothers. Several infants showed definite evidence of asphyxia with irregular respiration and cyanosis. Younoszai, et al. (*210*) found, in addition to elevated carboxyhemoglobin levels among the infants of smoking mothers, significant elevation of mean capillary hematocrits and significant reduction of standard bicarbonate levels, as compared to the infants of nonsmoking mothers. As no evidence for nicotine effects upon blood glucose, serum-free fatty acid levels, urinary catecholamines, or hypoxia was present, they concluded that the higher hematocrit levels in the infants of smoking mothers may have represented a compensatory response to the

decreased oxygen-carrying capacity of the blood due to the presence of carboxyhemoglobin.

As noted elsewhere in this chapter, mothers who smoke have a higher incidence of complications such as abruptio placenta with resulting stillbirth, placenta previa, and other causes of bleeding during pregnancy (*2, 63, 89, 101, 102, 115, 116, 189*). The incidence of premature rupture of the fetal membranes also increases (*116, 189*), while the incidence of the hypertensive disorders of pregnancy decreases (*2, 20, 89, 165, 189*). Unfortunately, the physiologic basis for these disorders is not known. It can be postulated that abruptio placenta may follow spasm of uterine vessels such as the spiral arterioles secondary to nicotine and other compounds. It is of interest that abruptio placentae and other disorders occur more frequently in women whose pregnancies are complicated by the hypertensive disorders of pregnancy. On the other hand, the decreased incidence of hypertensive disorders among pregnant women who smoke may result from the vasodilating action of the thiocyanate present in tobacco smoke.

Carbon Monoxide

Although there are few studies of carbon monoxide effects on human pregnancy, those reports of maternal and fetal blood carboxyhemoglobin concentrations during maternal smoking will be considered in this section.

The blood carboxyhemoglobin concentration of normal nonsmoking pregnant women, [$HbCO_m$], normally is 0.5 to 1.0 percent while that in the fetus is about 10 to 20 percent higher, that is, 0.6 to 1.2 percent. Figure 14 depicts the steady-state fetal and maternal carboxyhemoglobin concentrations as a function of the carbon monoxide concentration. Several studies have reported carboxyhemoglobin concentrations in the blood of smoking mothers and their newborns (Table 14). Reported fetal carboxyhemoglobin concentrations range from 2 to 10 percent and maternal concentrations range from 2 to 14 percent. These blood samples, obtained at the time of vaginal delivery or Cesarean section, probably fail to reflect accurately the normal values of carboxyhemoglobin. For instance, the number of cigarettes smoked during labor might have been less than the number normally consumed; blood samples were collected at varying time intervals following the cessation of smoking, and many samples were probably taken in the morning before the carboxyhemoglobin concentrations had built up to the values reached after prolonged periods of smoking. Therefore, the average values for normal smoking mothers and their fetuses could be well above the concentrations reported in maternal and fetal blood.

Using a mathematical model, Hill, et al. (*73*) calculated the theoretical relations of fetal and maternal carboxyhemoglobin concen-

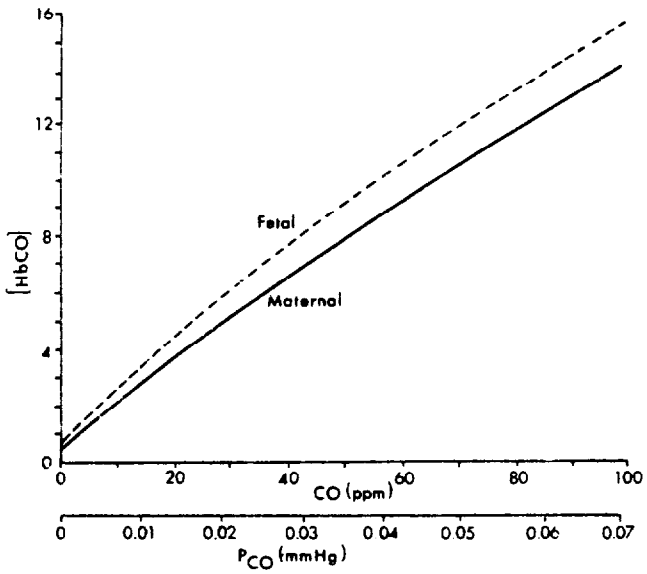

FIGURE 14.—Percent carboxyhemoglobin in maternal and fetal blood as a function of carbon monoxide partial pressure and concentration (parts per million) in inspired air. These carboxyhemoglobin concentrations were calculated from the Haldane relation correcting for the carbon monoxide effect on the oxyhemoglobin saturation curves

SOURCE: Hill, E.P. (*75*).

trations in human subjects. During carbon monoxide uptake, fetal carboxyhemoglobin concentrations would lag behind the maternal concentrations for the first few hours. After 14 to 24 hours they would equal maternal carboxyhemoglobin concentrations. Eventually the fetal carboxyhemoglobin would equilibrate at concentrations 10 to 15 percent higher than the maternal concentrations. During the washout phase, fetal carbon monoxide elimination would lag behind the maternal elimination and the carboxyhemoglobin concentration in the fetus would be significantly greater than that of the mother. The time required to reach one-half of the final value would average about 2 hours for the mother and 7 hours for the fetus. The pattern of carbon monoxide uptake and elimination in this theoretical analysis (*73*) is similar to that of the experimental results in sheep (*97*).

Carbon monoxide markedly shifts the oxyhemoglobin saturation curve to the left and alters the shape of the curve toward a more hyperbolic form. Figure 10 shows this effect for several concentrations of human maternal and fetal carboxyhemoglobin (*93*). The oxyhemoglobin saturation is for that percentage of hemoglobin not bound as

TABLE 14.—The relation of the concentrations of fetal to maternal carboxyhemoglobin in mothers who smoke during pregnancy

Fetal carboxyhemoglobin concentration	Maternal carboxyhemoglobin concentration	Fetal/maternal carboxyhemoglobin ratio	reference
7.5†	4.1	1.8	(27)
7.6(SEM ± 1.14)*	6.2(±0.75)*	1.2(±0.2)*	(65)
3.1(±0.84)**	3.6(±1.06)**	0.7(±0.14)	
5.0(±0.48)	6.7(±0.61)	0.7(±0.04)	(71)
3.6(±0.7)	6.3(±1.7	0.7(±0.15)	(95)
5.3(±0.22)	5.7(±0.24)	0.9(±0.06)	(183)
2.4(±0.30)	2.0(±0.31)	1.2(±0.08)	(209)
7.3	8.3	0.9	(211)

*One or more cigarettes 1 hr or less prior to delivery.
**One or more cigarettes 1 to 24 hrs. prior to delivery.
†Calculated from $[HbCO_m]$ and the ratio of $[HbCO_f]$ to $[HbCO_m]$.
SOURCE: Longo L.D. (*93*).

carboxyhemoglobin. Figure 11 shows the change in the oxygen partial pressure corresponding to 50 percent oxyhemoglobin saturation, the P50, for maternal and fetal blood as a function of blood carboxyhemoglobin concentration. For instance, at 10 percent carboxyhemoglobin concentration, the P50 for maternal blood decreases to 23.0 torr from a control value of 26.5 torr. At this same carboxyhemoglobin concentration, the fetal P50 decreases to 17.3 torr from a normal value of 20.5 torr.

In a theoretical analysis of the effects of elevated blood carboxyhemoglobin on fetal oxygenation, Longo, et al. (*73, 93*) have shown that either markedly increased tissue blood flow or considerably reduced oxygen tensions are the price that must be paid to maintain normal oxygen delivery. The upper part of Figure 15 shows the predicted decrease in oxygen tension as carboxyhemoglobin concentrations increase. The lower portion shows the compensatory or equivalent change in fetal blood flow necessary to maintain a steady-state oxygen exchange in the placenta, assuming no drop in umbilical artery oxygen tension. A 10 percent carboxyhemoglobin concentration would be equivalent to a drastic reduction in blood flow. Fetal blood flow would have to increase 62 percent (from 350 to 570 ml/min) to maintain normal oxygen exchange. Higher levels of fetal carboxyhemoglobin require even more dramatic compensations. However, it seems doubtful that much, if any, compensatory increase in blood flow occurs in the presence of carbon monoxide in the fetus (*97*). Therefore, the

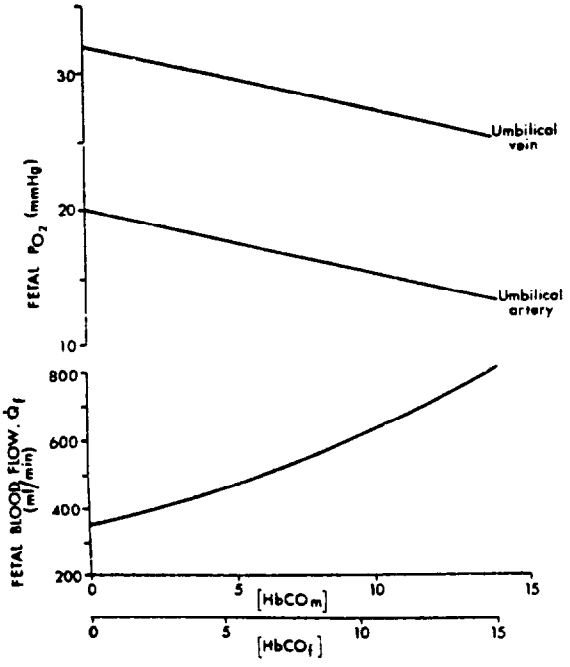

FIGURE 15.—The degree of compensation necessary to offset the effects of elevated fetal carboxyhemoglobin concentrations. Upper portion: Decrease in umbilical artery P_{O_2} and umbilical vein (placental end-capillary) P_{O_2} necessary to maintain normal oxygen exchange across the placenta in the presence of increasing amount of fetal carboxyhemoglobin. Lower portion: Increase in fetal blood flow (Qf) which would be required to maintain the normal O_2 exchange in the placenta with no change in umbilical artery P_{O_2}

SOURCE: Longo, L.D. (*95*).

changes in P_{O_2} values probably illustrate the *in vivo* situation more closely than do the equivalent changes in blood flow.

Vitamin B_{12} and Cyanide Detoxification

McGarry and Andrews (*110*) determined serum vitamin B_{12} levels in 826 women at their first prenatal clinic visit. They found that the serum levels for smokers were significantly lower than for nonsmokers. After adjustment for gestational age, parity, social class, hemoglobin level, hypertension, and maternal weight, smokers still had significantly lower levels of B_{12}. They also found a direct, statistically significant dose-response relationship between cigarettes smoked and serum vitamin B_{12} level. They again confirmed the relationship between smoking and low birth weight. The authors suggested that the lower

vitamin B_{12} levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (*83, 132, 134, 138, 144, 153, 176*).

Vitamin C

Venulet and Danysz (*195, 196*) have demonstrated that the vitamin C level is significantly lower in the serum of women who smoke cigarettes during pregnancy, compared to values for their nonsmoking counterparts.

Research Issues

Nutrients and oxygen provided by the maternal circulation are essential to normal fetal growth and development. It may be anticipated that some alterations may be produced in the developing fetus when the nutrients are accompanied by toxins in the inhaled smoke of burning tobacco and paper and when carbon monoxide is mixed with the oxygen. Some of the observed alterations may be considered innocuous in themselves, but the evidence to date justifies high priority investigation to determine whether they are indicators of processes that are fundamentally dangerous to either the immediate or long-term health of the fetus and the child.

A number of important questions relating to the possible biological effects of tobacco smoke and its constituents on the fetus *in utero* and the newborn infant remain unanswered. The ethical issue of experiments in pregnant human subjects and newborn infants affects further research. The problems of such studies are obvious but will not be resolved in the foreseeable future. Mathematical models, while useful, require considerable data based on human or animal studies. Models, in addition, possess serious limitations and restrictions because any mathematical abstraction encompasses only a very minute portion of the finite world or a given problem. Thus, future progress in our understanding of the effects of tobacco products in these areas of investigation will require appropriate animal studies with extrapolation to humans.

The research objectives are (1) to identify risk of perinatal loss or damage in women who smoke during pregnancy, and (2) to define the effects on the fetus and the new-born infant resulting from maternally-inhaled tobacco smoke.

In considering the epidemiologic, biologic, and pharmacologic facets of the problem of cigarette smoking and its impact on fetal and infant well-being, the following areas of study are suggested:

Fetal Death

1. Do available data sets confirm the evidence that maternal smoking may lead to anoxic death *in utero* of a normal fetus in an uncomplicated pregnancy?

2. Can the risk of such a death be calculated in terms of the mother's capacity to offset the hypoxic stress of smoking by such mechanisms as increasing hemoglobin or hematocrit; increasing cardiac output; increasing placental ratio, surface area, and area of attachment; or by other mechanisms?

3. Are there indications in existing data sets that anoxic fetal deaths occurred in smoking mothers with, for example, anemia, poor cardiac function, poor pulmonary function, poor general health, unfavorable age (older), or low socioeconomic status?

4. Do these deaths occur more frequently in mothers who, besides being heavy smokers, are anemic or live at high altitudes?

5. Do these deaths occur later in pregnancy when there is less reserve capacity to supply oxygen because of the greater oxygen demand of the larger fetus, the reduction of the placental ratio, and the reaching of the natural limits of increase of hematocrit and cardiac output?

6. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified prospectively by measurement of exhaled CO and carboxyhemoglobin, relating these levels to hematocrit, cardiac output, and other tests of reserve capacity to increase oxygen supply to the fetus?

7. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified by use of exercise testing during prenatal care?

8. Do available data sets confirm the evidence that maternal smoking during pregnancy causes fetal death by increasing the incidence of abruptio placentae, other antepartum bleeding, and related complications?

9. Do available data sets confirm the evidence that the above complications occur more frequently among women with other risk factors such as low socioeconomic status, older age, higher parity, unfavorable previous pregnancy history, and more frequently the more the mother smokes?

10. Are the higher incidences of placental complications and fetal deaths among women who smoke due to poorer diet and lower levels of vitamin C, vitamin B_{12}, folic acid, and other substances that help to maintain tissue integrity?

11. Is there a relationship between the increased incidence of vaginal bleeding in the above cases and the pathological changes in placental blood vessels from smoking women observed by Asmussen?

12. If there is a generalized effect of smoking on the integrity of blood vessel linings and other tissues, what role does this play in the bleeding and abruptio placentae observed in such cases?

13. Can fetal death associated with maternal smoking and placental complications be predicted by careful monitoring of any pregnancy with signs of bleeding after 20 weeks of pregnancy?

14. Can these deaths be prevented by cessation of smoking, supplements of vitamins and folic acid, and other treatment to maintain fetal oxygenation?

Neonatal Death

15. Do available data sets confirm the evidence that maternal smoking leads to neonatal death of otherwise normal babies by increasing the occurrence of preterm birth?

16. What proportion of preterm deliveries of smoking mothers is associated with a history of bleeding early in pregnancy?

17. What proportion of preterm deliveries of smoking mothers is associated with premature rupture of membranes?

18. What is the relationship of maternal smoking to the incidence of bleeding early in pregnancy and of premature rupture of membranes, whether or not there is a preterm delivery and whether or not there is a fetal or neonatal death?

19. Through investigation of characteristics such as age, parity, socioeconomic status, and reproductive history, is it possible to identify women who will be at particularly high risk of pregnancy complications and pregnancy loss if they smoke?

20. Besides the warning sign of bleeding, what other measurements will help to identify the woman who must stop smoking in order to maintain the pregnancy?

21. Will measurement of levels of carboxyhemoglobin, vitamin C, vitamin B_{12}, folic acid, and other indices help to elucidate the mechanisms leading to bleeding and to premature rupture of membranes among smoking mothers?

22. Is there evidence that the tensile strength of fetal membranes is reduced if the mother smokes?

23. Is there evidence that amniotic fluid infection plays a part in the smoking-related increase in the incidence of premature rupture of the membranes?

24. Will elucidation of the mechanisms whereby maternal smoking causes complications of pregnancy, early delivery, and neonatal death help to persuade pregnant women to stop smoking—particularly if they have bleeding early or late in pregnancy—and to persuade obstetricians that cessation of maternal smoking is of crucial importance for a successful pregnancy?

25. Will monitoring of exhaled CO levels in all prenatal care clinics help to reverse the recent trend toward more frequent and heavier smoking among young women?

Spontaneous Abortion

26. Can the increased incidence of spontaneous abortion with maternal smoking be confirmed by further studies, allowing for measurement of dose-response relationships and an accurate estimate of risk ratios?

27. Can the mechanisms of action be worked out, using the same approach as has been done for perinatal mortality?

28. To what extent is a previous spontaneous abortion in a smoker related to a subsequent unfavorable outcome of pregnancy if the woman continues to smoke?

29. Is there an overall increase in the risk of spontaneous abortion as a result of maternal smoking, or is the increased risk confined to women already at risk for other reasons?

Preeclampsia

30. What is the mechanism linking smoking during pregnancy to a reduced incidence of preeclampsia and toxemia?

31. Could components of this mechanism, if understood, be applied so that the risk of preeclampsia could be reduced without incurring the risks associated with smoking?

Sudden Infant Death Syndrome

32. Do existing data sets with postnatal follow-up confirm the association of maternal smoking with an increased risk of SIDS?

33. Do the smoking mothers of SIDS victims have other signs of impairment of their oxygen supply system such as anemia, heart trouble, impaired pulmonary function, or high altitude residence, as indicated in prenatal records?

34. Do the smoking mothers of SIDS victims have early or late bleeding, premature rupture of the membranes, abruptio placentae, or preterm delivery?

Long-Term Follow-Up

35. Can studies with long-term follow-up of growth and development identify groups with smoking-related impairment of a serious nature as opposed to very slight changes in overall means?

36. Could case-control studies using prospective long-term follow-up data (such as that from the British Perinatal Mortality Study) identify maternal smoking patterns and other prenatal factors associated with the problems of physical, intellectual, and emotional development of the children?

Birth Weight and Placenta

37. To what extent does the reduction of birth weight of smokers' babies represent a physiological adaptation to reduced oxygen availability?

38. What are the combined effects on birth weight of maternal smoking, anemia, and high altitude?

39. What are the combined effects of maternal smoking, anemia, and high altitude on weight, shape, area and site of attachment, and placental-fetal ratio?

40. How are these relationships affected by other maternal antecedent factors, such as age, socioeconomic status, and previous history?

41. Is the increased incidence of placenta previa with maternal smoking and high altitude related to an adaptive increase in the placental site of attachment?

42. To what extent do placental changes with maternal smoking represent physiological adaptations to hypoxic and other stresses?

43. To what extent do placental changes represent pathological effects of smoking and what is their role in unfavorable pregnancy outcomes?

Experimental Studies

44. Can experimental studies of exposure to cigarette smoke or to the components of cigarette smoke elucidate the mechanism of reduced birth weight?

45. Is the smoking-associated reduction of fetal growth due to a reduction in the rate of mitosis resulting in a decreased number of cells?

46. Is the smoking-associated reduction of fetal growth rate due to a decreased number of cells in some parts of the body but not in others?

47. Is the smoking-associated reduction of fetal growth rate accompanied by deficiencies in learning ability, emotional development, or physical growth?

Lactation and Breast Feeding

48. Does smoking inhibit milk production in humans? This question could be approached through epidemiological and experimental studies. Surveys of a large population of smoking and nonsmoking women are desirable to correlate the number of cigarettes consumed and the pattern of smoking with the amount of milk produced and the concentration of nicotine and other constituents of smoke in milk throughout the lactation cycle.

49. How does nicotine affect prolactin release, and can this phenomenon be reversed? Appropriate experimental animal research

could provide the basis for understanding mechanism(s) of action and the mapping of appropriate interventions.

50. How much nicotine is excreted in breast milk ingested by the nursing infant? A well-planned pharmacokinetic study should be done involving the mother-infant dyad.

51. Is it possible to determine the complete profile of other components of cigarette smoke in breast milk? The answer to this question will permit the identification of potential carcinogenic agents and their degree of ingestion by the infants.

52. Does the interaction between nicotine and other drugs excreted in breast milk affect the physiology of the infants? The presence of DDT and benzo(*a*)pyrene, inducers of the activity of drug-metabolizing enzymes, may cause unexpected, subtle side effects in the growing infant which may manifest at a later date.

Tobacco Smoke

53. To what extent does maternal smoking in humans affect maternal and fetal blood catecholamine concentrations?

54. To what extent does maternal smoking affect uterine and placental blood flow?

55. To what extent does maternal smoking affect fetal heart rate, breathing pattern, electroencephalographic activity, or other parameters that can be monitored (that is, dose-response relationships)?

56. To what extent does smoking marijuana differ in its effects on the mother and fetus as compared with smoking tobacco in cigarettes?

57. To what extent are there interactions between the effects of the major (and perhaps minor) components of tobacco smoke?

58. How can efforts to actively discourage smoking during pregnancy be made more effective?

59. To what extent will smoking withdrawal during pregnancy result in changes in infant weight, perinatal mortality, and long-term sequelae?

Nicotine

60. How does nicotine affect ganglionic development in the embryo and fetus?

61. What is the relationship between development of essential hypertension and nicotine imprint on fetal development?

62. Does nicotine accumulation in the fetal adrenal glands, heart, and kidneys modify development of these organs?

63. What is the effect of nicotine on the hormonal systems of the adrenal and those organs regulating adrenal function?

64. To what extent is nicotine accumulation in the fetal kidney involved in a possible antidiuretic hormone abnormality or other complications in later development?

65. What factors are involved in prolonging gestational length in laboratory animals?

66. Since nicotine modulates neurological function in adults at several areas (central nervous system, skeletal-muscular, ganglia, and so forth), how does it modify development and function?

67. To what extent does the effect of nicotine on neurological function contribute to hyperkinetic syndrome in children?

68. What is the potential for nicotine metabolites being carcinogenic in combination with benzo(*a*)pyrene?

Carbon Monoxide

69. To what extent are embryonic, fetal, or newborn tissues more or less sensitive to the effects of carbon monoxide than those of adults?

70. How does exposure to carbon monoxide physiologically affect the developing fetus or newborn?

71. To what extent do dose-response relationships exist for various carboxyhemoglobin concentrations?

72. Does a "threshold" level result in adverse effects?

73. Does the fetus adapt to low CO concentrations, and if so, by what mechanism?

74. To what extent does CO affect oxygen consumption by the fetus or by individual organs?

75. How does the decrease in blood oxygen tension physiologically affect oxygen availability to the fetal brain, heart, and other vital organs?

76. To what extent do decreases in the mean partial pressures of capillary oxygen affect cellular respiration?

77. How does increased carboxyhemoglobin concentration affect tissue oxygenation?

78. To what extent are the patterns of growth, development, and maturation of the central nervous system and other organ systems interrelated and affected by chronic low-level carbon monoxide exposure?

79. How does carbon monoxide affect developing neuroblasts?

80. To what extent does carbon monoxide increase the risk of prematurity or adversely affect the rate of infant growth?

81. To what extent does the interference with fetal oxygenation result in problems such as mental retardation, cerebral palsy, and perhaps subclinical neurologic, intellectual, or behavioral deficits?

82. Can modifications significantly decrease carbon monoxide levels in tobacco smoke?

83. Do the carbon monoxide concentrations encountered in association with maternal smoking adversely affect the infant's physical or psychomotor development?

84. What are the legal and regulatory considerations concerning the maximum carbon monoxide exposure allowed for pregnant women and newborn infants?

Polycyclic Hydrocarbons

85. To what extent does benzo(*a*)pyrene cross the placenta and enter the fetus?

86. What is its distribution in the fetal organs and tissues?

87. To what extent do the benzo(*a*)pyrene concentrations encountered in smoking mothers affect the growth and development of the fetal brain and other organs?

88. To what extent does benzo(*a*)pyrene have long term effects on the developing embryo and fetus; that is, to what extent are fetuses so exposed subject to the later development of neoplasms or malignancies?

Pregnancy and Infant Health: References

(1) ABERNATHY, J.R., GREENBERG, B.G., WELLS, H.B., FRAZIER, T.M. Smoking as an independent variable in a multiple regression analysis upon birth weight and gestation. American Journal of Public Health and the Nation's Health 56(4): 626-633, April 1966.

(2) ANDREWS, J., MCGARRY, J.M. A community study of smoking in pregnancy. Journal of Obstetrics and Gynaecology of the British Commonwealth 79(12): 1057-1073, December 1972.

(3) ASMUSSEN, I. Ultrastructure of the human placenta at term. Observations on placentas from newborn children of smoking and nonsmoking mothers. Acta Obstetrica et Gynecologica Scandinavica 56: 119-126, 1977.

(4) ASMUSSEN, I., KJELDSEN, K. Intimal ultrastructure of human umbilical arteries. Observations on arteries from newborn children of smoking and nonsmoking mothers. Circulation Research 36(5): 579-589, May 1975.

(5) ASTRUP, P., OLSEN, H.M., TROLLE, D., KJELDSEN, K. Effect of moderate carbon-monoxide exposure on fetal development. Lancet 2: 1220-1222, December 9, 1972.

(6) AYRES, S.M., GIANNELLI, S., JR., MUELLER, H. Myocardial and systemic responses to carboxyhemoglobin. Annals of the New York Academy of Sciences 174: 268-293, October 1970.

(7) BAILEY, R.R. The effect of maternal smoking on the infant birth weight. New Zealand Medical Journal 71(456): 293-294, May 1971.

(8) BAIRD, D. The epidemiology of prematurity. Journal of Pediatrics 65:(6) Part 1: 909-924, December 1964.

(9) BALLANTYNE, J.W. Manual of Antenatal Pathology and Hygiene. The Fetus. Edinburgh, William Green and Sons, 1902, p. 272.

(10) BARTLETT, D., JR. Pathophysiology of exposure to low concentrations of carbon monoxide. Archives of Environmental Health 16: 719-727, May 1968.

(11) BECKER, R.F., KING, J.E. Studies on nicotine absorption during pregnancy. II. The effects of acute heavy doses on mother and neonates. American Journal of Obstetrics and Gynecology 95(4): 515-522, June 15, 1966.

(12) BECKER, R.F., LITTLE, C.R.D., KING, J.E. Experimental studies on nicotine absorption in rats during pregnancy. III. Effect of subcutaneous injection of small chronic doses upon mother, fetus, and neonate. American Journal of Obstetrics and Gynecology 100(7): 957-968, April 1, 1968.

(13) BECKER, R.F., MARTIN, J.C. Vital effects of chronic nicotine absorption and chronic hypoxic stress during pregnancy and the nursing period. American Journal of Obstetrics and Gynecology 110(4): 522-533, June 15, 1971.

(14) BEISCHER, N.A. The effects of maternal anemia upon the fetus. Journal of Reproductive Medicine 6(6): 21-24, June 1971.

(15) BERGMAN, A.B., WIESNER, L.A. Relationship of passive cigarette-smoking to sudden infant death syndrome. Pediatrics 58(5): 665-668, November 1976.

(16) BISDOM, C.J.W. Alcohol en nicotinever giftigung bij zuigelingen (Alcohol and nicotine poisoning in infants (sucklings)). Maandscrift voor Kindergeneeskunde 6: 332-341, 1937.

(17) BLAKE, C.A., SAWYER, C.H. Nicotine blocks the suckling-induced rise in circulating prolactin in lactating rats. Science 177(4049): 619-621, August 18, 1972.

(18) BRADT, P.T., HERRENKOHL, R.C. DDT in human milk. What determines the levels? Science of the Total Environment 6(2): 161-163, September 1976.

(19) BUNCHER, C.R. Cigarette smoking and duration of pregnancy. American Journal of Obstetrics and Gynecology 103(7): 942-946, April 1, 1969.

(20) BUTLER, N.R., ALBERMAN, E.D. (Editors). Perinatal Problems. The Second Report of the 1958 British Perinatal Mortality Survey. London, E. and S. Livingston, Ltd., 1969, pp. 36-84.

(21) BUTLER, N.R., GOLDSTEIN, H. Smoking in pregnancy and subsequent child development. British Medical Journal 4: 573-575, December 8, 1973.
(22) BUTLER, N.R., GOLDSTEIN, H., ROSS, E.M. Cigarette smoking in pregnancy: Its influence on birth weight and perinatal mortality. British Medical Journal 2: 127-130, April 15, 1972.
(23) CAMPBELL, A.M. The effect of excessive cigaret smoking on maternal health. American Journal of Obstetrics and Gynecology 31: 502-508, 1936.
(24) CAMPBELL, A.M. Excessive cigarette smoking in women and its effect upon their reproductive efficiency. Journal of the Michigan Medical Society 34: 146-151, March 1935.
(25) CLOEREN, S.E., LIPPERT, T.H., FRIDRICH, R. The influence of cigarette smoking on fetal heart rate and uteroplacental blood volume. Archiv fuer Gynaekologie 216: 15-22, 1974.
(26) COBURN, R.F. (Editor). Carbon Monoxide. Washington, D.C. National Academy of Sciences, National Research Council, Division of Medical Sciences, 1977, pp. 83-104.
(27) COLE, P.V., HAWKINS, L.H., ROBERTS, D. Smoking during pregnancy and its effects on the fetus. Journal of Obstretrics and Gynaecology of the British Commonwealth. 79(9): 782-787, September 1972.
(28) COMSTOCK, G.W., ABBEY, H., LUNDIN, F.E., JR. The nonofficial census as a basic tool for epidemiologic observations in Washington County, Maryland. In: Kessler, I.I., Levin, M.L. (Editors). The Community as an Epidemiological Laboratory. A Casebook of Community Studies. Baltimore, The Johns Hopkins Press, 1970, pp. 73-99.
(29) COMSTOCK, G.W., LUNDIN, F.E., JR. Parental smoking and perinatal mortality. American Journal of Obstetrics and Gynecology 98(5): 708-718, July 1, 1967.
(30) COMSTOCK, G.W., SHAH, F.K., MEYER, M.B., ABBEY, H. Low birth weight and neonatal mortality rate related to maternal smoking and socioeconomic status. American Journal of Obstetrics and Gynecology 111(1): 53-59, September 1, 1971.
(31) COPE, I., LANCASTER, P., STEVENS, L. Smoking in pregnancy. Medical Journal of Australia 1: 673-677, April 7, 1973.
(32) CULVER, B., NORTON, S. Juvenile hyperactivity in rats after acute exposure to carbon monoxide. Experimental Neurology 50: 80-98, 1976.
(33) DAVIE, R., BUTLER, N., GOLDSTEIN, H. From Birth to Seven. The Second Report of the National Child Development Study (1958 Cohort). London, Longman, in association with the National Children's Bureau, 1972, 198 pp.
(34) DAVIES, D.P., GRAY, O.P., ELLWOOD, P.C., ABERNETHY, M. Cigarette smoking in pregnancy: Associations with maternal weight gain and fetal growth. Lancet 1: 385-387, February 21, 1976.
(35) DE HAAS, J.H. Parental smoking: Its effects on fetus and child health. European Journal of Obstetrics Gynecology and Reproductive Biology. Excerpta Medica 5(5): 283-296, 1975.
(36) DENSON, R., NANSON, J.L., MCWATTERS, M.A. Hyperkinesis and maternal smoking. Canadian Psychiatric Association Journal 20(3): 183-187, April 1975.
(37) DOMAGALA, J., DOMAGALA, L. Zachowanie sie wagi urodzeniowej oraz czestosc wystepowania wczesniactwa I wad wrodzonych u noworodkow kobiet palacych tyton (Birth weight and incidence of prematurity and congenital anomalies in newborns of mothers smoking tobacco). Pediatria Polska T.47(6): 735-738, 1972.
(38) DONOVAN, J.W. Effect on child of maternal smoking during pregnancy. Lancet 1: 376, February 17, 1973. (Letter)

(39) DOUGLAS, C.G., HALDANE, J.S., HALDANE, J.B.S. The laws of combination of haemoglobin with carbon monoxide and oxygen. Journal of Physiology (London). 44(4): 275-304, June 12, 1912.

(40) DOW, T.G.B., ROONEY, P.J., SPENCE, M. Does anaemia increase the risks to the fetus caused by smoking in pregnancy? British Medical Journal 4(5991): 253-254, November 1, 1975.

(41) DOWNING, G.C., CHAPMAN, W.E. Smoking and pregnancy. A statistical study of 5,659 patients. California Medicine 104(3): 187, March 1966.

(42) DUFFUS, G.M., MACGILLIVRAY, I. The incidence of pre-eclamptic toxaemia in smokers and non-smokers. Lancet 1(7550): 994-995, May 11, 1968.

(43) DUNN, H.G., MCBURNEY, A.K., INGRAM, S., HUNTER, C.M. Maternal cigarette smoking during pregnancy and the child's subsequent development: I. Physical growth to the age of 6 1/2 years. Canadian Journal of Public Health 67: 499-505, November/December 1976.

(44) DUNN, H.G., MCBURNEY, A.K., INGRAM, S., HUNTER, C.M. Maternal cigarette smoking during pregnancy and the child's subsequent development: II. Neurological and intellectual maturation to the age of 6 1/2 years. Canadian Journal of Public Health 68: 43-50, January/February 1977.

(45) EMANUEL, W. Ueber das vorkommen von nicotin in der frauenmilch nach zigarettengenuss (On the presence of nicotine in breast milk following the use of cigarettes). Zeitschrift fuer Kinderheilkunde 52: 41-46, 1931.

(46) ESSENBERG, J.M., SCHWIND, J.V., PATRAS, A.R. The effects of nicotine and cigarette smoke on pregnant female albino rats and their offsprings. Journal of Laboratory and Clinical Medicine 25: 708-717, 1940.

(47) FABIA, J. Cigarettes pendant la grossesse, poids de naissance et mortalite perinatale (Cigarette smoking during pregnancy, birth weight and perinatal mortality). Canadian Medical Association Journal 109: 1104-1109, December 1, 1973.

(48) FECHTER, L.D., ANNAU, Z. Toxicity of mild prenatal carbon monoxide exposure. Science 197(4304): 680-682, August 12, 1977.

(49) FEDRICK, J., ADELSTEIN, P. Factors associated with low birth weight of infants delivered at term. British Journal of Obstetrics and Gynaecology 85:(1): 1-7, January 1978.

(50) FERGUSON, B.B., WILSON, D.J., SCHAFFNER, W. Determination of nicotine concentrations in human milk. American Journal of Diseases of Children 130: 837-839, August 1976.

(51) FIELDING, J.E. Smoking and pregnancy. New England Journal of Medicine 298(6): 337-339, February 9, 1978.

(52) FISCHER, H. Kapillarschaden durch nikotin; eine experimentelle studie zur frage der pathologie des keimlings und der plazenta (Damage to the capillaries produced by nicotine; an experimental study on the pathology of the fetus and placenta). Zeitschrift fuer Geburtshilfe und Gynaekologie 149: 30-65, 1957.

(53) FORSTER, R.E. Carbon monoxide and the partial pressure of oxygen in tissue. Annals of the New York Academy of Sciences 174: 233-241, October 1970.

(54) FRAZIER, T.M., DAVIS, G.H., GOLDSTEIN, H., GOLDBERG, I.D. Cigarette smoking and prematurity: A prospective study. American Journal of Obstetrics and Gynecology 81(5): 988-996, May 1961.

(55) GARN, S.M., SHAW, H.A., MCCABE, K.D. Relative effect of smoking and other variables on size of newborn. Lancet 2(8039): 667, September 24, 1977. (Letter)

(56) GARVEY, D.J., LONGO, L.D. Chronic low level maternal carbon monoxide exposure and fetal growth and development. Biology of Reproduction 19: 8-14, 1978.

(57) GELLER, L.M. Failure of nicotine to affect development of offspring when administered to pregnant rats. Science 129: 212-214, January 23, 1959.

(58) GENNSER, G., MARSAL, K., BRANTMARK, B. Maternal smoking and fetal breathing movements. American Journal of Obstetrics and Gynecology 123(8): 861-867, December 15, 1975.

(59) GINSBERG, M.D., MYERS, R.E. Fetal brain damage following maternal carbon monoxide intoxication: An experimental study. Acta Obstetricia et Gynecologica Scandinavica. 53: 309-317, January 1974.

(60) GINSBERG, M.D., MYERS, R.E. Fetal brain injury after maternal carbon monoxide intoxication: Clinical and neuropathologic aspects. Neurology 26(1): 15-23, January 1976.

(61) GOLDSTEIN, H., GOLDBERG, I.D., FRAZIER, T.M., DAVIS, G.E. Cigarette smoking and prematurity. Public Health Reports 79(7): 553-560, July 1964.

(62) GOUJARD, J., ETIENNE, C., EVRARD, F. Caracteristiques maternelles et poids de naissance (Maternal characteristics and birth weight). Revue du Practicien 19(28, Supplement): 54, 59-62, 65, November 1, 1969.

(63) GOUJARD, J., RUMEAU, C., SCHWARTZ, D. Smoking during pregnancy, stillbirth and abruptio placentae. Biomedicine 23: 20-22, 1975.

(64) GREINER, I. Nikotinvergiftung, beobachtet bei einem saeugling (Nicotine poisoning observed in a breast feeding infant). Jahrbuch fuer Kinderheilkunde 96(146): 131-132, 1936.

(65) HADDON, W., JR., NESBITT, R.E.L., GARCIA, R. Smoking and pregnancy: Carbon monoxide in blood during gestation and at term. Obstetrics and Gynecology 18(3): 262-267, September 1961.

(66) HANSSON, E., SCHMITERLOW, C.G. Physiological disposition and fate of C^{14}-labelled nicotine in mice and rats. Journal of Pharmacology and Experimental Therapeutics 137: 91-102, July 1962.

(67) HARDY, J.B., MELLITS, E.D. Does maternal smoking during pregnancy have a long-term effect on the child? Lancet 2: 1332-1336, December 23, 1972.

(68) HATCHER, R.A., CROSBY, H. The elimination of nicotin in the milk. Journal of Pharmacology and Experimental Therapeutics 32(1): 1-6, November 1927.

(69) HAWORTH, J.C., FORD, J.D. Comparison of the effects of maternal undernutrition and exposure to cigarette smoke on the cellular growth of the rat fetus. American Journal of Obstetrics and Gynecology 112(5): 653-656, March 1, 1972.

(70) HELLMAN, L.M., JOHNSON, H.L., TOLLES, W.E., JONES, E.H. Some factors affecting the fetal heart rate. American Journal of Obstetrics and Gynecology 82(5): 1055-1063, November 1961.

(71) HERON, H.J. The effects of smoking during pregnancy: A review with a preview. New Zealand Medical Journal 61: 545-548, November 1962.

(72) HERRIOT, A., BILLEWICZ, W.Z., HYTTEN, F.E. Cigarette smoking in pregnancy. Lancet 1: 771-773, April 14, 1962.

(73) HILL, E.P., HILL, J.R., POWER, G.G., LONGO, L.D. Carbon monoxide exchanges between the human fetus and mother: A mathematical model. American Journal of Physiology 232(3): H311-H323, 1977.

(74) HOLLINGSWORTH, D.R., MOSER, R.J., CARLSON, J.W., THOMPSON, K.T. Abnormal adolescent primiparous pregnancy: Association of race, human chorionic somatomammotropin production, and smoking. American Journal of Obstetrics and Gynecology 126(2): 230-237, September 15, 1976.

(75) HOTOVY, R. Versuche zur frage des einflusses der chronischen nikotinschaedigung auf fruchtbarkeit und nachkommenschaft (Experiments to determine the effect of chronic exposure to nicotine upon fertility and subsequent progeny). Naunyn-Schmiedeberg's Archives of Pathology 205: 54-56, 1948.

(76) HOWREN, H.H., JR. A review of the literature concerning smoking during pregnancy. Virginia Medical Monthly 92: 274-279, June 1965.

(77) HUDSON, D.B., MEISAMI, E., TIMIRAS, P.S. Brain development in offspring of rats treated with nicotine during pregnancy, Experientia 29(3): 286-288, 1973.

(78) HUDSON, D.B., TIMIRAS, P.S. Effects of prenatal administration of nicotine on the biochemical development of the rat brain. Transactions of the American Society of Neurochemistry 2: 83, 1971. (Abstract)

(79) HUDSON, D.B., TIMIRAS, P.S. Nicotine injection during gestation: Impairment of reproduction, fetal viability, and development. Biology of Reproduction 7(2): 247-253, October 1972.

(80) JAEGER, J.J., MCGRATH, J.J. Effects of hypothermia on heart and respiratory responses of chicks to carbon monoxide. Journal of Applied Physiology 34(5): 564-567, May 1973.

(81) JARVINEN, P.A., OSTERLUND, K. Effect of smoking during pregnancy on the fetus, placenta and delivery. Annales Paediatriae Fenniae 9: 18-26, 1963.

(82) JOHNSON, D.E., RHOADES, J.W. N-nitrosamines in smoke condensate from several varieties of tobacco. Journal of the National Cancer Institute 48(6): 1845-1847, June 1972.

(83) KEITH, C.H., TESH, P.G. Measurement of the total smoke issuing from a burning cigarette. Tobacco Science 9: 61-64, July 1965.

(84) KING, J.E., BECKER, R.F. Studies on nicotine absorption during pregnancy. I. LD_{50} for pregnant and nonpregnant rats. American Journal of Obstetrics and Gynecology 95(4): 508-514, June 15, 1966.

(85) KIRSCHBAUM, T.H., DILTS, P.V. JR., BRINKMAN, C.R., III. Some acute effects of smoking in sheep and their fetuses. Obstetrics and Gynecology 35(4): 527-536, April 1970.

(86) KIZER, S. Influencia del habito de fumar sobre el embarazo, parto y recien nacido (Effect of the smoking habit on pregnancy, delivery, and the newborn). Revista de Obstetricia y Ginecologia de Venezuela 27(4): 595-643, 1967.

(87) KLINE, J., STEIN, Z.A., SUSSER, M., WARBURTON, D. Smoking: A risk factor for spontaneous abortion. New England Journal of Medicine 297(15): 793-796, October 13, 1977.

(88) KRUGER, H., ARIAS-STELLA, J. The placenta and the newborn infant at high altitudes. American Journal of Obstetrics and Gynecology 106(4): 586-591, February 15, 1970.

(89) KULLANDER, S., KAELLEN, B. A prospective study of smoking and pregnancy. Acta Obstetrica et Gynecologica Scandinavica 50(1): 83-94, 1971.

(90) KUMAR, D., ZOURLAS, P.A. Studies on human premature births. II. In vivo effect of smoking and in vitro effect of nicotine on human uterine contractility. American Journal of Obstetrics and Gynecology 87(3): 413-417, October 1, 1963.

(91) LANDAUER, W. Nicotine-induced malformations of chicken embryos and their bearing on the phenocopy problem. Journal of Experimental Zoology 143: 107-122, 1960.

(92) LOEHR, J., ARDELT, W., DEHNHARD, F. Nikotinarteriopathie der plazenta (Nicotine arteriopathy of the placenta). Geburtshilfe und Frauenheilkunde 32: 932-934, 1972.

(93) LONGO, L.D. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. American Journal of Obstetrics and Gynecology 129(1): 69-103, September 1, 1977.

(94) LONGO, L.D. Carbon monoxide: Effects on oxygenation of the fetus in utero. Science 194: 523-525, October 29, 1976.

(95) LONGO, L.D. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Annals of the New York Academy of Sciences 174(Article 1): 313-341, October 5, 1970.

(*96*) LONGO, L.D. Pollution and infant capabilities. In: Kretchmer, N., Hasselmeyer, E.G. (Editors). Horizons in Perinatal Research. Implications for Clinical Care. New York, John Wiley and Sons, 1974, pp. 62-79.

(*97*) LONGO, L.D., HILL, E.P. Carbon monoxide uptake and elimination in fetal and maternal sheep. American Journal of Physiology 232(3): H324-H330, 1977.

(*98*) LONGO, L.D., POWER, G.G., FORSTER, R.E., II. Placental diffusing capacity for carbon monoxide at varying partial pressures of oxygen. Journal of Applied Physiology 26(3): 360-370, March 1969.

(*99*) LONGO, L.D., POWER, G.G., FORSTER, R.E., II. Respiratory function of the placenta as determined with carbon monoxide in sheep and dogs. Journal of Clinical Investigation 46(5): 812-828, May 1967.

(*100*) LONGO, L.D., WYATT, J.F., HEWITT, C.W., GILBERT, R.D. A comparison of circulatory responses to hypoxic hypoxia and carbon monoxide hypoxia in fetal blood flow and oxygenation. In: Longo, L.D., Reneau, D.D. (Editors). Fetal and Newborn Cardiovascular Physiology: Fetal and Newborn Circulation. Volume 2. New York, Garland STPM Press, 1978, pp. 259-287.

(*101*) LOWE, C.R. Effect of mothers' smoking habits on birth weight of their children. British Medical Journal 2: 673-676, October 10, 1959.

(*102*) LUBS, M-L.E. Racial differences in maternal smoking effects on the newborn infant. American Journal of Obstetrics and Gynecology 115(1): 66-76, January 1, 1973.

(*103*) MACMAHON, B., ALPERT, M., SALBER, E.J. Infant weight and parental smoking habits. American Journal of Epidemiology 82(3): 247-261, November 1966.

(*104*) MANNING, F.A., FEYERABEND, C. Cigarette smoking and fetal breathing movements. British Journal of Obstetrics and Gynaecology 83(4): 262-270, April 1976.

(*105*) MANNING, F., WYN PUGH, E., BODDY, K. Effect of cigarette smoking on fetal breathing movements in normal pregnancies. British Medical Journal 1(5957): 552-553, March 8, 1975.

(*106*) MARTIN, J.C., BECKER, R.F. The effects of maternal nicotine absorption or hypoxic episodes upon appetitive behavior of rat offspring. Developmental Psychobiology 4(2): 133-147, 1971.

(*107*) MAU, G. Smoking and the fetus. Lancet 1(7966): 972, May 1, 1976. (Letter)

(*108*) MCCLUNG, J. Effects of High Altitude on Human Birth. Observations on Mothers, Placentas, and the Newborn in Two Peruvian Populations. Cambridge, Harvard University Press, 1969, 150 pp.

(*109*) MCDONALD, R.L., LANFORD, C.F. Effects of smoking on selected clinical obstetric factors. Obstetrics and Gynecology 26(4): 470-475, October 1965.

(*110*) MCGARRY, J.M., ANDREWS, J. Smoking in pregnancy and vitamin B_{12} metabolism. British Medical Journal 2: 74-77, April 8, 1972.

(*111*) MCGRATH, J.J., JAEGER, J. Effect of iodoacetate on the carbon monoxide tolerance of the chick. Respiration Physiology 12: 71-76, April 1971.

(*112*) MEYER, M.B. Effects of maternal smoking and altitude on birth weight and gestation. In: Reed, D.M., Stanley, F.J. (Editors). The Epidemiology of Prematurity. Baltimore, Urban and Schwarzenberg, 1977, pp. 81-101.

(*113*) MEYER, M.B. How does maternal smoking affect birth weight and maternal weight gain? Evidence from the Ontario Perinatal Mortality Study. American Journal of Obstetrics and Gynecology 131(8): 888-893, August 15, 1978.

(*114*) MEYER, M.B., COMSTOCK, G.W. Maternal cigarette smoking and perinatal mortality. American Journal of Epidemiology 96(1): 1-10, July 1972.

(*115*) MEYER, M.B., JONAS, B.S., TONASCIA, J.A. Perinatal events associated with maternal smoking during pregnancy. American Journal of Epidemiology 103(5): 464-476, 1976.

(116) MEYER, M.B., TONASCIA, J.A. Maternal smoking, pregnancy complications, and perinatal mortality. American Journal of Obstetrics and Gynecology 128(5): 494-502, July 1, 1977.

(117) MEYER, M.B., TONASCIA, J.A., BUCK, C. The interrelationship of maternal smoking and increased perinatal mortality with other risk factors. Further analysis of the Ontario perinatal mortality study, 1960-1961. American Journal of Epidemiology 100(6): 443-452, 1975.

(118) MILLER, H.C., HASSANEIN, K. Maternal smoking and fetal growth of full term infants. Pediatric Research 8: 960-963, 1964.

(119) MILLER, H.C., HASSANEIN, K., HENSLEIGH, P.A. Fetal growth retardation in relation to maternal smoking and weight gain in pregnancy. American Journal of Obstetrics and Gynecology 125(1): 55-60, May 1, 1976.

(120) MILLS, C.A. Tobacco smoking: Some hints of its biologic hazards. Ohio State Medical Journal 46(12): 1165-1170, December 1950.

(121) MOHR, U., ALTHOFF, J. Carcinogenic activity of aliphatic nitrosamines via the mother's milk in the offspring of Syrian Golden hamsters. Proceedings of the Society for Experimental Biology and Medicine 136(3): 1007-1009, March 1971.

(122) MOSIER, H.D., ARMSTRONG, M.K. Effects of maternal intake of nicotine on fetal and newborn rats. Proceedings of the Society of Experimental Biology and Medicine 116: 956-958, 1964.

(123) MUKHERJEE, S.M., MUKHERJEE, S.N. A study of premature births. Indian Journal of Pediatrics 38(285): 389-392, October 1971.

(124) MULCAHY, R., KNAGGS, J.F. Effect of age, parity, and cigarette smoking on outcome of pregnancy. American Journal of Obstetrics and Gynecology 101(6): 844-849, July 15, 1968.

(125) MULCAHY, R., MURPHY, J., MARTIN, F. Placental changes and maternal weight in smoking and nonsmoking mothers. American Journal of Obstetrics and Gynecology 106(5): 703-704, March 1, 1970.

(126) MURDOCH, D.E. Birth weight and smoking. Nebraska State Medical Journal 48(11): 604-606, November 1963.

(127) MURPHY, J.F., MULCAHY, R. The effect of age, parity, and cigarette smoking on baby weight. American Journal of Obstetrics and Gynecology 111(1): 22-25, September 1, 1971.

(128) MURPHY, J.F., MULCAHY, R. The effects of cigarette smoking, maternal age and parity on the outcome of pregnancy. Journal of the Irish Medical Association 67(11) 309-313, June 15, 1974.

(129) NAEYE, R.L. Causes of perinatal mortality in the U.S. Collaborative Perinatal Project. Journal of the American Medical Association 238(3): 228-229, July 18, 1977.

(130) NAEYE, R.L., LADIS, B., DRAGE, J.S. Sudden infant death syndrome. A prospective study. American Journal of Diseases of Children 130: 1207-1210, November 1976.

(131) NAEYE, R.L., HARKNESS, W.L., UTTS, J. Abruptio placentae and perinatal death: A prospective study. American Journal of Obstetrics and Gynecology 128(7): 740-746, August 1, 1977.

(132) NALL, J.F. Complexed cyanide in collected cigarette smoke. Abstracts of the 20th Tobacco Chemists' Research Conference. November 1-3, 1966, Winston-Salem, N.C., 1966, pp. 25,27.

(133) NEBERT, D.W., WINKER, J., GELBOIN, H.V. Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. Cancer Research 29: 1763-1769, October 1969.

(134) NEWSOME, J.R., NORMAN, V., KEITH, C.H. Vapor phase analysis of tobacco smoke. Tobacco Science 9: 102-110, July 23, 1965.

(135) NIKONOVA, T.V. Transplacental action of benzo(a)pyrene and pyrene. Bulletin of Experimental Biology and Medicine 84: 1025-1027, 1977.

(*136*) NISHIMURA, H., NAKAI, K. Developmental anomalies in offspring of pregnant mice treated with nicotine. Science 127: 877-878, April 1958.

(*137*) NISWANDER, J.R., GORDON, M. (Editors). Maternal characteristics. Section 1. Demographic characteristics. Cigarette smoking. In: The Women and Their Pregnancies. The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. DHEW Publication No. (NIH) 73-379, 1972, pp. 72-80.

(*138*) NORMAN, V., NEWSOME, J.R., KEITH, C.H. Smoking machines for the analysis of the vapor phase of cigarette smoke. Tobacco Science 12: 216-221, 1968.

(*139*) NORTON, S., MULLENIX, P., CULVER, B. Comparison of the structure of hyperactive behavior in rats after brain damage from x-irradiation, carbon monoxide and pallidal lesions. Brain Research 116: 49-67, 1976.

(*140*) NYMAND, G. Maternal smoking and neonatal hyperbilirubinaemia. Lancet 2(7873): 173, July 20, 1974. (Letter)

(*141*) O'LANE, J.M. Some fetal effects of maternal cigaret smoking. Obstetrics and Gynecology 22(2): 181-184, August 1963.

(*142*) ONTARIO DEPARTMENT OF HEALTH. Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals. Toronto, Canada, Ontario Department of Health, Ontario Perinatal Mortality Study Committee, Volume I, 1967, 275 pp.

(*143*) ONTARIO DEPARTMENT OF HEALTH. Supplement to the Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals. Toronto, Canada, Ontario Department of Health, Ontario Perinatal Mortality Study Committee, Volume II, 1967, pp. 95-275.

(*144*) OSBORNE, J.S., ADAMEK, S., HOBBS, M.E. Some components of gas phase of cigarette smoke. Analytical Chemistry 28(2): 211-215, February 1956.

(*145*) OUNSTED, M. Maternal constraint of foetal growth in man. Developmental Medicine and Child Neurology 7: 479-491, October 1965.

(*146*) PALMGREN, B., WAHLEN, T., WALLANDER, B. Toxaemia and cigarette smoking during pregnancy: Prospective consecutive investigation of 3927 pregnancies. Acta Obstetrica et Gynecologica Scandinavica 52: 183-185, 1973.

(*147*) PALMGREN, B., WALLANDER, B. Cigarettrokning och abort. Konsekutiv prospektiv undersokning av 4312 graviditeter (Cigarette smoking and abortion. Consecutive prospective study of 4,312 pregnancies). Lakartidningen 68(22): 2611-2616, May 26, 1971.

(*148*) PELKONEN, O., JOUPPILA, P., KARKI, N.T. Effect of maternal cigarette smoking on 3,4-benzypyrene and n-methylaniline metabolism in human fetal liver and placenta. Toxicology and Applied Pharmacology 23: 399-407, 1972.

(*149*) PERLMAN, H.H., DANNENBERG, A.M., SOKOLOFF, N. The excretion of nicotine in breast milk and urine from cigaret smoking. Its effect on lactation and the nursling. Journal of the American Medical Association 120(13): 1003-1009, November 28, 1942.

(*150*) PERNOLL, M.L., METCALFE, J., SCHLENKER, T.L., WELCH, J.E., MATSUMOTO, J.A. Oxygen consumption at rest and during exercise in pregnancy. Respiration Physiology 25: 285-293, December 1975.

(*151*) PETERSON, W.F., MORESE, K.N., KALTREIDER, D.F. Smoking and prematurity. A preliminary report based on study of 7740 Caucasians. Obstetrics and Gynecology 26(6): 775-779, December 1965.

(*152*) PETTERSSON, F. Retrospective study of the influence of some factors on birth weight. Acta Socio-Medica Scandinavica 1(1): 13-18, 1969.

(*153*) PHILIPPE, R.J., HOBBS, M.E. Some components of the gas phase of cigarette smoke. Analytical Chemistry 28(12): 2002-2006, December 1956.

(*154*) POWER, G.G., LONGO, L.D. Fetal circulation times and their implications for tissue oxygenation. Gynecologic Investigation 6: 342-355, 1975.

(155) RANTAKALLIO, P. Groups at Risk in Low Birth Weight Infants and Perinatal Mortality. A prospective study of the biological characteristics and socioeconomic circumstances of mothers in 12,000 deliveries in North Finland 1966. A discriminant function analysis. Acta Paediatrica Scandinavica (Supplement 193): 1969, 71 pp.

(156) RAVENHOLT, R.T., LEVINSKI, M.J., NELLIST, D.J., TAKENAGA, M. Effects of smoking upon reproduction. American Journal of Obstetrics and Gynecology 96(2): 267-281, September 15, 1966.

(157) REINKE, W.A., HENDERSON, M. Smoking and prematurity in the presence of other variables. Archives of Environmental Health 12(5): 600-606, May 1966.

(158) RESNIK, R., BRINK, G.W., WILKES, M.M. Catecholamine mediated reduction in uterine blood flow following nicotine infusion in the pregnant ewe. Society for Gynecologic Investigation. Program and Abstracts, 25th Annual Meeting, March 15-18, 1978, p. 93.

(159) RHEAD, W.J. Smoking and SIDS. Pediatrics 59(5): 791-792, May 1977.

(160) RHOADES, J.W., JOHNSON, D.E. Method for the determination of N-nitrosamines in tobacco-smoke condensate. Journal of the National Cancer Institute 48(6): 1841-1843, June 1972.

(161) ROBINSON, P. Yishun nashim burmanyot bizman haheraiom vehashpaato al ha-em hauber vehaielot (Smoking of Burmese women during pregnancy and its influence on the mother, the fetus and the newborn). Harefuah 69(2): 37-39, 1965.

(162) RUSH, D. Examination of the relationship between birth weight, cigarette smoking during pregnancy and maternal weight gain. Journal of Obstetrics and Gynaecology of the British Commonwealth 81: 746-752, October 1974.

(163) RUSH, D., KASS, E.H. Maternal smoking: A reassessment of the association with perinatal mortality. American Journal of Epidemiology 96(3): 183-196, September 1972.

(164) RUSSELL, C.S., TAYLOR, R., LAW, C.E. Smoking in pregnancy, maternal blood pressure, pregnancy outcome, baby weight and growth, and other related factors. A prospective study. British Journal of Preventive and Social Medicine 22(3): 119-126, July 1968.

(165) RUSSELL, C.S., TAYLOR, R., MADDISON, R.N. Some effects of smoking in pregnancy. Journal of Obstetrics and Gynaecology of the British Commonwealth 73: 742-746, October 1966.

(166) SAVEL, L.E., ROTH, E. Effects of smoking in pregnancy: A continuing retrospective study. Obstetrics and Gynecology 20(3): 313-316, September 1962.

(167) SCHLEDE, E., MERKER, H.J. Effect of benzo(a)pyrene treatment on the benzo(a)pyrene hydroxylase activity in maternal liver, placenta, and fetus of the rat during day 13 to day 18 of gestation. Naunyn-Schmiedeberg's Archives of Pharmacology 272(1): 89-100, December 21, 1972.

(168) SCHOENECK, F.J. Cigarette smoking in pregnancy. New York State Journal of Medicine 41: 1945-1948, October 1, 1941.

(169) SCHWARTZ, D., GOUJARD, J., KAMINSKI, M., RUMEAU-ROUQUETTE, C. Smoking and pregnancy: Results of a prospective study of 6,989 women. Revue Europeene d'Etudes Cliniques et Biologiques 17(9): 867-879, 1972.

(170) SCHWETZ, B.A., LEONG, B.K.J., STAPLES, R.E. Teratology studies on inhaled carbon monoxide and imbibed ethanol in laboratory animals. Teratology 11: 33A, 1975. (Abstract)

(171) SILVERMAN, D.T. Maternal smoking and birth weight. American Journal of Epidemiology 105(6): 513-521, June 1977.

(172) SIMPSON, W.J. A preliminary report on cigarette smoking and the incidence of prematurity. American Journal of Obstetrics and Gynecology 73(4): 808-815, April 1957.

(*173*) SINGER, P.R., SCIBETTA, J.J., ROSEN, M.G. Simulated marihuana smoking in the maternal and fetal guinea pig. American Journal of Obstetrics and Gynecology 117: 331-340, October 1, 1973.

(*174*) SMITH, E., MCMILLAN, E., MACK, L. Factors influencing the lethal action of illuminating gas. Journal of Industrial Hygiene and Toxicology 17(1): 18-20, January 1935.

(*175*) SONTAG, L.W., WALLACE, R.F. The effect of cigaret smoking during pregnancy upon the fetal heart rate. American Journal of Obstetrics and Gynecology 29: 77-83, 1935.

(*176*) SPEARS, A.W., ROUTH, W.E. A combined approach to the quantitative analysis of the violatile components of cigarette smoke. Abstracts of the 18th Tobacco Chemists Research Conference, October 20-22, 1964, Raleigh, N.C., 1964, pp. 47,49.

(*177*) SPIRA, A., PHILLIPE, E., SPIRA, N., DREYFUS, J., SCHWARTZ, D. Smoking during pregnancy and placental pathology. Biomedicine 27: 266-270, 1977.

(*178*) STAINSBY, W.N., OTIS, A.B. Blood flow, blood oxygen tension, oxygen uptake, and oxygen transport in skeletal muscle. American Journal of Physiology 206(4): 858-866, April 1964.

(*179*) STALHANDSKE, T., SLANINA, P., TJALVE, H., HANSSON, E., SCHMITERLOW, C.G. Metabolism *in vitro* of ^{14}C-nicotine in livers of foetal, newborn and young mice. Acta Pharmacologica et Toxicologica 27: 363-380, 1969.

(*180*) STEELE, R., LANGWORTH, J.T. The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. Canadian Medical Association Journal 94: 1165-1171, May 28, 1966.

(*181*) SUZUKI, K., HORIGUCHI, T., COMAS-URRUTIA, A.C., MUELLER-HEUBACH, E., MORISHIMA, H.O., ADAMSONS, K. Pharmacologic effects of nicotine upon the fetus and mother in the rhesus monkey. American Journal of Obstetrics and Gynecology 111(8): 1092-1101, December 15, 1971.

(*182*) SUZUKI, K., HORIGUCHI, T., COMAS-URRUTIA, A.C., MUELLER-HEUBACH, E., MORISHIMA, H.O., ADAMSONS, K. Placental transfer and distribution of nicotine in the pregnant rhesus monkey. American Journal of Obstetrics and Gynecology 119(2): 253-262, May 15, 1974.

(*183*) TANAKA, M. Studies on the etiological mechanism of fetal developmental disorders caused by maternal smoking during pregnancy. Nippon Sanka-Fujinka Gakkai Zasshi (Japanese edition) 17(1): 1107-1114, October 1, 1965.

(*184*) TERKEL, J., BLAKE, C.A., HOOVER, V., SAWYER, C.H. Pup survival and prolactin levels in nicotine-treated lactating rats. Proceedings of the Society for Experimental Biology and Medicine 143: 1131-1135, 1973.

(*185*) TERRIS, M., GOLD, E.M. An epidemiologic study of prematurity. I. Relation to smoking, heart volume, employment, and physique. American Journal of Obstetrics and Gynecology 103(3): 358-370, February 1, 1969.

(*186*) THOMPSON, W.B. Nicotine in breast milk. American Journal of Obstetrics and Gynecology 26: 662-667, 1933.

(*187*) TJALVE, H., HANSSON, E., SCHMITERLOW, C.G. Passage of ^{14}C-nicotine and its metabolites into mice foetuses and placentae. Acta Pharmacologica et Toxicologica 26: 539-555, 1968.

(*188*) UNDERWOOD, P., HESTER, L.L., LAFFITTE, T., JR., GREGG, K.V. The relationship of smoking to the outcome of pregnancy. American Journal of Obstetrics and Gynecology 91(2): 270-276, January 15, 1965.

(*189*) UNDERWOOD, P.B., KESLER, K.F., O'LANE, J.M., CALLAGAN, D.A. Parental smoking empirically related to pregnancy outcome. Obstetrics and Gynecology 29(1): 1-8, January 1967.

(190) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 71-7513, 1971, pp. 387-418.

(191) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 72-7516, 1972, pp. 81-91.

(192) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 73-8704, 1973, pp. 99-149.

(193) VAN DEN BERG, B.J. Epidemiologic observations of prematurity: Effects of tobacco, coffee, and alcohol. In: Reed, D.M., Stanley, F.J. (Editors). The Epidemiology of Prematurity. Baltimore, Urban and Schwarzenberg, 1977, pp. 157-176.

(194) VAN VUNAKIS, H., LANGONE, J.J., MILUNSKY, A. Nicotine and cotinine in the amniotic fluid of smokers in the second trimester of pregnancy. American Journal of Obstetrics and Gynecology 120(1): 64-66, September 1, 1974.

(195) VENULET, F. Nastepstwa niedoboru witaminy c u palaczy (Consequences of vitamin C deficiency in smokers). Polskie Archiwum Medycyny Wewnetrznej 26: 393-402, 1956.

(196) VENULET, F., DANYSZ, A. Wplyw palenia tytoniu na poziom witaminy c w mleku kobiecym (The influence of tobacco on the level of vitamin C in human milk). Pediatria Polska 30(9): 811-817, 1955.

(197) WAGNER, B., LAZAR, P., CHOUROULINKOV, I. The effects of cigarette smoke inhalation upon mice during pregnancy. Revue Europeene d'Etudes Clinques et Biologiques 17: 943-948, 1972.

(198) WEISBURGER, E.K. Mechanisms of chemical carcinogenesis. In: George, R., Okun, R., Cho, A.K. (Editors). Annual Review of Pharmacology and Toxicology 18: 395-415, 1978.

(199) WELCH, R.M., GOMMI, B., ALVARES, A.P., CONNEY, A.H. Effect of enzyme induction on the metabolism of benzo(a)pyrene and 3-methyl-4-monomethylaminoazobenzene in the pregnant and fetal rat. Cancer Research 32(5): 973-978, May 1972.

(200) WELLS, L.L. The prenatal effect of carbon monoxide on albino rats and the resulting neuropathology. Biologist 15: 80-81, 1933.

(201) WILLIAMS, I.R., SMITH, E. Blood picture, reproduction, and general condition during daily exposure to illuminating gas. American Journal of Physiology 110(3): 611-615, January 1935.

(202) WILSON, E.W. The effect of smoking in pregnancy on the placental coefficient. New Zealand Medical Journal 74(475): 384-385, 1972.

(203) WINGERD, J., CHRISTIANSON, R., LOVITT, W.V., SCHOEN, E.J. Placental ratio in white and black women: Relation to smoking and anemia. American Journal of Obstetrics and Gynecology 124(7): 671-675, April 1, 1976.

(204) WINGERD, J., SCHOEN, E.J. Factors influencing length at birth and height at five years. Pediatrics 53(5): 737-741, May 1974.

(205) YERUSHALMY, J. Congenital heart disease and maternal smoking habits. Nature 242(5395): 262-264, March 23, 1973.

(206) YERUSHALMY, J. Mother's cigarette smoking and survival of infant. American Journal of Obstetrics and Gynecology 88(4): 505-518, February 15, 1964.

(207) YERUSHALMY, J. The relationship of parents' cigarette smoking to outcome of pregnancy—implications as to the problem of inferring causation from observed associations. American Journal of Epidemiology 93(6): 443-456, June 1971.

(*208*) YERUSHALMY, J. Statistical considerations and evaluation of epidemiological evidence. In: James, G., Rosenthal, T. (Editors). Tobacco and Health. Springfield, Charles C. Thomas, 1962, pp. 208-230.

(*209*) YOUNG, I.M., PUGH, L.G.C.E. The carbon monoxide content of foetal and maternal blood. Journal of Obstetrics and Gynaecology of the British Commonwealth. 70: 681-684, 1963.

(*210*) YOUNOSZAI, M.K., KACIC, A., HAWORTH, J.C. Cigarette smoking during pregnancy: The effect upon the hematocrit and acid-base balance of the newborn infant. Canadian Medical Association Journal 99(5): 197-200, August 3, 1968.

(*211*) YOUNOSZAI, M.K., PELOSO, J., HAWORTH, J.C. Fetal growth retardation in rats exposed to cigarette smoke during pregnancy. American Journal of Obstetrics and Gynecology 104(8): 1207-1213, August 15, 1969.

(*212*) ZABRISKIE, J.R. Effect of cigaret smoking during pregnancy. Study of 2000 cases. Obstetrics and Gynecology 21(4): 405-411, April 1963.

9. PEPTIC ULCER DISEASE.

National Institute of Arthritis, Metabolism, and
Digestive Diseases

CONTENTS

LIST OF TABLES

Epidemiology

For over half a century the medical literature has carried reports of an association between peptic ulcer disease (PUD), including gastric ulcer and duodenal ulcer, and cigarette smoking. Barnett (*2*) in 1927 was the first to examine the epidemiological evidence for this suspected relationship. Although he found that patients with duodenal and gastric ulcer smoked more than controls, the difference was not significant, and he concluded that the purported relationship between smoking and PUD did not exist. However, the majority of subsequent reports have found a significant association between smoking and PUD. Some recent reviews of the older studies (*3, 59, 60*) present support for the conclusions that (1) the prevalence of smoking is increased in persons with PUD, and (2) both gastric and duodenal ulcers are more prevalent in smokers than in nonsmokers. During the past decade several studies have been published which support these conclusions. These will now be considered.

Prevalence of Smoking in Persons with Peptic Ulcer Disease

Kasanen and Forsstroem (*33*) studied the stresses and habits of 100 patients with gastric or duodenal ulcer and found that 90 percent of ulcer patients smoked compared to 60 percent of controls and that 61 percent of ulcer patients smoked one or more packs per day as opposed to 36 percent of controls ($p < .01$). Smoking was the only variable significantly related to ulcer in this study, as no relation to stress (financial, work, or family) was found.

Monson (*38*) studied 10,000 Massachusetts physicians and found that those with gastric or duodenal ulcers smoked significantly more than comparable control subjects. About 1.3 times as many duodenal ulcer patients as control subjects smoked. He did not find a difference between PUD patients and controls in years of smoking or in number of packs per day smoked.

In a Danish study (*32*), 78 percent of PUD patients smoked compared to 71 percent among controls, a difference which was not statistically significant. Bock (*6*), in a South African study, found that 89 percent of men and 45 percent of women with gastric ulcer smoked, but he did not study a control group.

Doll (*18*), who has written extensively on the subject of smoking and ulcer disease (*17, 19*), found a significantly increased frequency of smoking in both duodenal and gastric ulcer patients as compared to controls: gastric ulcer—91 percent smokers, control—79 percent smokers; duodenal ulcer—85 percent smokers, control—81 percent smokers ($p < 0.01$).

Although there is some problem in determining the adequacy of controls in these studies, all five in which controls as well as ulcer

patients were studied (*6, 19, 32, 33, 38*) show a higher proportion of smokers among ulcer patients than among controls.

Prevalence of Peptic Ulcer Disease in Smokers

We turn now to studies of the prevalence of PUD among smokers and nonsmokers, which are described below and summarized in Table 1.

Edwards and coworkers (*22*) examined 1,753 men over age 59 in regard to smoking and health. A history of peptic ulcer was present in 6.0 percent of nonsmokers and in 10.0 percent of cigarette smokers ($p < .01$). Also, the prevalence of peptic ulcer increased with increasing number of cigarettes smoked daily.

Higgins and Kjelsberg (*28*), in a large community health study in Tecumseh, Michigan, discovered a greater frequency of peptic ulcer in male and female smokers and ex-smokers than among nonsmokers (the increased frequency reached statistical significance only in women).

The interrelationships among coffee, alcohol, and smoking were examined by Friedman, et al. (*23*). They studied 36,656 men and women, aged 30 to 59, 2,597 of them with a history of peptic ulcer disease. They found that men who smoked had a 2.1-fold greater frequency of ulcer disease than those who did not smoke, and women had a 1.6-fold greater frequency. The degree of smoking was evaluated by looking at three variables: quantity, years of smoking, and inhalation; all showed positive relationships with the frequency of PUD. On the other hand, since neither coffee drinking nor alcohol consumption was related to an increased occurrence of peptic disease, they concluded that the association of cigarette smoking with PUD is independent of any possible association between smoking and alcohol or coffee consumption.

Similar results were found in a study of 4,000 Polish men and women (*31*) in which the prevalence of PUD was evaluated. Among men, ulcers were found with greater frequency in smokers and ex-smokers than among nonsmokers; and, among smokers, the prevalence of ulcers was greater in those persons who had smoked for more than 5 years and in those smoking more than 14 cigarettes per day. Women smokers did not show an increased frequency of PUD, but only 7 percent of those studied were current smokers. Among women smokers, however, PUD prevalence was higher for those with a longer smoking history and for heavier smokers. On the other hand, in a study of 402 Czechoslovakian men with PUD (*43*), smoking did not make a strong contribution to a stepwise regression predicting the presence of PUD (the data were not provided in the paper and therefore could not be included in Table 1).

In the only truly prospective study (*41*), a 16- to 50-year follow-up study using smoking history in college, PUD was found in 2.2 percent of those who smoked in college as opposed to 1.5 percent of

TABLE 1.—Peptic ulcer prevalence in smokers and nonsmokers (no. per 100)

Reference	How diagnosed	No. with ulcers	Rates: age-adjusted	Sex	Current cigarette smokers	Non-smokers	Ratio	Dose-response
Edwards, F. (1959) (*22*)	Doctor	143	no	M	10.1	6.0	1.7[a]	yes
Higgins, M.W. (1966) (*28*)	Doctor	140	yes	M	7.1	5.2	1.4	—
		47	yes	F	2.8	1.4	2.0	—
Friedman, G.D. (1974) (*23*)	History	1520[b]	yes	M	12.2	5.8	2.1[c]	yes
		1092[b]	yes	F	6.3	3.9	1.6	yes
Jedrychowski, W. (1974) (*31*)	Doctor	106[b]	no	M	6.4	1.9	3.4	yes
		26[b]	no	F	.8	1.3	.6	yes
Paffenbarger, R.S. (1974) (*41*)	History	389	yes	M	2.2[d]	1.5[d]	1.5[d]	yes
Goldbourt, U. (1975) (*25*)	X-ray	895	no	M	10.2	6.2	1.6	no

[a]Also, ratio > 1 within age and social class.

[b]Not given - estimated, using total population and reported rates.

[c]Also, ratio > 1 within occupational groups.

[d]Smoking categories in college, ulcers developed in 16 to 50 year follow-up.

nonsmokers, with a trend of increased risk with increased number of cigarettes smoked.

In Israel, the lifetime prevalence of PUD is 89/1000 men (*37*), similar to that in the United States. Smokers or ex-smokers had a prevalence of PUD (primarily duodenal) of 10.2 percent compared to 6.2 percent of nonsmokers (*25*). These differences were highly significant. Medalie, et al. made the interesting observation that as the smoking habits of first-generation Israelis of European descent increased, so did the prevalence of duodenal ulcer in this group (*37*).

Thus, when the question, "Do cigarette smokers have more peptic ulcers than nonsmokers?" is asked, results are strikingly consistent. Table 1 lists the six studies which investigated this problem (*22, 23, 25, 28, 31, 41*) with a summary of their characteristics and results. In each of the studies there was an increased prevalence of PUD in cigarette smokers compared to nonsmokers. Despite the fact that these studies were done at different times and in four different countries, the ratios for men are very similar, the median being 1.7 and the mean 1.9. The ratios for women are similar with the exception of the Polish study, in which very few women smoked. The ratios for ex-smokers (not shown) are also consistently greater than 1.0. In addition, the majority of the studies provided evidence of increased frequency of peptic ulcer with increases in the amount smoked.

Course of Peptic Ulcer Disease

Since cigarette smoking appears to be related to the prevalence of PUD, several other issues must be addressed. First, if a smoker does develop PUD, will cigarette smoking influence its healing and should the patient therefore be advised to stop smoking? Second, what, if any, role will smoking play in the chances of the patient dying from PUD?

Effect on Healing and Recurrence

In a classic study, Doll, et al. (*18*) examined the effect of continued smoking on the healing rate of gastric ulcers. Of the 80 smokers in the study, half were advised to stop smoking, the other half were allowed to continue smoking. Treatment for the ulcer disease was otherwise equivalent (although not the same for all patients). The investigators then compared the two groups in regard to percent showing marked healing of the ulcer at 4 weeks (marked healing is defined as 2/3 or greater reduction in ulcer size). Of those who were advised to discontinue smoking, 75 percent showed marked healing, compared to only 58 percent of those who continued to smoke. In fact, 45 percent of the patients advised to stop smoking did not do so completely. Of those who did, 86 percent (19/22) healed as opposed to 61 percent of those who only decreased their smoking. The healing rate of the 24 nonsmokers was 58 percent, similar to that of smokers. Study design

and technical aspects were offered as explanation for this latter observation.

Herrmann and Piper (*27*) retrospectively looked at 101 patients with benign gastric ulcer, all radiologically diagnosed. At 3 weeks, 67 percent of nonsmokers had healed compared to 43 percent of smokers who continued smoking. Differences were less marked at 6 weeks (85 percent vs. 75 percent). Although the numbers were smaller, those smokers who stopped did not do as well as either of the other two groups. The mean ulcer size in smokers was larger than in nonsmokers (120 mm^2 vs. 40 mm^2). Those who smoked cigarettes and ingested salicylates had the largest ulcers, but mean ulcer size was significantly larger in smokers than in nonsmokers, even when those ingesting salicylates were excluded.

Piper, et al. (*44*), while investigating gastric ulcer, noted increased rates of recurrence for those discharged unhealed, for those with larger ulcers, and for smokers. In a 4-year follow-up study of these patients, Piper, et al. (*46*) recently confirmed their previous report. They found that, of the 33 patients who were discharged with unhealed ulcers, 47 percent (8/17) of nonsmokers had recurrence, whereas 75 percent (12/16) of smokers had recurrence.

Only one study has been made on the effect of smoking on the healing of duodenal ulcers. Peterson, et al. (*42*) recently showed for the first time the efficacy of antacids over placebo in the healing of duodenal ulcer (Table 2). In this study, 78 percent of the antacid-treated group healed at 4 weeks as compared to 45 percent of the placebo group. When these groups were broken down into smokers and nonsmokers, 69 percent of the ulcers of nonsmokers who took placebo healed versus 32 percent of ulcers of smokers who took placebo ($p < .05$). In the antacid group, 87 percent of nonsmokers healed versus 75 percent of smokers ($p > .05$). Nonsmokers showed good healing even on placebo; antacids appeared to make the most difference in treating the duodenal ulcers of smokers.

Although there have been many recent clinical trials concerning the treatment of both gastric and duodenal ulcers using the new histamine H_2 receptor antagonist, cimetidine, none of these has carefully addressed the question of the influence of smoking on healing rates (*67*). Certainly, with all the international trials being undertaken to evaluate the plethora of new ulcer treatments, such as cimetidine, prostaglandins, bismuth, etc., the smoking habits of the patients should be examined. Such studies would provide information on the effect of smoking on the healing of untreated ulcers and on whether any of the treatments can overcome the presumed adverse effect of smoking on healing.

In summary, cigarette smoking in males probably retards the healing rates of both gastric and duodenal ulcers.

TABLE 2.—Percentage of patients whose duodenal ulcers were healed by endoscopic examination at 4 weeks, classified according to treatment with placebo or antacid and according to whether patients were smokers or nonsmokers of cigarettes. Numbers in parentheses are the number healed over the total number observed in each category.

	Percent healed at 4 weeks		
	Smokers	Nonsmokers	Total
Placebo	32% (8/25)	69% (9/13)	45% (17/38)
Antacid	75% (21/28)	88% (7/8)	78% (28/36)
Total	55% (29/53)	76% (16/21)	

SOURCE: Peterson, W. L. (*42*).

TABLE 3.—Ulcer mortality of male cigarette smokers and nonsmokers

Reference	No. of deaths	Rates: age-adjusted	Ulcer type	Mortality ratio	Dose response
Hammond, E.C. (1958)	62	yes	DU	2.2[a]	yes
(*26*)	46	yes	GU	>1.0[a,b]	yes
Dorn, H.F. (1959) (*20*)	51	yes	PU	2.8	yes
Weir, J.N. (1970) (*64*)	24	yes	DU	.5[c]	no
	20	yes	GU	>1.7[c,d]	yes
Doll, R. (1976) (*19*)	79	yes	PU	2.5	yes

[a]Smokers include regular cigarette smokers, many of whom also smoked cigars and pipes.
[b]Ratio is 46/0.
[c]Smokers include ex-smokers; nonsmokers include pipe and/or cigar.
[d]Ratio for smokers of 1 pack/day to those smoking less.
DU = deodenal ulcer; GU = gastric ulcer; PU = peptic ulcer.

Effect on Mortality

Mortality, as well as morbidity, in PUD is related to cigarette smoking. The four studies discussed below are summarized in Table 3. In one of the earliest and largest studies on smoking and death rates, Hammond and Horn (*26*) pointed out smoking's harmful influence on PUD. Deaths from duodenal ulcer for smokers of more than a half pack per day of cigarettes were 2.5 times the rate for nonsmokers; for those smoking one-half pack per day or less, the rate was 1.5 times the rate for nonsmokers. There were no gastric ulcer deaths among nonsmokers, but there were 46 among smokers; the death rate also increased with smoking more than a half pack per day of cigarettes. Thus, smoking was clearly associated with a higher occurrence of death in both types of ulcer disease.

Dorn (*20*), in another large study, had similar results. The ratio of observed deaths from both duodenal ulcer and gastric ulcer in smokers

to expected deaths from these diseases was 2.8. Those who smoked more than two packs per day had more deaths than those who smoked one to two packs per day, who in turn fared worse than those who smoked less than one pack per day.

In a prospective study of smoking and mortality in 68,153 middle-aged men, Weir and Dunn (*64*), just as Hammond and Horn (*26*), found no deaths from gastric ulcer in nonsmokers but a significant number of smokers dying from gastric ulcer disease. Their results, however, for duodenal ulcer were completely opposite, in that the relative risk of death from duodenal ulcer in smokers was half that in nonsmokers. Why this discrepancy should exist is not clear.

Doll and Peto (*19*), in a study of more than 10,000 British physicians, found a significant increase in death from peptic ulcer disease (specific location of ulcer not stated) in smokers as compared to nonsmokers, with a higher rate in moderate or heavy smokers than in light smokers.

Finally, Din and Small (*15*) proposed that the long-term survival of patients after gastrectomy was decreased by smoking. They felt the increased mortality rate was due to cigarette smoking (and perhaps alcohol, too) and not to the operation. The evidence for this is unclear.

A summary of the important data from the four studies (*19*, *20*, *26*, *64*) which bear on the epidemiological question, "Does smoking influence a person's chance of dying from his ulcer disease?" can be found in Table 3. These data show that mortality from gastric ulcer is greater in male cigarette smokers than in nonsmokers and, except in one study (*64*), also is greater in male cigarette smokers with duodenal ulcer disease. In the study that was the exception, the results are clouded by inclusion of ex-smokers in the smoking group. So, in general, it can be concluded that male cigarette smokers have more than a twofold greater chance of dying from ulcer disease than nonsmokers. It is not clear how much of this excess risk is due to the increased prevalence of ulcer disease in smokers and how much is due to the reduced ability of the smoker to survive an ulcer due to a greater prevalence of chronic heart and lung disease.

The Question of the Etiological Role of Smoking in Peptic Ulcer Disease

The studies reviewed have consistently shown an increased frequency of PUD in smokers as opposed to nonsmokers. In addition, the frequency of PUD rises with increases in the amount smoked, and smoking appears to retard peptic ulcer healing. All this, of course, does not provide a definitive answer to the question: "Is cigarette smoking a cause of peptic ulcer disease, or is it just associated with a cause such as genetic predisposition, personality type, and so on?" Epidemiological, case-control, and genetic studies cannot exclude the possibility that cigarette smoking is only associated with the cause(s) of PUD. An

essential link in establishing whether cigarette smoking is a causative factor in PUD is a convincing demonstration that smoking has an effect on physiological mechanisms that might allow an ulcer to develop. This question is difficult to deal with since it is still not known why certain patients develop PUD under any condition. We do know that (with rare exceptions) acid must be present (*30*). Although there is marked overlap with normals, on the average, patients with duodenal ulcer hypersecrete acid (*68*), so the effect of smoking on gastric acid secretion is of interest. Pancreatic buffering of acid may serve to protect the duodenum; does smoking interfere with this defense mechanism? Finally, since the pathogenesis of gastric ulcer may be different from duodenal ulcer (*49*), what other factors may smoking influence that might alter the stomach's defenses?

Gastric Secretion

Studies of the effects of smoking or nicotine on gastric acid secretion have been performed in rats, cats, dogs, and man—many with contradictory results even in the same species. One of the earliest studies (*53*) in dogs showed that neither cigarette smoking nor subcutaneous injections of 0.2, 0.4, or 1 mg of nicotine increased gastric acid secretion in the fasting state. Konturek, et al. (*36*) studied the effect of intravenous nicotine (100 μg/kg) in dogs and found no change in either basal acid output or half-maximal gastric acid secretion stimulated by histamine or pentagastrin. In addition, they found no effect on mucosal blood flow, and no interruption of the mucosal barrier to back diffusion of hydrogen ions by either intravenous or topical nicotine.

Nicotine, 100 μg/kg, injected into rats, depressed histamine-stimulated secretion of acid and pepsin. It also depressed basal secretion and submaximal pentagastrin-stimulated secretion. Tobacco smoke in 10 percent ethanol had no effect on acid secretion but reduced pepsin output (*56*). The effects of chronic nicotine administration in rats was also studied by the same investigators (*58*). Rats receiving 100 μg/kg nicotine 3 times daily for 15 days (the equivalent of smoking 10 to 15 cigarettes per day) doubled their gastric acid output and increased their pepsin output ($p < 0.01$). This effect could be blocked by either vagotomy or anterior hypothalamic lesions (*57*). Acute administration of nicotine to the chronically treated rats inhibited gastric acid and pepsin output. Robert and his colleagues have shown that nicotine can increase the number and severity of duodenal ulcers formed in rats by hydrochloric acid perfusion (*51*) or by subcutaneous infusion of pentagastrin and carbachol (*50*). Nicotine alone did not produce any ulcers in the animals.

Radecki, et al. (*47*) studied the response of cats to nicotine in both the basal and pentagastrin-stimulated states. Doses of nicotine up to 200 μg/kg did not alter acid secretion in either state. A dose of 400 μg/kg

depressed stimulated acid secretion by 30 percent; it also produced restlessness, vomiting, and diarrhea. Nicotine (200 μg/kg) did, however, potentiate the development of pentagastrin-induced experimental duodenal ulcers in these cats (*35*).

Studies of the effects of smoking on acid secretion in human subjects have given contradictory results. Schnedorf and Ivy (*53*) studied the effect of acute smoking on acid secretion in 40 normals (smokers and nonsmokers) and in 20 patients with duodenal ulcer. Mean acid output fell during smoking in both the normals and the ulcer patients, but no statistical analysis was done, so the significance of the decrease cannot be evaluated. Steigmann, et al. (*55*) reported that 26 of 44 controls and 40 of 45 ulcer patients increased acid production while smoking an unfiltered cigarette; a control study without smoking was not done. Cooper and Knight (*12*) recorded no difference in basal acid secretion between 60 patients with duodenal ulcer who smoked during the test and 60 patients who did not. Fung and Tye (*24*) investigated the effects of smoking 3 cigarettes per hour on 16 smokers and 16 nonsmokers, 23 of whom had duodenal ulcer and 7, gastric ulcer. There was no significant difference between basal acid output and acid output during smoking in either group. Another study showed that smoking four cigarettes an hour did not alter acid, pepsin, or mucus production in either normal subjects or ulcer patients who were smokers (*65*). This is particularly interesting in that the same laboratory reported different findings 15 years earlier when they found that smoking increased gastric secretion in man (*45*). Murthy, et al. (*40*) studied secretory response to smoking one cigarette per 15 minutes for 1 hour in smokers with duodenal ulcer and in normal smokers and nonsmokers. In the first 15 minutes, there was a significant increase in acid secretion in the ulcer patients. No significant effect was seen in either group of normals. Debas, et al. (*14*) studied 12 subjects, 6 smokers and 6 nonsmokers, of both sexes. The subjects smoked three cigarettes per hour while gastric secretion was maintained at half maximal rate with pentagastrin. Smoking caused no significant change in mean rate of acid secretion or pepsin secretion in either group. In a separate study (*10*), the same investigators found that while cigarettes alone had no effect on acid output, nausea induced by smoking in nonsmokers did inhibit acid production. Debas and Cohen (*13*) noted that smoking produced substantial inhibition of acid secretion in the majority of subjects during the first test but this could not be reproduced on repeated testing. They suspected that the inhibition was due to nausea, not smoking, per se. They also reported (*13*) that intravenous infusion of 2 mg of nicotine produced essentially no change in pentagastrin-stimulated acid and pepsin secretion in eight subjects.

Wilkinson and Johnston (*66*) also studied the effects of smoking on pentagastrin-stimulated acid secretion and found depression of acid output in response to smoking one or two cigarettes in three groups (38

percent in normals, 21 percent in duodenal ulcer patients, and 18 percent in gastric ulcer patients). All subjects experienced tachycardia and elevation of blood pressure while smoking.

In summary, most of the studies in human subjects have shown that smoking one or a few cigarettes exerts an inconsistent effect on acid secretion. A few studies found inhibition of acid secretion by smoking, but these involved first attempts at smoking with a gastric tube in place. Such procedures often produce nausea which by itself can inhibit acid secretion. There has been no systematic study of the effect of chronic smoking on acid secretion.

Pancreatic Secretion

It is generally accepted that an acid milieu is required for the development of duodenal ulcers; thus, smoking might influence duodenal ulcer formation by an effect on duodenal acidity. Smoking has not been clearly shown to increase gastric secretion, so perhaps it affects pancreatic buffering mechanisms. Murthy, et al. (*39*) showed that smoking may alter the duodenal environment. They found that smoking lowered duodenal pH from a range of 6.2–7.4 to 1.7–2.5 in five hypersecretors (BAO 5 to 16.5 mEq hr), but produced only a small effect in normal secretors.

Schnedorf and Ivy (*53*) found no significant change in either pancreatic or biliary secretion in dogs during smoking. Konturek and his colleagues (*36*) gave graded doses of nicotine (12.5 to 100 $\mu g\ kg^{-1}\ h^{-1}$ intravenously) to dogs on a background of maximal secretin stimulation and noted graded inhibition of bicarbonate secretion (23 to 62 percent). All values returned to control levels after cessation of the nicotine. Similarly, nicotine (100 $\mu g\ kg^{-1}\ h^{-1}$) reduced hepatic bile volume and bicarbonate by 50 percent. In a subsequent study (*34*), they reconfirmed that intravenous nicotine reduced the pancreatic response to intravenous secretin. Topical nicotine, however, did not alter the response to secretin. In addition, as the dose of secretin was increased from .37 to 3 U $kg^{-1}\ h^{-1}$, the inhibition of bicarbonate secretion by intravenous nicotine decreased from 75 to 15 percent. To examine the effect of nicotine on pancreatic secretion induced by endogenous secretin, pancreatic secretion was stimulated by intraduodenal administration of HCl with a response equivalent to .75 U $kg^{-1}\ h^{-1}$ of intravenous secretin. Both intravenous nicotine and topical nicotine reduced the response to the acid by about 25 percent. However, nicotine had no significant effect on cholecystokinin-induced stimulation of pancreatic secretion.

Boden and his associates (*7*) found in their dog experiments that basal and HCl (9.6 mEq/30 min) stimulated bicarbonate outputs were insignificantly decreased by intravenous infusion of nicotine (100 $\mu g\ kg^{-1}\ h^{-1}$), and nicotine did not decrease bicarbonate output in response to intravenous secretin (1.0 U $kg^{-1}\ h^{-1}$). In addition, nicotine had no

significant effect on the serum secretin level (measured by radioimmunoassay) except to delay the appearance of the peak value. It should be noted that Boden used 2.4 times as much acid to stimulate pancreatic secretion as did Konturek, et al. (*34*).

Solomon, et al. (*54*) studied the effect of nicotine on the rabbit pancreas. Nicotine infused at rates of 100 to 400 $\mu g\ kg^{-1}\ h^{-1}$ decreased pancreatic secretion in a dose-dependent fashion. Since nicotine is a stimulant of autonomic ganglia (*62*), the effect of norepinephrine and epinephrine was studied. Norepinephrine at 2 or 4 $\mu g\ kg^{-1}\ min^{-1}$ and epinephrine at 2 $\mu g\ kg^{-1}$ inhibited secretory flow and bicarbonate output. Phenoxybenzamine, an α-adrenergic blocker, increased water and bicarbonate secretion and blocked the inhibitory action of nicotine and norepinephrine on pancreatic secretion. On the basis of these results, they concluded that nicotine indirectly inhibits pancreatic secretion by stimulating catecholamine release, an effect that is negated by alpha adrenergic blockade.

The evidence for smoking's effect in man parallels that in animals. Bynum and his colleagues (*9*) studied the acute effects in light and heavy chronic smokers of smoking four cigarettes an hour on bicarbonate output in response to secretin. The light smokers responded normally to secretin during the control period but had decreased pancreatic bicarbonate output while smoking. Heavy smokers had a decreased response to secretin during the control period and this was not further affected by smoking. In a study of subjects who smoked regularly (*5*), smoking three cigarettes significantly decreased basal bicarbonate output.

Brown (*8*) investigated the effect of smoking on pancreatic secretion in 14 healthy smokers, 7 heavy and 7 light smokers. Heavy smokers had lower responses to secretin (2 U/kg) than light smokers. In addition, smoking cigarettes reduced even further the volume and bicarbonate content of the duodenal juice in both groups.

Murthy, et al. (*40*) studied the effects of smoking in smokers with and without duodenal ulcer and in nonsmokers. They found that smoking depressed basal bicarbonate and volume in both normals and patients with duodenal ulcer and in both smokers and nonsmokers. Changes in plasma nicotine were inversely correlated with pancreatic secretion. In addition, smoking had no effect on gastrin or secretin levels as measured by radioimmunoassay.

Bloom and Ward (*4*) reported depressed secretin release in response to intraduodenal acid instillation in patients with duodenal ulcer in contrast to controls. Actually, the increase in secretin over basal values was approximately the same in the ulcer patients as in the normal controls. Those patients who smoked more had smaller peak secretin values than lighter smokers. There was no difference in secretin release between smoking and nonsmoking controls. A subsequent study by Isenberg, et al. (*29*), using the same radioimmunoassay for

secretin, did not demonstrate a difference in secretin release between duodenal ulcer patients and normals. In light of this, the purported effect of smoking on secretin release must be questioned.

Four studies in man (*5*, *8*, *9*, *40*) all show decreases in bicarbonate output in response to smoking. There is no evidence that this is due to inhibition of secretin release.

Pyloric Reflux and Gastric Ulcer

What is smoking's relationship to the pathogenesis of gastric ulcer? The possible causes of gastric ulcer have been reviewed (*49*), and several hypotheses have been proposed. Various pharmacologic agents have been shown to disrupt the mucosal barrier to back diffusion of hydrogen ions, which might contribute to the development of gastric ulcer. However, no such effect has been demonstrated with smoking (*36*). Another hypothesis is that excessive reflux of duodenal contents, i.e. bile and pancreatic juice, through an incompetent pyloric sphincter, may be implicated in the pathogenesis of gastric ulcer (*52*). Recently, manometric studies of the human pylorus showed that smoking one cigarette decreased basal pressure significantly from 10.2 to 7.9 mm Hg (*61*). This supported previous work by Read and Grech (*48*) who found that smoking increased radiologic evidence of duodenogastric reflux. Whitecross, et al. (*65*), while studying the effect of smoking on gastric secretion, also noticed more marked bile staining of their gastric aspirates during the hour of smoking as compared to the control hour. Dippy and his colleagues found that smoking increased the degree of bile reflux in gastric ulcer patients (*16*).

Other possible etiological relationships have been examined. Edwards and Coghill (*21*) found that chronic atrophic gastritis was twice as common in persons who smoked more than 20 cigarettes a day as in nonsmokers. Since the majority of patients with gastric ulcer have chronic atrophic gastritis (*1*), smoking may predispose to gastric ulcer by producing chronic atrophic gastritis, which in turn may be a precursor of gastric ulcer.

Summary

If smoking does indeed influence the development and course of peptic ulcer disease, how does it do so? Experiments investigating the effect of smoking and nicotine on gastrointestinal function in animals and man have not established conclusively any mechanisms by which smoking might contribute to peptic ulcer formation. Most studies show little or no effect of smoking on acid secretion. Smoking and nicotine inhibit pancreatic secretion of bicarbonate; the consequent lowered capacity to neutralize gastric acid is a plausible but unproven mechanism by which smoking could favor occurrence of duodenal ulcer. Smoking also appears to increase reflux of duodenal contents into the stomach, which could be relevant in the light of the hypothesis

that injury to the gastric mucosa by bile acids and other constituents of duodenal contents is a factor in the pathogenesis of gastric ulcer.

Medical-Economic Implications

Peptic ulcer disease is one of the major health problems in the United States today. During their lifetime, about 10 percent of the persons in the United States can expect to suffer with this problem. Each year 400,000 patients are hospitalized and 150,000 undergo surgery for PUD. In addition, physicians see 2.5 million patients with peptic ulcers every year. Considering these facts, it comes as no surprise that, in 1975, the four million persons with ulcers cost the country an estimated $2.6 billion and are calculated to have cost it $3.7 billion in 1977 (*63*). These amounts include both medical care costs as well as indirect costs of earnings lost because of illness and disability and lifetime earnings lost because of early death.

Conclusions

The previous sections of this chapter have reviewed the various pieces of epidemiological and experimental evidence linking cigarette smoking with peptic ulcer disease. Three epidemiological questions have been addressed: (1) Does smoking increase the risk of getting an ulcer? (2) Does smoking retard healing of an ulcer? (3) Does smoking increase the risk of dying from ulcer?

Five studies show a higher proportion of smokers among PUD patients than among controls. Six studies show a greater prevalence of PUD among male cigarette smokers than among nonsmokers, the median ratio being 1.7. Results in women and the positive relationship between prevalence and amount smoked provide additional support. There is suggestive evidence for males that smoking retards ulcer healing. Four studies indicate that mortality due to ulcer is more than twice as high among male smokers as among nonsmokers.

What physiological effects produced by smoking might be relevant to the pathogenesis of ulcer? In regard to duodenal ulcer, evidence suggests that smoking inhibits pancreatic secretion of bicarbonate. As for gastric ulcer, smoking allows increased reflux of duodenal contents into the stomach. These effects, however, have not been shown to be directly related to the development of an ulcer.

Peptic Ulcer Disease: References

(1) AUKEE, S. Gastritis and acid secretion in patients with gastric ulcers and duodenal ulcers. Scandinavian Journal of Gastroenterology 7(6): 567-574, 1972.

(2) BARNETT, C. W. Tobacco smoking as a factor in the production of peptic ulcer and gastric neurosis. Boston Medical and Surgical Journal 197(12): 457-459, September 22, 1927.

(3) BENNETT, J. R. Smoking and the gastrointestinal tract. Gut 13(8): 658-665, August 1972.

(4) BLOOM, S. R., WARD, A. S. Failure of secretin release in patients with duodenal ulcer. British Medical Journal 1: 126-127, January 18, 1975.

(5) BOCHENEK, W. J., KORONCZEWSKI, R. Effects of cigarette smoking on bicarbonate and volume of duodenal contents. American Journal of Digestive Diseases 18(9): 729-733, September 1973.

(6) BOCK, O. A. A. Alcohol, aspirin, depression, smoking, stress and the patient with a gastric ulcer. South African Medical Journal 50: 293-297, February 28, 1976.

(7) BODEN, G., SHORE, L. S., ESSA-KOUMAR, N., LANDOR, J. H. Effect of nicotine on serum secretin and exocrine pancreatic secretion. American Journal of Digestive Diseases 21(11): 974-977, November 1976.

(8) BROWN, P. The influence of smoking on pancreatic function in man. Medical Journal of Australia 2: 290-293, August 21, 1976.

(9) BYNUM, T. E., SOLOMON, T. E., JOHNSON, L. R., JACOBSON, E. D. Inhibition of pancreatic secretion in man by cigarette smoking. Gut 13(5): 361-365, May 1972.

(10) COHEN, M. M., DEBAS, H. T., HOLUBITSKY, I. B., HARRISON, R. C. Effect of nausea on human gastric secretory responses. American Journal of Digestive Diseases 16(2): 156-159, February 1971.

(11) COOKE, A. R. The role of the mucosal barrier in drug-induced gastric ulceration and erosions. American Journal of Digestive Diseases 21(2): 155-164, February 1976.

(12) COOPER, P., KNIGHT, J. B. Effect of cigarette smoking on gastric secretions of patients with duodenal ulcer. New England Journal of Medicine 255(1): 17-21, July 5, 1956.

(13) DEBAS, H. T., COHEN, M. M. Effect of smoking on gastric secretion stimulated by pentagastrin. Lancet 1: 43-44, January 1, 1972.

(14) DEBAS, H. T., COHEN, M. M., HOLUBITSKY, I. B., HARRISON, R. C. Effect of cigarette smoking on human gastric secretory responses. Gut 12(2): 93-96, February 1971.

(15) DIN, N. A., SMALL, W. P. Death after partial gastrectomy for peptic ulcer—A long term study. Gut 15(4): 335, April 1974. (Abstract)

(16) DIPPY, J. E., RHODES, J., CROSS, S. Bile reflux in gastric ulcer: The effect of smoking, metoclopramide and carbenoxolone sodium. Current Medical Research and Opinion 1(9): 569-575, 1973.

(17) DOLL, R., HILL, A. B. Mortality in relation to smoking: Ten years' observations of British doctors. British Medical Journal 1: 1399-1410, May 30, 1964.

(18) DOLL, R., JONES F. A., PYGOTT, F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet 1: 657-662, March 29, 1958.

(19) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2: 1525-1536, December 25, 1976.

(20) DORN, H. F. Tobacco consumption and mortality from cancer and other diseases. Public Health Report 74(7): 581-593, July 1959.

(21) EDWARDS, F. C., COGHILL, N. F. Aetiological factors in chronic atrophic gastritis. British Medical Journal 2: 1409-1415, December 10, 1966.

(22) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. Lancet 1: 196-201, January 24, 1959.

(23) FRIEDMAN, G. D., SIEGELAUB, A. B., SELTZER, C. C. Cigarettes, alcohol, coffee and peptic ulcer. New England Journal of Medicine 290(9): 469-473, February 28, 1974.

(24) FUNG, W.-P., TYE, C.-Y. Effect of smoking on gastric acid secretion. Australian and New Zealand Journal of Medicine 3: 251-254, June 1973.

(25) GOLDBOURT, U., MEDALIE, J. H. Characteristics of smokers, nonsmokers and ex-smokers among 10,000 adult males in Israel. I. Distribution of selected sociodemographic and behavioral variables and the prevalence of disease. Israel Journal of Medical Science 11(11): 1079-1101, November 1975.

(26) HAMMOND, E. C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. Journal of the American Medical Association 166(11): 1294-1308, March 15, 1958.

(27) HERRMANN, R. P., PIPER, D. W. Factors influencing the healing rate of chronic gastric ulcer. American Journal of Digestive Diseases 18(1): 1-6, January 1973.

(28) HIGGINS, M. W., KJELSBERG, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurements and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86: 60-77, 1967.

(29) ISENBERG, J. I., CANO, R., BLOOM, S. R. Effect of graded amounts of acid instilled into the duodenum on pancreatic bicarbonate secretion and plasma secretin in duodenal ulcer patients and normal subjects. Gastroenterology 72(1): 6-8, January 1977.

(30) ISENBERG, J. I., SPECTOR, H., HOOTKIN, L. A., PITCHER, J. L. An apparent exception to Schwartz's dictum, "no acid—no ulcer." New England Journal of Medicine 285: 620, September 9, 1971.

(31) JEDRYCHOWSKI, W., POPIELA, T. Association between the occurrence of peptic ulcers and tobacco smoking. Public Health, London 88(4): 195-200, 1974.

(32) JORGENSEN, T. G., GYNTELBERG, F. Occurrence of peptic ulcer disease in Copenhagen males age 40-59. Danish Medical Bulletin 23(1): 23-28, February 1976.

(33) KASANEN, A., FORSSTROEM, J. Social stress and living habits in the etiology of peptic ulcer. Annales Medicinae Internal Fenniae 55(1): 13-22, 1966.

(34) KONTUREK, S. J., DALE, J., JACOBSON, E. D., JOHNSON, L. R. Mechanisms of nicotine-induced inhibition of pancreatic secretion of bicarbonate in the dog. Gastroenterology 62(3): 425-429, March 1972.

(35) KONTUREK, S. J., RADECKI, T., THOR, P., DEMBINSKI, A., JACOBSON, E. D. Effects of nicotine on gastric secretion and ulcer formation in cats. Proceedings of the Society for Experimental Biology and Medicine 138: 674-677, 1971.

(36) KONTUREK, S. J., SOLOMON, T. E., MCCREIGHT, W. G., JOHNSON, L. R., JACOBSON, E. D. Effects of nicotine on gastrointestinal secretions. Gastroenterology 60(6): 1098-1105, June 1971.

(37) MEDALIE, J. H., BIRNBAUM, D., GOLDBOURT, U., NEUFELD, H. N., RISS, E., ORAN, D., PERLSTEIN, T. Peptic ulcer history among 10,000 adult males. I. Prevalence and incidence. Israel Journal of Medical Science 8(10): 1673-1679, October 1972.

(38) MONSON, R. R. Cigarette smoking and body form in peptic ulcer. Gastroenterology 58(3): 337-344, March 1970.

(39) MURTHY, S. N. S., DINOSO, V. P., CLEARFIELD, H. R. Serial pH changes in the duodenal bulb during smoking. Gastroenterology 75(1): 1-4, July 1978.

(40) MURTHY, S. N. S., DINOSO, V. P., CLEARFIELD, H. R., CHEY, W. Y. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. Gastroenterology 73(4, Part 1): 758-761, October 1977.

(41) PAFFENBARGER, R. S., WING, A. L., HYDE, R. T. Chronic disease in former college students. XIII. Early precursors of peptic ulcer. American Journal of Epidemiology 100(4): 307-315, 1974.

(42) PETERSON, W. L., STURDEVANT, R. A. L., FRANKL, H. D., RICHARDSON, C. T. ISENBERG, J. I., ELASHOFF, J. D., SONES, J. Q., GROSS, R. A., MCCALLUM, R. W., FORDTRAN, J. S. Healing of duodenal ulcer with an antacid regimen. New England Journal of Medicine 297(7): 341-345, August 18, 1977.

(43) PFEIFFER, C. J., FODOR, J., GEIZEROVA, H. An epidemiologic study of the relationships of peptic ulcer disease in 50-54 year old, urban males with physical, health and smoking factors. Journal of Chronic Diseases 26: 291-302, 1973.

(44) PIPER, D. W., GREIG, M., COUPLAND, G. A. E., HOBBIN, E., SHINNERS, J. Factors relevant to the prognosis of chronic gastric ulcer. Gut 16(9): 714-718, September 1975.

(45) PIPER D. W., RAINE, J. M. Effect of smoking on gastric secretion. Lancet 1: 696-698, April 4, 1959.

(46) PIPER, D. W., SHINNERS, J., GREIG, M., THOMAS, J., WALLER, S. L. Effect of ulcer healing on the prognosis of chronic gastric ulcer. Four-year follow-up. Gut 19(5): 419-424, May 1978.

(47) RADECKI, T., BIERNAT, J., THOR, P., MITIS, M., DEMBINSKI, A., KONTUREK, S. Effect of nicotine on the development of peptic ulcers. Acta Physiologica Polonica 23(5): 853-858, 1972.

(48) READ, N. W., GRECH, P. Effect of cigarette smoking on competence of the pylorus: Preliminary study. British Medical Journal 3: 313-316, August 11, 1973.

(49) RHODES, J. Etiology of gastric ulcer. Gastroenterology 63(1): 171-182, July 1972.

(50) ROBERT, A. Potentiation, by nicotine, of duodenal ulcers in the rat (36134). Proceedings of the Society for Experimental Biology and Medicine 139: 319-322, 1972.

(51) ROBERT, A., STOWE, D. F., NEZAMIS, J. E. Possible relationship between smoking and peptic ulcer. Nature 233(5320): 497-498, October 15, 1971.

(52) ROVELSTAD, R. A. The incompetent pyloric sphincter. American Journal of Digestive Diseases 21(2): 165-173, February 1976.

(53) SCHNEDORF, J. G., IVY, A. C. The effect of tobacco smoking on the alimentary tract. An experimental study of man and animals. Journal of the American Medical Association 112(10): 898-904, March 11, 1939.

(54) SOLOMON, T. E., SOLOMON, N., SHANBOUR, L. L., JACOBSON, E. D. Direct and indirect effects of nicotine on rabbit pancreatic secretion. Gastroenterology 67(2): 276-283, August 1974.

(55) STEIGMANN, F., DOLEHIDE, R. H., KAMINSKI, L. Effects of smoking tobacco on gastric acidity and motility of hospital controls and patients with peptic ulcer. American Journal of Gastroenterology 22: 399-409, 1954.

(56) THOMPSON, J. H. Effects of nicotine and tobacco smoke on gastric secretion in rats with gastric fistulas. American Journal of Digestive Diseases 15(3): 209-217, March 1970.

(57) THOMPSON, J. H., GEORGE, R., ANGULO, M. Some effects of nicotine on gastric secretion in rats. Proceedings of the Western Pharmacology Society 14: 173-177, 1971.

(58) THOMPSON, J. H., SPEZIA, C. A., ANGULO, M. Chronic effects of nicotine on rat gastric secretion. Experientia 26(6): 615-617, 1970.

(59) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report to the Surgeon General: 1971. U.S. Department of Health Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 71-7513, 1971, pp. 423-430.

(60) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: 1973. U.S. Department of Health Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM) 73-8704, 1973, pp. 155-164.

(61) VALENZUELA, J. E., DEFILIPPI, C., CSENDES, A. Manometric studies on the human pyloric sphincter. Effect of cigarette smoking, metoclopramide, and atropine. Gastroenterology 70(4): 481-483, April 1976.

(62) VOLLE, R. L., KOELLE, G. B. Ganglionic stimulating and blocking agents. In: Goodman, L. S., Gilman, A. (Editors). The Pharmacologic Basis of Therapeutics. New York, McMillan, 1970, p. 588.

(63) VON HAUNALTER, G., CHANDLER, V. V. Cost of ulcer disease in the United States. Menlo Park, California, Stanford Research Institute, February 1977, 12 pp.

(64) WEIR, J. M., DUNN, J. E. Smoking and mortality: A prospective study. Cancer 25: 105-112, January 1970.

(65) WHITECROSS, D. P. CLARKE, A. D., PIPER, D. W. The effect of cigarette smoking on human gastric secretion. Scandinavian Journal of Gastroenterology 9(4): 399-403, June 1974.

(66) WILKINSON, A. R., JOHNSTON, D. Inhibitory effect of cigarette smoking on gastric secretion stimulated by pentagastrin in man. Lancet 2(7725): 628-632, September 18, 1971.

(67) WINSHIP, D. H. Cimetidine in the treatment of duodenal ulcer. Review and commentary. Gastroenterology 74(2, Part 2): 402-406, February 1978.

(68) WORMSLEY, K. G., GROSSMAN, M. I. Maximal histalog test in control subjects and patients with peptic ulcer. Gut 6(5): 427-435, October 1965.

10. ALLERGY AND IMMUNITY.

CONTENTS

Introduction

Tobacco and its products, including smoke, can affect the immune system in two ways. As antigens, they can interact with the immune system to induce specific responses evidenced by production of specific antibody or sensitized cells. Or, as irritant, pharmacologic, and toxic agents, they can interact with cellular elements of the host defense system, thereby influencing the functional ability of these elements.

Physicians have long noted the association between the development or aggravation of allergic or allergic-like symptoms and direct exposure to tobacco and tobacco products, including smoke, thus giving grounds for suspicion that tobacco can be causally related to the symptoms. There is evidence that tobacco smoke condensate can induce an immune response in animal models and in humans. The existence of a tobacco smoke allergy in humans is unproven, however, and is complicated by the difficulty of demonstrating a cause and effect relationship between the immunologic event and its manifestations.

The problem can best be understood by appreciating the current concept of that which characterizes an allergic individual—the ability to produce a unique serum antibody upon exposure to a given antigen. A property of that antibody is its selective fixation to cells located in certain tissues, such as skin and respiratory membranes.

Upon subsequent exposure, the antigen becomes bound at the cell surface by the preformed antibody. This phenomenon has been the basis of the skin test—an important aid in the diagnosis of allergy. In this procedure, introduction of the antigen into the skin, rendered sensitive by these previous events, induces pathophysiologic changes similar to those that occur in nasal and bronchial membranes upon natural exposure. The end result is an immediate wheal and flare inflammatory response.

Much of the past research in this area has relied heavily upon the use of skin tests. However, in the 15-year interval since the first Surgeon General's Report on smoking, research developments have made it possible to add new insights to the topic of tobacco allergy. In 1967, the Ishizakas (*51*) identified the skin sensitizing factor or reaginic antibody as immunoglobulin E (IgE), thus providing a major breakthrough in the understanding of allergy. Subsequently came descriptions of the specific localization of IgE on membranes of tissue mast cells (*111*) and the release of chemical mediators from the protoplasm of these cells when IgE reacts with corresponding surface antigens (*52*). In such instances, the antigen can be classified as an allergen.

Along with these advances came an appreciation of some of the limitations of skin testing. Among these is the fact that mast cell chemical mediators can also be released by nonspecific irritation (*81, 99*). Also, the presence of specific IgE fixed in the skin, as noted by the wheal and flare test response, is not the sole determinant for clinical expression of an allergy. Skin testing, done with appropriate materials

and controls, can give useful results to support a clinical impression, but it is not the sole diagnostic criterion.

Much of the previous work in assessing the possibility of tobacco allergy has been questioned because the extracts of the whole leaf or smoke used for skin testing represent a complex mixture of components; while one or more of the components may be allergenic, others are primarily irritant. However, a potential breakthrough has come about through the application of biochemical expertise in isolating and identifying a single component of tobacco which has been shown to cause positive, immediate reactions in skin tests in humans. (*9*, *10*). Whether this glycoprotein will ultimately be shown to be a causative agent of symptoms in humans awaits further study.

Even though skin testing remains the most sensitive indicator of reaginic antibody, in some cases there is reason to question its specificity. Verification of its validity is now possible because of the development of *in vitro* tests, such as the radioallergoabsorbent test (RAST) (*126*). While this assay is showing promise in diagnosis of pollen and insect venom allergy, further technology is required to make it suitable for general use. It may be possible to employ RAST in the study of tobacco smoke or leaf allergy, once the chemical properties of any true allergens that are discovered are characterized and adapted for the required solid phase studies.

The development of critical *in vitro* assays is important in the diagnosis of possible tobacco allergy because the nonspecific irritant qualities of tobacco extracts often leave the interpretation of skin tests and provocation tests in doubt. Awaiting such technology, several other approaches to exclude irritating effects have been employed: demonstration of the nonreactivity of the test extract in normal controls, end point titration, passive serum transfer (Prausnitz-Kuestner [P-K] test), and exhaustion of the response at the site of a passive serum transfer reaction by previous absorption of the test serum with a specific antigen.

Perhaps the term tobacco allergy has been used too loosely. In the past, reports of diagnosis have been based on a history of symptoms upon exposure to tobacco or its products, elimination of symptoms on withdrawal, demonstration of the occurrence of symptoms on reexposure, and emphasis on skin test results. These criteria must be reevaluated, since approaches for verification with precise methods and chemically-characterized specific tobacco antigen(s) are now on the horizon. In retrospect, it would appear that only those studies fulfilling a minimum set of criteria should have been considered acceptable as diagnostic of tobacco allergy. These criteria include the following:

1. Demonstration that tobacco smoke or a derivative product is capable of inducing those specific immune responses that are responsible for producing symptoms of allergy.

2. Demonstration upon exposure to tobacco smoke or a tobacco smoke product of reproducible symptoms characteristic of an allergic response, e.g., asthma, rhinitis or related upper respiratory symptoms, conjunctivitis, urticaria/angioedema, dermatitis, or anaphylactic shock. These symptoms must be reversible upon removal of tobacco or its derivatives; other possible effects of tobacco, such as irritant or pharmacological effects, must be excluded.

3. Demonstration of the affected person's ability to mount a reaginic response, as evidenced by an immediate wheal and flare response to the application of appropriate tobacco smoke extract by conventional prick, scratch, or intracutaneous routes, again provided nonspecific irritant properties have been excluded.

4. Demonstration of an association between the immunologically demonstrated reaction and the clinical symptoms. Further credence is given to this relationship if there is failure to manifest identical symptoms on exposure to potentially irritating gaseous or particulate matter that is not derived from tobacco.

While the discussion thus far and the thrust of this report will deal with the type of allergy known as immediate hypersensitivity, an additional fact to be considered is that tobacco can affect the immune system in a manner quite apart from the classic allergic state. It should be recognized that expressions of other immune mechanisms are often considered allergic. Thus, it is plausible that tobacco as an antigen could play a causative role in disease entities mediated by immunoglobulins in other classes (humoral IgG and IgM and secretory IgA at the mucous membrane surface). Direct cellular injury can arise from the action of cytotoxic antibodies, causing tissue inflammation by deposition of immune complexes through the sequence of antigen-antibody reactions, activation of the complement cascade, and migration of inflammatory cells into affected sites. In the case of delayed hypersensitivity, contact dermatitis of skin and mucous membranes emerges as a manifestation of cell-mediated immune mechanisms. Additionally, some physicians consider cardiovascular symptoms to be allergic because of the association of skin tests positive to tobacco extract with reproducible cardiac pathophysiologic expressions. However, exact differentiation between those responses that are truly immunologically mediated and those of pharmacologic idiosyncratic origin remains to be defined.

Though some of the reported studies may have adhered to one or more of the criteria listed above for diagnosis of an immediate allergic reaction, other demands of clinical investigation were not always met. Evaluation of many studies pertaining to tobacco allergy is difficult because of the lack of necessary data or because of poor experimental design. Controlled double-blind protocols have seldom been used. The presence of a positive skin test has been equated with the presence of clinical tobacco allergy, even in the absence of clinical

symptomatology. There have been failures in appreciating the role of tobacco smoke as a pollutant serving as a secondary or an aggravating factor rather than as an initiating agent, and provocative testing was not always carried out in patients in a basal asymptomatic state; thus, the influence of coincidentally present allergens and irritants could not be excluded. Other experimental deficiencies include failure to standardize the potency or antigenicity of extracts, inadequate definition of the term allergic when a subpopulation of "allergic patients" was studied, and failure to define the degree of exposure to tobacco among individual subjects.

When trying to compare studies, additional problems arise because of the many variables in the experimental protocols used. Criteria for scoring a skin test positive were not always defined, leaving no basis for comparison among different studies. Evident differences among the populations studied included age, sex, occupation, presence or absence of other allergies, environmental exposures, and smoking history. Additional variables included differences in source of tobacco used for testing, state of the tobacco (raw vs. cured), use of fractionated extracts as opposed to whole leaf extracts, differences in extraction methods, the presence or absence of additives or nicotine, and, most importantly, the use of smoke extracts as opposed to tobacco leaf extracts.

On the basis of clinical experience, many physicians are convinced that tobacco products can and do act through a primary allergic mechanism. However, this impression is not uniformly held and has not been unequivocally proven. That tobacco and/or its products can exacerbate underlying allergic conditions in both smokers and nonsmokers is generally accepted by clinicians on the basis of documented irritant and pharmacologic effects. Again, however, difficulties in the evaluation of studies examining these factors arise from problems in separating the effects of tobacco and smoke from other environmental allergens and pollutants and in knowing whether a given effect is primary or secondary.

The purpose of this chapter is to review critically the experimental evidence which may shed light on the unresolved relationship of tobacco smoking to allergy and other immune phenomena.

Basic Mechanisms

The term allergy, coined by Von Pirquet in 1906 (*115*), embraced any type of altered reaction to a substance brought about during the course of prior exposure. Hence, mechanisms both of enhanced resistance or immunity and of enhanced reactivity or hypersensitivity were referred to as the allergic state. During subsequent years, the term began to take on only the latter meaning; so that, currently, allergy is considered synonymous with hypersensitivity. Thus, whereas early in

the century allergy was given a broad scientific definition, the term is now more narrowly interpreted and, especially to a lay person, is associated with the symptoms of itching, sneezing, and wheezing characteristic of eczema, hives, hay fever, and asthma. Actually, however, there are several types of allergic states and their mechanisms are best understood in terms of the Gell and Coombs classification of hypersensitivity reactions (*23*).

1. Type I, or immediate hypersensitivity reaction, embraces the commonly-known classic allergic disorders mentioned above. A major portion of this report concerns itself with manifestations of this type of allergy; the details of its mediation involving the antibody known as IgE are presented in an earlier section.

2. Type II hypersensitivity is mediated by an antibody directed against a cell membrane or cell membrane-associated substance such as the injury to red blood cells that occurs during an incompatible blood transfusion. Serum complement is involved in this cytotoxic type reaction.

3. Type III is mediated by antigen-antibody combinations (immune complexes) resulting from their interaction and deposition in tissues. Serum sickness and the local Arthus-type reaction are the classic examples of this mechanism.

4. Type IV reaction is mediated by sensitized thymus-dependent lymphocytes (T cells), not by circulating antibodies. Contact dermatitis is an example of this delayed hypersensitivity reaction.

Tobacco as an Antigen

In order to demonstrate that any substance may be a cause of allergy, it is necessary (but not sufficient) to prove that the substance is antigenic. An antigen is capable of binding to the antibody whose formation it has induced, in humoral immunity, or is responsible for the development of sensitized cells, in delayed hypersensitivity. The term allergen has a slightly different connotation in that it is usually an environmental or food antigen to which only allergically predisposed individuals become specifically sensitized upon spontaneous contact by inhalation or ingestion. The mechanisms for allergenicity can proceed by any of the four types of hypersensitivity discussed above. There is evidence that tobacco leaf and its products are antigenic in animals and man, capable of both evoking a wide range of antibodies, including reaginic antibodies, and sensitizing small lymphocytes responsible for delayed type hypersensitivity (*4,41,53,60,80,104*). Evidence that tobacco smoke is antigenic in man, however, is meager and controversial at present.

There are several studies on experimental animals demonstrating stimulation of antibody production by tobacco products. Harkavy (*41*) injected rats with tobacco leaf extract. Upon subsequent challenge

with this material, he was able to demonstrate positive Schultz-Dale reactions with the sensitized intestinal strips. Armen and Cohen (*4*) were able to raise precipitating antibodies in rabbits injected with an extract of cured tobacco leaves but found this material to be weakly antigenic, requiring simultaneous injection of an adjuvant to induce the responses. Panayotopoulos, et al. (*80*) described the isolation of five components from tobacco leaf extracts capable of inducing precipitating antibodies. Recently, a mouse model for production of IgE and reaginic IgG against tobacco components has been developed by Justus and Adams (*53*), with identification of the antibodies by passive cutaneous anaphylaxis assay. Of potential importance are recent studies by Lehrer, et al. employing tobacco smoke and smoke in combination with host protein carriers. In these studies, sera from rabbits immunized with tobacco smoke components reacted by immunoprecipitation with tobacco smoke or leaf antigens (*62*). These investigators have also demonstrated reaginic antibodies in the sera of mice immunized with smoke extracts.

Human studies have also been revealing. Kreis, et al. (*60*) demonstrated that two of the five tobacco components inducing antibody formation in rabbits also reacted *in vitro* with human sera. Since these antigenic components were identified only in tobacco leaf extracts and not in the smoke, it was suspected that some contact with the leaf or cross reacting antigens must take place in humans. In the studies by Panayotopoulos, et al. (*80*), serum-precipitating antibodies to the five components of tobacco leaf were also identified in humans. Seventy-five percent of the subjects demonstrating this finding reacted with positive Arthus skin test reactions characteristic of this type of antibody when challenged intradermally with the extract, and smokers reacted more frequently than nonsmokers.

Of special interest and relevance are studies concerned with the demonstration of reaginic antibody against tobacco leaf in humans. This has been a controversial subject and is discussed in further detail in a later portion of this report. As early as 1923, Brown (*12*), attempting to demonstrate positive immediate skin tests to tobacco leaf extracts in humans, reported positive findings in 1 percent of asthmatic patients studied. This work was later extended (*9,10,38,42,43,64,83*) by workers who demonstrated not only the presence of positive skin test reactions to tobacco leaf extracts but also the ability to transfer this reaction passively to normal control subjects. Others (*20,104,105,113,124*), however,were unable to confirm the studies done with tobacco leaf extracts. Similar studies, perhaps more relevant to this report, have been done with extracts prepared from tobacco smoke, showing that these, too, are capable of reacting with reaginic antibody in humans (*9,10,85*). These studies were dependent primarily on skin reactivity, however, and, therefore, require further investigation. Delayed reactions following intradermal

test injections of tobacco extracts have also been reported in humans (*104*). This and other related studies discussed in a later section suggest that tobacco leaf may play a role as antigen in cell-mediated delayed hypersensitivity.

Identification of the Tobacco Antigen(s)

The tobacco plant is a member of the botanical family *Solonaceae*, as are potatoes and tomatoes. Since the raw leaf contains many high molecular weight proteins, theoretically it is potentially antigenic. In addition, the raw leaf may contain residues of insecticides or may be contaminated with bacteria, fungi, and even other known airborne allergens deposited on its surface, such as ragweed pollen. During curing and aging of the green leaves, chemical reactions take place within the tobacco leaf substance, and an array of additives further influences its composition. Aside from the exposure of tobacco and cigarette factory workers to raw and cured leaf, the possible antigens in tobacco smoke may be more relevant. Here again, this tobacco combustion product is a heterogeneous mixture of an estimated 2,000 particulate, gaseous, and semivolatile components (*75*). Furthermore, recent investigations show differences between the puff of smoke actively inhaled through the cigarette by the smoker and the so-called side-stream smoke discharged into the air by the burning cigarette tip, a source of potential inhalation by exposed nonsmokers (*48*). The issue is further complicated by the fact that tobacco and its products have both irritant and pharmacologic effects which can be mistakenly interpreted as allergenic. Isolation and purification of one or more substances responsible for the antigenicity of tobacco and its products will be necessary to clarify these findings.

Harkavy (*39, 40*) has shown that nicotine is not the responsible antigenic component of tobacco leaf, although its role as a hapten (*68*) is a possibility. Chu, et al. (*21*) have isolated five protein carbohydrate complexes with molecular weights varying between 20,000 and 60,000 from aqueous extracts of cigar and pipe tobacco. Kreis and coworkers (*60*) reported that two components of a soluble extract of tobacco leaf capable of stimulating antibody formation in rabbits and precipitating with human sera had molecular weights of 10,000 to 30,000. In another study (*80*), five antigenic plant proteins, immunoelectrophoretically localized in positions corresponding to the α_1-, α_2-, and β-globulins and isolated from the leaves of *Nicotiana tabacum*, had the property of precipitating with human sera. Differences in antigenic reactivity were described among different varieties of tobacco leaf tested. Because the serum precipitins were more prevalent in smokers, these investigators proposed that antigenic substances were carried in smoke passing through the cigarette, thus exposing the smoker. However, they did not attempt to demonstrate these substances in the tobacco

smoke. Becker, et al. (*9, 10*) reported that a tobacco glycoprotein gave positive and immediate skin test reactions in approximately one-third of the people tested, but the atopic status of these people and the irritant threshold of the extract were not determined.

Epidemiology

Few studies have attempted to relate the incidence of clinical allergy to active or passive effects of smoking. Asthma has occurred either in association with or following respiratory infections (*33*). Hence, any factor predisposing to infections of the lower respiratory tract, especially during childhood years, is relevant to this discussion on tobacco as a health hazard. One study (*75a*), surveying the incidence of respiratory symptoms and infections among 1,119 children, revealed that the percentage with symptoms increased with the definable level of smoking in the household. Another study, by Colley and coworkers (*22a*) surveying 2,205 infants, showed that the incidence of pneumonia and bronchitis in the first year of life was associated with parental smoking habits; the risk to the infant of parents both of whom smoked was almost twice that of nonsmoking parents. Cameron, et al. (*15*), in a survey of children from 727 families, found the prevalence of respiratory disorders to be 5.9 percent in homes where parents smoked compared with 3.1 percent in homes of nonsmoking parents.

Looking at the same problem from a different viewpoint, a study of hospital records of 10,762 infants by Harlap and Davies (*43a*) disclosed a significantly higher admission rate for bronchitis and pneumonia for those whose mothers smoked. It is, however, difficult to evaluate the impact of these infectious processes on the subsequent development of allergic diseases in the children studied because of several factors: differentiation among possible causative organisms (microbial or viral) was not always determined; the presence or absence of wheezing was not noted; and, apparently, follow-up studies were not undertaken.

Studies such as these also suffer from the criticism of failing to consider sufficiently other possible explanations for the increased prevalence of respiratory symptoms and disorders, such as socio-economic factors, genetic differences, and frequency of respiratory infection in parents. Thus, adverse consequences of passive smoking among healthy adults has been surveyed. Speer (*102*) examined the frequency of symptoms reported by 250 nonallergic, nonsmoking individuals, passively exposed in environments characterized by smoking. Nasal symptoms such as sneezing and itchiness were found in 29.2 percent, cough in 25.2 percent, headache in 33.0 percent, and eye irritation in 70.0 percent, emphasizing that irritant effects of smoke can simulate allergic symptoms.

As might be anticipated, persons with identified allergic disorders such as rhinitis or asthma have been more thoroughly investigated in

efforts to define causal connections between tobacco or smoke and their specific illnesses. Studies also have been made to ascertain whether smoking may aggravate preexisting allergic conditions. Zussman (*130, 131*) made an effort to learn whether tobacco leaf allergy played a causal role among allergic patients suffering from nasal, ocular, or bronchial involvement. Among a randomly selected group of 200 people, 16 percent were found to be clinically irritated by tobacco smoke. Thirteen of sixteen individuals manifesting positive skin tests to tobacco leaf extracts were reported to benefit from "desensitization" injections, in which tobacco extract was included among other allergens in the treatment mixtures. However, "benefit" was evaluated by the patient reporting without the advantage of objective assessment. It should also be noted that the tobacco leaf extract employed was contaminated with house dust antigen. In any case, the use of such a heterogenous mixture as tobacco extract in injection treatments is considered controversial.

In another study, Fontana and coworkers (*33*) found that 64 percent of 25 allergic children gave positive skin test reactions to tobacco leaf extract, compared with only 6 percent of nonallergic control subjects. Rosen (*91*) reported positive skin reactions to tobacco leaf extract in 12 percent of asthma patients, and Speer (*102*), in 15 percent of 191 allergically predisposed individuals. By retrospective survey, Pipes (*85*) made an effort to distinguish allergy to smoke from allergy to tobacco, noting that 13 percent of 370 allergic patients had positive skin test reactions to tobacco leaf extract. Ten percent of the study population also experienced aggravation of symptoms upon exposure to smoke, but none gave positive skin reactions to the tobacco smoke preparations utilized.

It is relevant to note that available tobacco leaf extracts utilized in skin testing are multicomponent mixtures that may contain both irritant and allergenic fractions and that it is a characteristic feature of the allergic state for an affected person to have positive skin reactions to allergenic extracts other than tobacco. Thus, the problem of precise interpretation of skin tests in clinical settings where allergic conditions have multifactorial features makes it impossible to determine what role, if any, allergy to tobacco smoke played in the clinical disorders of patients reported in these series. Fontana and coworkers (*33*) reported that 15 percent of 641 volunteers reacted with positive skin tests to one or more of the tobacco leaf extracts used, without a significant difference occurring between smokers and nonsmokers.

The above findings indicate that tobacco proteins are able to produce positive skin tests on an irritant basis. They further suggest that the predominant effect of smoke is an irritant superimposed upon an already pathophysiologically altered allergic membrane. In a study of 191 allergic nonsmokers and 250 nonallergic smokers, intolerance of tobacco smoke was a common occurrence in both groups (*102*).

Pediatricians have considered tobacco smoke exposure in the troubled allergic child an identifiable problem to be faced. McGovern and coworkers (*70*) emphasized that allergic disease represents a major school health problem because children with hay fever, allergic rhinitis, and asthma account for about one-third of all chronic conditions reported under age 17. A survey is cited in which it was noted that asthma accounted for 11.4 percent of all chronic conditions in children and for 22.9 percent of days lost from school (*8*). These clinical investigators have, therefore, emphasized the need and value of removing the allergic child from all environmental sources of tobacco smoke exposure as a valid preventive measure.

Since the chances for progression of disease are more likely to occur in the face of continued and uncontrolled presence of causative factors, the potential for chronicity among adults is evident. The magnitude of the problem can be appreciated by noting the large population surveys in the United States which estimate that as many as 15 to 17 percent of the population suffers from asthma or hay fever (*97*). Thus, to whatever extent tobacco and/or tobacco smoke play a causal or contributory role in allergy, if they are ultimately shown to be allergens, it would be important for allergic patients of all age groups to take appropriate precautions to avoid exposure.

Effects of Cigarette Smoking on the Immune System

That cigarette smoking can affect the immune system has been well documented in both animals and humans. For purposes of discussion, these alterations in immune function can be classified as local and systemic. The local host defense system is comprised of the mucociliary mechanisms and functionally specialized cells, such as the macrophages and lymphocytes. Systemic defense mechanisms divide conveniently along the lines of cellular and humoral immunity.

Microscopic examinations of the respiratory tract mucosa demonstrate that chronic smoking leads to denuding of the ciliated epithelium, an increased number of goblet cells, and squamous metaplasia (*89*). On the other hand, studies attempting to quantify toxicity of cigarette smoke to cilia have been difficult to evaluate because of variation of mucus transport rates both among and within species studied, differences in techniques used to measure ciliary activity, and variations in methods and periods of exposure employed.

Studies on the short-term effects of smoke on ciliary function *in vitro* and *in vivo* generally show decreased function. Ciliostasis has been produced by *in vitro* exposure of the epithelium of the human respiratory tract to smoke residue passed through an aqueous medium (*7*) and, along with decreased rates of mucus transport, has also been observed in many animal models (*1, 26, 50, 55*). However, the effects of short-term smoking on mucociliary function in man have been

contradictory. In studies by Yeates, et al. (*128*) which measured mucociliary tracheal transport rates, some smokers showed slower bronchial clearance rates, while others showed little or no change over nonsmokers. Camner and coworkers (*17*), on the other hand, found mucociliary transport to be significantly increased during periods of intensive smoking (to the point of discomfort) compared to nonsmoking periods.

Studies of long-term exposure have also been undertaken and, again, both animal and human studies are contradictory. Two studies were carried out in dogs exposed to forced smoke inhalation. One showed no change in tracheobronchial clearance (*6*) while the second, by different methodology, showed that tracheal mucus velocity was 30 percent of that found in controls (*118*).

In a study of 10 pairs of identical twins, discordant with regard to smoking (*16*), five of the smoking twins had decreased clearance rates while the other five demonstrated no differences over controls. Similarly, Albert, et al. (*2*) found bronchial clearance impaired in 8 out of 14 cigarette smokers tested. Lourenco and coworkers (*65*) found delayed clearance of particles, particularly in the central airways, at 1 hour after inhalation in nine smokers when compared to controls. On the other hand, Pavia, et al. (*82*) found no decrease in the efficiency of removal of particulate matter in the lungs of smokers compared to nonsmokers. However, the evidence indicates an adverse effect of long-term smoking on the mucociliary transport mechanisms and mucus composition (*58*).

It is necessary to understand the functions of alveolar macrophages and lung phagocytic cells as well as the population of immunocompetent lymphocytes in pulmonary tissue in order to appreciate how these elements and their modification can affect the processing of tobacco antigen and the resultant production of antibody and cell-mediated immunity. Since hypersensitivity phenomena are products of the immune system, these cellular elements can serve as determinants of allergic inflammation as well as of immunity.

Alveolar macrophages are important to lung function because of their role as phagocytes, engulfing and digesting particulate matter in the lung. Also, these cells process antigens and interact with lymphocytes in immune and allergic processes.

Many studies have examined the effect of smoking on macrophage function and metabolism. Even though most of these are *in vitro* studies, comparison is difficult because of differences inherent in the human and animal models used. In addition, in some cases, human subjects or animals were exposed to the smoke before the cells were harvested, while in others, cells were exposed directly to the smoke. Other variables included serious differences in amounts and lengths of exposures, filtration of smoke, and different methods of harvesting

cells. Nevertheless, it is clear from these studies that profound alterations in macrophages result from smoke exposure.

One consistent finding concerning the effect of smoking on macrophages is that the total number is increased in smokers. Keast and Holt (*57*) used a special apparatus simulating human smoking in exposed mice. They found initial and sustained elevations in macrophage populations. Other workers (*56*) also found increased macrophage numbers after only 2 weeks of cigarette smoking in humans. Studies by Pratt, et al. (*88*) and Harris, et al. (*44*) showed that smokers had strikingly increased numbers of macrophages when compared to nonsmokers and, furthermore, that macrophages accounted for 90 to 95 percent of lavaged lung cells found in smokers. The authors (*44*) speculate that increased alveolar macrophages in smokers might play an important role in pulmonary defense against toxic components of cigarette smoke. Also important is the possibility that macrophage accumulations could contribute to the pathogenesis of chronic pulmonary disease by the release of lysosmal enzyme content.

Changes in ultrastructure of macrophages have also been reported in smokers. Pratt and associates (*88*) observed that macrophages obtained in lung fluids of smokers were filled with cytoplasmic inclusions, and Martin (*67*) identified multinucleated giant cells in some smokers but none in nonsmokers. Martin (*67*) also noted that crystalloid refractile cytoplasmic inclusions were more common among the smokers. Harris, et al. (*44*) found the most salient feature of the macrophages from smokers to be larger and more numerous lysosomal bodies.

The study by Holt and Keast (*47*) demonstrated that the immediate toxic effects of tobacco smoke *in vitro* were greater in macrophages than fibroblasts, with surviving macrophages showing an increase in measured protein synthesis. Keast and Holt (*57*) also found that the macrophages from mice exposed to smoke for many weeks were no longer as susceptible to the untoward effects of smoke and had apparently adapted to the toxic conditions in a fashion similar to that seen in the tissue culture experiments.

Enzyme systems have also been shown to be affected by smoking. Martin (*67*) demonstrated that increased macrophage acid hydrolase directly correlated with daily cigarette consumption. Meyer, et al. (*72*) examined the effect of various concentrations of nicotine on the ATPase activity of sheep pulmonary alveolar macrophages and showed significant inhibition of this activity. Additionally, lower concentrations of this alkaloid stimulated cell respiration while higher concentrations were inhibitory. Kasemir and Kerp (*56*) recorded decreased oxygen uptake in sheep macrophages in contact with tobacco extracts. The *in vitro* studies of Harris and coworkers (*44*) on human alveolar macrophages demonstrated increased glucose utilization in smokers.

In pertinent studies, macrophage function has been measured by several methods. Green and Carolin (*34*), using an *in vitro* system to

measure phagocytosis, showed that added cigarette smoke had a depressant effect on the phagocytic activity of alveolar macrophages for *Staphylococcus albus*. The studies by Maxwell, et al. (*69*) on lung macrophages from guinea pigs exposed to tobacco prior to cell harvest showed that, although these alveolar cells phagocytosed bacteria at normal rates, their capacity for bacterial inactivation was impaired.

Laurenzi, et al. (*61*) demonstrated a 50 percent reduction in clearance of staphylococci from the lungs of smoke-exposed mice. In two human studies (*22, 44*) which measured phagocytic properties of alveolar macrophages, no significant differences were found between smokers and nonsmokers. Other studies of *in vitro* function of macrophages after *in vivo* exposure to smoke (employing rat alveolar macrophages) revealed no impairment of bactericidal inactivation of *S. albus* (*49*).

In the studies of Warr and Martin (*119, 120*), macrophages of smokers demonstrated an impaired response to an immune effector, MIF, paralleling those situations characterized by the absence of cell-mediated delayed hypersensitivity as well as acquired resistance to aggregate under *in vitro* conditions.

Though more work is needed to define the total qualitative and quantitative influences of tobacco smoking on alveolar macrophages, there is sufficient evidence in these studies to indicate measurable degrees of physiological impairment. Since interference with phagocytosis, endocytosis, and antigen processing can be anticipated as a consequence, there is the potential diminution of specific immune functions by these cells. In turn, the impairment of local immune processes as the first line of host defense exerts its toll on the dependent development of systemic immunity and influences emerging allergic inflammation.

The B and T lymphocytes are involved respectively in the humoral and cell-mediated arms of the immune system that functions both locally and systemically. It is therefore pertinent to examine the effect of smoking on these elements that provide the immunologic basis of hypersensitivity.

Of the immunoglobulins, secretory IgA is known to be predominant in bronchial mucus (*29*) (although the IgG/IgA ratio is increased in smokers (*90*)) and presumably plays a role in first-line defense against microbial invasion. Soutar's (*101*) studies on the distribution of plasma and other immunoglobulin-containing cells in the respiratory tract indicated more IgA-containing cells then those of other immunoglobulin classes. However, the only differential finding between smokers and nonsmokers was localized to the lobar bronchi of smokers where significant increases in IgA-containing cells were identified. Smoking was found to have significant suppressive action on salivary secretory IgA levels in normals, but not in patients with chronic diseases whose IgA levels were already elevated above normal (*63*). While these

studies show alterations in the expressions of local humoral immunity, the clinical significance of these changes is unknown.

Investigations have also been done to determine the effect of smoking on systemic humoral immunity. An assay which reflects antibody production is the plaque-forming cell (PFC) response. Thomas, et al. (*108*) examined PFC responses in samples of immunocompetent lung cells from mice exposed to fresh cigarette smoke and found progressive impairment of these responses over the exposure period of up to 10 months. In the studies of Holt, Keast, Nulsen, and Thomas (*76,106,108,109,110*) concerning the long-term effects of smoking on mice, PFC responses to intratracheally or intraperitoneally introduced antigens were shown to be initially enhanced and then depressed by chronic smoking (*108,109*). The direct measurement of serum hemolytic and hemagglutinating antibodies also showed depression, but the humoral response to a T cell-independent immunogen was unaffected (*109*). The secondary PFC response reflecting another aspect of humoral immunity was unaffected by smoking (*109*). PFC response depression was found to be reversible in a group when smoking was discontinued for 16 weeks (*110*). Other measurements of humoral immunity in mouse models exposed to tobacco also demonstrated impairment of the production of hemagglutinating antibodies, including those raised in response to the influenza virus (*66*), although some degree of suppression was reversible (*28*). Tar content of cigarettes may also play an important role (*46*).

Roszman, et al. (*93, 94, 95*), investigating several aspects of smoking and immunity in rabbits, found suppression of mitogen-induced blastogenesis and suppression of the immunoglobulin M and G antibody responses which correlated directly with the concentration either of nicotine or of the water-soluble fraction from cigarette smoke that was added to cultures.

Several surveys have attempted to address the issue of whether smoking influences serum immunoglobulin levels. Vos-Brat and Ruemke (*116*) found significant depression of IgG in smokers, Kosmider, et al. (*59*) also found a decreased IgG but increased IgM and IgA, while Wingerd and Sponzilli (*127*) found a decrease in the entire gamma globulin fraction. A decrease in lymphocytotoxic antibodies among smokers has also been demonstrated in pregnant women (*77*). On the other hand, no reported differences in mean concentrations of immunoglobulins were found when smokers were compared to nonsmokers by geographic location (*71*).

While these reports suggest that humoral antibody responses are influenced by cigarette smoke in a variety of ways, critical to this issue is a consideration of possible biologic impact in humans. Whether susceptibility to infection may be the end result of smoking effects on constituent elements of the immune system should be addressed. Thus, especially pertinent are the influenza vaccination studies of Waldman,

et al. (*117*), indicating that smoking more than one-half pack of cigarettes per day increased the risk of influenza-like illness, although the duration of the illness was unaltered. Finklea and associates (*32*) showed that the incidence of clinical influenza was 21 percent higher among smokers than nonsmokers. Serological data from this study suggested that smokers also had more frequent subclinical influenza. In pursuing this observation, Finklea, et al. (*31*) showed that, while serologic response to vaccination did not significantly differ between smokers and nonsmokers, the persistence of antibody titers after either natural infection or vaccination with A_2 antigens was significantly decreased among smokers. Nymand (*77*), examining histories of pregnant women, found that urinary tract infections and viral illness were observed more often in smokers than nonsmokers.

That elements indicative of immune function appear in the lung is evidenced by the identification of both T and B cells in fluid samples recovered from this site (*121*). Of interest is the finding of both an increased number of T and B cells and an increase in the T/B ratio in smokers.

Several aspects of cell-mediated immunity have been studied in animal models, including the ability of immunocompetent lymphocytes to proliferate after mitogenic stimulation by phytohemagglutin (PHA), pokeweed (PW), and Concanavalin A (Con-A). In mice, initial increases of PHA responses in blood and regional lymph node lymphocytes were found after brief exposure to cigarette smoke, but decreases were found after prolonged exposure (*107*). Another study (*18*) demonstrated inhibition of proliferation of mouse lymphocytes to both PHA and pokeweed mitogen by an aqueous fraction of tobacco. In the rabbit (*94*), both nicotine and water-soluble fractions from whole cigarette smoke diminished peripheral lymphocyte blastogenic response to lectin stimulation.

Because of variation in methodology, data from human studies are difficult to compare. While increased numbers of T cells in peripheral blood lymphocytes and enhanced PHA response were noted among younger smokers, responses of older smokers or of those with a history of heavier cigarette consumption did not differ from normals (*100*). In examining peripheral bloods, Suciu-Foca, et al. (*103*) found no differences in percent of T lymphocytes, PHA responses, or behavior in mixed lymphocyte cultures between smokers and nonsmokers. In another study (*125*), samples of blood taken from humans after smoking showed no differences in PHA responses even when physiologic levels of nicotine were added directly to the cultures. In contrast, Neher (*74*) found decreased DNA synthesis in response to PHA in the presence of nicotine. Desplaces, et al. (*27*) showed that smoke inhibited lymphocyte transformation by PHA yet stimulated lymphocytes in the absence of PHA. The clinical significance of this single aspect of T-cell function has yet to be determined.

Effects on other cellular elements of the immune system have also been described. Vos-Brat and Ruemke (*116*) and Silverman, et al. (*100*) demonstrated increased granular leukocytic levels in smokers. Others (*54,79,98,129*) have shown that smokers have hypereosinophilia. In two studies (*79,98*) the hypereosinophilia was reversible with abstinence from smoking. Similar lymphocytic and eosinophilic increases among smokers have been noted in patients' post-myocardial infarctions (*129*).

Serum abnormalities also have been described in smokers, including increased C-reactive (*45*) protein and an abnormal seroflocculant in smokers. Effects of smoking on manifestations of immune hyperresponsiveness add further evidence to the purported suppressive action of tobacco. Of interest are the reports of diminution of amyloid formation in the hamster model (*123*) and the inexplicable increase in survival of cardiac transplants in patients who resumed smoking postoperatively (*35*).

Target Organs of the Allergic Response

Despite the limitations, as previously noted, in appropriate materials and methods to define any possible effects of tobacco and smoking on allergic people, studies dealing with their roles in affecting various organs are noteworthy. A variety of clinical conditions have been ascribed to allergic manifestations to tobacco leaf or smoke, including asthma, rhinitis, hives, dermatitis, migraine headaches, cardiac and other vascular disturbances, as well as gastrointestinal disorders. The respiratory system has been the most widely studied.

Allergic rhinitis, typified by hay fever due to seasonal pollens and molds, is caused by exposure to a wide range of ubiquitous allergens. Apart from investigations of tobacco workers, there are no available studies to date to suggest that tobacco smoke or tobacco allergens are in fact a cause of allergic rhinitis in the general population. Many studies, however, have been reported showing that rhinitis patients suffer exacerbation of symptoms upon exposure to smoke. Speer (*102*) reported that 67 percent of allergic persons noted aggravation of nasal symptoms upon exposure to smoke, compared to 29 percent of nonallergic persons similiarly exposed. Broder, et al. (*11*) found that most symptoms of allergic rhinitis could be attributed to other definable allergens with smoking or smoke exposure playing only a minor role. Allergic rhinitis believed to be related specifically to hypersensitivity to tobacco leaf products was reported to occur in 14.6 percent of 355 tobacco plantation workers and 8.7 percent of 722 tobacco factory workers (*114*).

Another study (*86*) among tobacco workers demonstrated that allergic rhinitis thought to be related to tobacco leaf occurred in approximately 4 percent of cases. However, possible contamination of

tobacco by molds or other allergens or irritants was not excluded in these studies.

It is relevant to note that symptoms of nasal congestion and excess mucous gland secretion, which may mimic those of allergic rhinitis or hay fever, can be caused by the nonspecific irritant or pharmacologic effects of vapor from the constituents of tobacco smoke. Thus, although it is not known whether allergy to tobacco or tobacco smoke plays a primary etiologic role in the usual case of allergic rhinitis, tobacco smoke per se is known to aggravate this condition via an irritant effect.

It is well known (*102*) that eye irritation manifested by itching, burning, swelling, and lacrimation occurs commonly among both allergic nonsmokers and nonallergic nonsmokers. To date, no studies are available suggesting that this manifestation is due to anything other than the nonspecific irritating effect of cigarette smoke.

Many studies have attempted to assess the relation between tobacco or smoking and asthma. Early investigators, using a variety of skin test materials (*64, 91*), inferred that allergy to tobacco could be causally related to asthma. Subsequent reports have examined the possible role of passive smoking in asthma. Speer (*102*) found that wheezing occurred more frequently in allergic people than in nonallergic people upon exposure to smoke. O'Connell and Logan (*78*), in studying the effects of parental smoking, found that smoke aggravated attacks of asthma in 26 percent of asthmatic children of nonsmoking parents, in contrast to 67 percent of asthmatic children of smoking parents. Importantly, they assessed the effects upon asthmatic children whose parents stopped smoking and reported improvement in 18 of 20 children. In contrast, only 4 of 15 asthmatic children improved when parents continued to smoke. Cameron and coworkers (*15*) concluded that asthmatic children of smoking parents were more often ill with respiratory disease but that this was related to nonspecific irritation rather than hypersensitivity. On the other hand, Rosen and Levy (*92*) published a case report of an infant who developed bronchial asthma associated with exposure to smoke. In this study, reaginic antibody to tobacco extract was documented by passive cutaneous transfer. More conclusive studies that tobacco may be causally related to asthma are reported among tobacco workers. Among 286 persons exposed to raw or fermented tobacco, the incidence of allergic manifestations was 8 percent, of which 17 percent had asthma (*86*). The possible role of tobacco additives has also been considered. Burge, et al. (*13*) reported the occurrence of occupationally-related asthma in a group of 21 industrial workers where colophony or pine resin, a substance also present in cigarettes as adhesives and filter fillings, was implicated.

The consequences of cigarette smoking in the asthmatic patient have also been examined. Townley and coworkers (*112*) reported similar

bronchial airway responses to lung function tests by methacholine inhalation in both smoking and nonsmoking asthmatics. Pimm and associates also reported that passive exposure of asthmatics to cigarette smoke resulted in no consistent significant effect on lung volumes and expiratory flow rates when compared with parallel room air exposure (*84*). On the other hand, Burrows, et al. (*14*), in a study of smoking and tests of lung function, found that an allergic predisposition, asthma or allergic rhinitis, as defined by positive skin reactivity, were associated with an increased susceptibility to bronchoconstrictor effects of cigarette smoking and to recurrent chest infections. That smoking can adversely effect an asthmatic patient in an indirect manner is illustrated by the finding of Powell, et al. (*87*) demonstrating interference with normal metabolism of the bronchodilator agent, theophylline, in smokers.

The concept that hyperreactive airways in asthmatics are due to a regulatory dysfunction of the autonomic nervous system is pertinent to this discussion (*30*). In addition to the effects of specific allergens inducing responsible mediators of bronchoconstriction, it is appreciated that nonspecific irritants (for example odors, temperature extremes, exercise, chemicals) can also act upon the affected cell receptors to precipitate asthmatic attacks.

Thus, apart from any putative allergenic effects of tobacco in a specifically sensitized patient, inhaled tobacco smoke carries the irritant potential to trigger or to aggravate asthmatic symptoms in the patient so affected. Hence, there is further support offered for both cessation of smoking and the following of avoidance procedures of passive exposure in the asthmatic individual.

Allergic effects of tobacco on the cardiovascular system have also received considerable attention. It is well documented that cardiac abnormalities occur in association with allergic phenomena, for example, anaphylaxis or allergic shock (*5*, *25*, *73*). However, whether tobacco may play a role in cardiovascular alterations apart from known pharmacologic effects is still not clear. Harkavy's series of observations (*36*, *37*, *38*, *39*, *40*, *42*, *43*) would support the concept that allergy to tobacco leaf may have important implications in a variety of cardiac and vascular diseases. In these he would include cardiac arrythmias, intensification of coronary artery insufficiency, thromboangiitis obliterans, migrating phlebitis, and some forms of allergic vasculitis. Although acknowledging the pharmacologic effects of nicotine on the cardiovascular system, Harkavy also suggests that it may act as a hapten in inducing allergic responses. Recent observations by Becker and coworkers (*10*), using a partially characterized antigenic component of tobacco, led them to hypothesize that circulating tobacco antigens in sensitive individuals might react with corresponding antibody to produce focal injury of blood vessels. If this hypothesis is corroborated, design of further studies of potential adverse conse-

quences of possible tobacco allergy on the cardiovascular system will be possible.

That tobacco may operate through the mechanism of cell-mediated immunity or delayed hypersensitivity is suggested by case reports of contact dermatitis caused by tobacco smoke and tobacco smoke residue (*19, 24, 122*). Recent surveys among tobacco workers have shown that contact dermatitis related to tobacco was responsible for 14 percent of skin eruptions occurring in this industrial sample (*3*). By contrast, however, an earlier survey (*96*) could not implicate tobacco as a cause of dermatitis among cigar factory workers. It has been pointed out that dermatitis among tobacco workers probably represents a nonspecific response due to injury, moisture, or irritants, especially those from the chemicals or other fertilizers used in the growing process (*122*). To date, therefore, there is little evidence that allergic skin manifestations due to tobacco occur with any significant frequency.

Summary

1. Tobacco and tobacco smoke extracts have been found to act as antigens inducing both precipitating and reaginic antibodies in experimental animals. Tobacco leaf products can also sensitize lymphocytes participating in cell-mediated immune functions.

2. Tobacco and its combustion products are known to be heterogeneous mixtures of particulate and gasous materials. Additionally, natural contaminants and intentional additives increase the array of components, presenting a complex of toxic, pharmacologic, irritant, and inflammatory effects that can complicate interpretation of a precisely defined role for tobacco in immune and allergic processes.

3. Several tobacco antigens have been isolated by chemical procedures. Of special interest is a glycoprotein common to both tobacco extracts and smoke antigenically corresponding with reaginic antibody in humans.

4. Epidemiologic samplings to define the presence of true allergy to tobacco, either among healthy persons or among those suffering from known allergic conditions, are inconclusive.

5. Tobacco smoking exerts a variety of effects on respiratory tract structures involved in local host defense, and chronic smoking leads to consistent histological changes in the respiratory tract.

(a) There is evidence to indicate an adverse effect of long-term smoking on the mucociliary transport mechanisms and mucus composition.

(b) The number of macrophages isolated from lung fluids of smokers is increased over nonsmokers.

(c) Changes in the ultrastructure of macrophages—most notably the presence of cytoplasmic inclusions—are found in smokers.

(d) Alveolar macrophages from smokers have altered metabolism and measurable degrees of physiologic impairment.

6. Alterations of indicators of humoral immunity have been demonstrated in the respiratory tracts of smokers, and smoking may impair systemic humoral immunity both *in vitro* and *in vivo*.

7. Alterations in assays of cell-mediated immunity are noted locally and systemically in smokers.

8. Leukocytosis and reversible hypereosinophilia have been seen in smokers.

9. The ability to make a definitive diagnosis of tobacco allergy is complicated by the difficulty of demonstrating a cause and effect relationship between immunologic events and disease manifestations; additional evidence is required to establish whether there is a definitive role for tobacco smoke sensitization in causing allergic diseases.

10. Studies concerned with the adverse consequences of either active or passive smoking have shown that allergic individuals, especially those with rhinitis or asthma, may, in fact, be more sensitive to the nonspecific noxious effects of cigarette smoke than healthy individuals.

Conclusion and Comment

Apart from symptom-relieving drugs, there are no known effective therapeutic measures to prevent or combat the adverse effects of smoking on immune function and on allergy-related problems. It is evident that further studies defining tobacco antigens, determining the clinical incidence of tobacco allergy, further clarifying the nature of immune responses to tobacco, and improving the diagnostic agents and materials should be undertaken. Such studies, however, can not be expected to have an impact on improving the health of individuals subject to tobacco's adverse effects comparable to that which would result from adhering to the mainstay of management of the allergic patient—complete avoidance of the incriminated substance.

Allergy and Immunity: References

(1) ALBERT, R.E., BERGER, J., SANBORN, K., LIPPMANN, M. Effects of cigarette smoke components on bronchial clearance in the donkey. Archives of Environmental Health 29: 96-101, August 1974.

(2) ALBERT, R.E., LIPPMANN, M. BRISCOE, W. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. Archives of Environmental Health 18: 738-755, May 1969.

(3) ANDREICHUK, I.E. K voprosu o tabochnom dermatite (On tobacco dermatitis). Vestnik Dermatologii I Venerologii (4): 57-59, 1975.

(4) ARMEN, R.N., COHEN, S.G. The effect of forced inhalation of tobacco smoke on the electrocardiogram of normal and tobacco-sensitized rabbits. Diseases of the Chest 35: 663-676, June 1959.

(5) AUER, J., ROBINSON, G.C. An electrocardiographic study of the anaphylactic rabbit. Journal of Experimental Medicine 18: 450-460, 1931.

(6) BAIR, W.J., DILLEY, J.V. Pulmonary clearance of $^{59}Fe_2O_3$ and $^{51}Cr_2O_3$ in rats and dogs exposed to cigarette smoke. In: Davies, C.N. (Editor). Inhaled Particles and Vapours II. New York, Pergamon Press, 1967, pp. 251-268.

(7) BALLENGER, J.J. Experimental effect of cigarette smoke on human respiratory cilia. New England Journal of Medicine 263(17): 832-835, October 27, 1960.

(8) BARKIN, G.D., MCGOVERN, J.P. What the classroom teacher can do for the asthmatic child. National Education Association Journal 56(8): 40-41, November 1967.

(9) BECKER, C.G., DUBIN, T. Activation of factor XII by tobacco glycoprotein. Journal of Experimental Medicine 146: 457-467, 1977.

(10) BECKER, C.G., DUBIN, T., WIEDEMANN, H.P. Hypersensitivity to tobacco antigen. Proceedings of the National Academy of Sciences 73(5): 1712-1716, May 1976.

(11) BRODER I., HIGGINS M.W., MATHEWS K.P., KELLER J.B. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan, III. Second Survey of the Community. Journal of Allergy and Clinical Immunology 53(3): 127-138, March 1974.

(12) BROWN, A. Present day treatment of asthma. New York Medical Journal and Medical Review 98(6): 333-336, September 19, 1923.

(13) BURGE, P.S., HARRIES, M.G., O'BRIEN, I.M., PEPYS, J. Respiratory disease in workers exposed to solder flux fumes containing colophony (pine resin). Clinical Allergy 8: 1-14, 1978.

(14) BURROWS, B., LEBOWITZ, M.D., BARBEE, R.A. Respiratory disorders and allergy skin-test reactions. Annals of Internal Medicine 84(2): 134-139 1976.

(15) CAMERON, P., KOSTIN, J.S., ZAKS, J.M., WOLFE, J.H., TIGHE, G., OSELETT, B., STOCKER, R., WINTON, J. The health of smokers' and nonsmokers' children. Journal of Allergy 43(6): 336-341, June 1969.

(16) CAMNER, P., PHILIPSON, K. Tracheobronchial clearance in smoking-discordant twins. Archives of Environmental Health 25: 60-63, July 1972.

(17) CAMNER, P., PHILIPSON, K., ARVIDSSON, T. Cigarette smoking in man. Short-term effect on mucociliary transport. Archives of Environmental Health 23: 421-426, December 1971.

(18) CARLENS, E. Smoking and the immune response in the airpassages. Broncho-Pneumologie 26(4): 322-323, July/August 1976.

(19) CHANIAL, G., JOSEPH, J., COLIN, L., DUCLAUX, C. Les dermites chez les travailleurs du tabac (a propos de 9 observations) (Cases of Dermatitis in tobacco workers [reference to nine observations]). Bulletin de la Societe Francaise de Dermatologie et de Syphiligraphie 77(2): 281-283, July 1970.

(20) CHOBOT, R. The significance of tobacco reactions in allergic children. Journal of Allergy 6: 383-386, 1934.

(21) CHU, Y.M., PARLETT, R.C., WRIGHT, G.L., JR. A preliminary investigation of some immunologic aspects of tobacco use. American Review of Respiratory Disease 102(1): 118-123, 1970.

(22) COHEN, A.B., CLINE, M.J. The human alveolar macrophage: Isolation, cultivation in vitro, and studies of morphologic and functional characteristics. Journal of Clinical Investigation 50(7): 1390-1398, July 1971.

(22a) COLLEY, J.R.T., HOLLAND, W.W., CORKHILL, R.T. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. Lancet:1031-1034, November 2, 1974.

(23) COOMBS, R.R.A., GELL, P.G.H., Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell, P.G.H., Coombs, R.R.A. (Editors). Clinical Aspects of Immunology. Oxford, Blackwell Scientific Publications, 1963, pp. 575-596.

(24) CORMIA, F.E., DE GARA, P.F. Vesiculobullous dermatitis from tobacco smoke. Journal of the American Medical Association 193(5): 141-142, August 2, 1965.

(25) CRIEP, L.H. Electrocardiographic studies on the effect of anaphylaxis on the cardiac mechanism. Archives of Internal Medicine 48(6): 1098-1109, 1931.

(26) DALHAMN, T. Studies on tracheal ciliary activity. American Review of Respiratory Diseases 89(6): 870-877, 1964.

(27) DESPLACES, A., CHARREIRE, J., IZARD, C. Action de la phase gazeuse de fumee de cigarette sur la transformation lymphoblastique du petit lymphocyte humain (observations preliminaires) (Smoke inhibition of lymphocytes transformation by PHA but stimulation of lymphocytes in the absence of PHA [preliminary observations]). Revue European Etudes Clinque et Biologique 16: 822-826, 1971.

(28) ESBER, H.J., MENNINGER, F.F., JR., BOGDEN, A.E., MASON, M.M. Immunological deficiency associated with cigarette smoke inhalation by mice. Primary and secondary hemagglutinin response. Archives of Environmental Health 27(2): 99-104, August 1973.

(29) FALK, G.A., OKINAKA, A.J., SISKIND, G.W. Immunoglobulins in the bronchial washings of patients with chronic obstructive pulmonary disease. American Review of Respiratory Disease 105: 14-21, 1972.

(30) FARR, R.S. Asthma in adults: The ambulatory patient. Hospital Practice: 113-123, April 1978.

(31) FINKLEA, J.F., HASSELBLAD, V., RIGGAN, W.B., NELSON, W.C. HAMMER, D.I., NEWILL, V.A. Cigarette smoking and hemagglutination inhibition response to influenza after natural disease and immunization. American Review of Respiratory Disease 104(3): 368-376, September 1971.

(32) FINKLEA, J.F., SANDIFER, S.H., SMITH, D.D. Cigarette smoking and epidemic influenza. American Journal of Epidemiology 90(1): 390-399, 1969.

(33) FONTANA, V.J., REDISCH, W., NEMIR, R.L., SMITH, M.K., DECRINIS, K., SULZBERGER, M.B. Studies in tobacco hypersensitivity. III. Reactions to skin tests and peripheral vascular responses. Journal of Allergy 30(3): 241-249, May/June 1959.

(34) GREEN, G.M., CAROLIN, D. The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. New England Journal of Medicine 276(8): 422-427, February 23, 1967.

(35) GRIEPP, R.B., STINSON, E.B., BIEBER, C.P., REITZ, B.A., COPELAND, J.G., OYER, P.E., SHUMWAY, N.E. Control of graft arteriosclerosis in human heart transplant recipients. Surgery 81(3): 262-269, March 1977.

(36) HARKAVY, J. Cardiac manifestations due to hypersensitivity. Annals of Allergy 28(6): 242-251, June 1970.

(37) HARKAVY, J. Cardiovascular manifestations due to hypersensitivity. New York State Journal of Medicine 69(21): 2757-2765, November 1, 1969.

(38) HARKAVY, J. Hypersensitiveness to tobacco and biopsy studies of skin reactions in vascular disease. Journal of Allergy 9: 475-488, 1938.

(39) HARKAVY, J. Tobacco sensitiveness in angina pectoris and coronary artery disease. Proceedings of the Society for Experimental Biology and Medicine 30(104): 683-684, 1932.

(40) HARKAVY, J. Tobacco sensitiveness in thromboangiitis obliterans, migrating phlebitis and coronary artery disease. Bulletin of the New York Academy of Medicine 9: 318-322, 1933. (Abstract)

(41) HARKAVY, J. Tobacco sensitization in rats. Proceedings of the Society for Experimental Biology and Medicine 36(3): 381-383, April 1937.

(42) HARKAVY, J. Tobacco skin reactions and their clinical significance. Journal of Investigative Dermatology 2: 257-279, 1939.

(43) HARKAVY, J., WITEBSKY, E. Studies of specificity in multiple hypersensitiveness by quantitative titration and absorption of reagins. Journal of Allergy 6: 437-447, 1935.

(43a) HARLAP, S., DAVIES, A.M. Infant admissions to hospital and maternal smoking. Lancet :529-532, March 30, 1974.

(44) HARRIS, J.O., SWENSON, E.W., JOHNSON, J.E., III. Human alveolar macrophages: Comparison of phagocytic ability, glucose utilization, and ultrastructure in smokers and nonsmokers. Journal of Clinical Investigation 49: 2086-2096, 1970.

(45) HEISKELL, C.L., MILLER, J.N., ALDRICH, H.J., CARPENTER, C.M. Smoking and serologic abnormalities. Journal of the American Medical Association 181(8): 674-677, August 25, 1962.

(46) HOLT, P.G., CHALMER, J.E., ROBERTS, L.M., PAPADIMITRIOU, J.M., THOMAS, W.R., KEAST, D. Low-tar and high-tar cigarettes. Comparison of effects in two strains of mice. Archives of Environmental Health 31(5): 258-265, September/October 1976.

(47) HOLT, P.G., KEAST, D. Acute effects of cigarette smoke on murine macrophages. Archives of Environmental Health 26(6): 300-304, June 1973.

(48) HOSEN, H. Letter to the editor. Tobacco Sensitivity. Annals of Allergy 29(11): 608-610, November 1971.

(49) HUBER, G.L., SHEA, J. Does tobacco smoke impair alveolar macrophage function. Chest 70(3): 429, September 1971. (Abstract)

(50) IRAVANI, J. Effects of cigarette smoke on the ciliated respiratory epithelium of rats. Respiration 29: 480-487, 1972.

(51) ISHIZAKA, K., ISHIZAKA, T. Identification of γE-antibodies as a carrier of reaginic activity. Journal of Immunology 99(6): 1187-1198, 1967.

(52) ISHIZAKA, T., ISHIZAKA, K., ORANGE, R.P., AUSTEN, K.F. The capacity of human immunoglobulin E to mediate the release of histamine and slow reacting substance of anaphylaxis (SRS-A) from monkey lung. Journal of Immunology 104(2): 335-343, 1970.

(53) JUSTUS, D.E., ADAMS, D.A. Evaluation of tobacco hypersensitivity responses in the mouse. A potential animal model for critical study of tobacco allergy. International Archives of Allergy and Applied Immunology 51(6): 687-695, 1976.

(54) KAMESWARAN, L., KANAKAMBAL, K., VIJAYASEKARAN, V. Studies on plasma histaminase levels in normal and allergic individuals. Indian Journal of Physiology and Pharmacology 12(4): 159-165, October 1968.

(55) KAMINSKI, E.J., FANCHER, O.E., CALANDRA, J.C. In vivo studies of the ciliastatic effects of tobacco smoke. Archives of Environmental Health 16: 188-193, February 1968.

(56) KASEMIR, H., KERP, L. Gesamteinwirkungen von luftverunreinigungen auf den menschen aus der sicht der immunologie (Total effects of air pollution on man from an immunological viewpoint). Praxis Der Pneumologie 28(special issue): 776-780, December 1974.

(57) KEAST, D., HOLT, P. Smoking and the immune response. New Scientist 61(891): 806-807, March 28, 1974.

(58) KOLLERSTROM, N., LORD, P.W., WHIMSTER, W.F. A difference in the composition of bronchial mucus between smokers and non-smokers. Thorax 32(2): 155-159, 1977.

(59) KOSMIDER, S., FELUS, E., WYSOCKI, J. Ocena niektorych wyznacznikow odpornosci humoralnej palaczy papierosow (Evaluation of some humoral resistance determinants in smokers). Polski Tygodnik Lekarski 28(2): 47-50, January 8, 1973.

(60) KREIS, B., PELTIER, A., FOURNAUD, S., DUPIN-GIROD, S. Reaction de precipitation entre certains serums humains et des extraits solubles de tabac (Precipitation reaction between some human serums and soluble tobacco extracts). Annales de Medecine Interne 121(4): 437-440, April 1970.

(61) LAURENZI, G.A., GUARNERI, J.J., ENDRIGA, R.B., CAREY, J.P. Clearance of bacteria by the lower respiratory tract. Science 142: 1572-1573, 1963.

(62) LEHRER, S., WILSON, M., SALVAGGIO, J.E. Immunogenic properties of tobacco smoke. Journal of Allergy and Clinical Immunology 62: 368-370, 1978.

(63) LEWIS, D.M., LAPP, N. LeR., BURRELL, R. Quantitation of secretory immunoglobulin A in chronic pulmonary disease. American Review of Respiratory Disease 101(1): 55-61, January 1970.

(64) LIMA, A.O., ROCHA, G. Cutaneous reactions to tobacco antigen in allergic and nonallergic children. Annals of Allergy 7(4): 528-531, July/August 1949.

(65) LOURENCO, R.V., KLIMEK, M.F., BOROWSKI, C.J. Deposition and clearance of 2 μ particles in the tracheobronchial tree of normal subjects—smokers and nonsmokers. Journal of Clinical Investigation 50: 1411-1420, 1971.

(66) MACKENZIE, J.S. The effect of cigarette smoke on influenza virus infection: A murine model system. Life Sciences 19(3): 409-412, August 1, 1976.

(67) MARTIN, R.R. Altered morphology and increased acid hydrolase content of pulmonary macrophages from cigarette smokers. American Review of Respiratory Disease 107: 596-601, 1973.

(68) MATSUSHITA, H., NOGUCHI, M., TAMAKI, E. Conjugate of bovine serum albumin with nicotine. Biochemical and Biophysical Research Communications 57(4): 1006-1010, 1974.

(69) MAXWELL, K.W., MARCUS, S., RENZETTI, A.D., JR. Effect of tobacco smoke on the phagocytic and cytopeptic activity of guinea pig alveolar macrophages. American Review of Respiratory Disease 96(1): 156, 1967.

(70) MCGOVERN, J.P., PEIRCE, K.E., LEE R.E., JR. The allergic child and his challenge to the school. Clinical Pediatrics 10(11): 636-644, November 1971.

(71) MELOY LABORATORIES, INC. Air pollution exposure and immunoglobulin levels. Springfield, Virginia, Meloy Laboratories, Inc., Biological Products Division, March 1974, pp. 1-15.

(72) MEYER, D.H., CROSS, C.E., IBRAHIM, A.B., MUSTAFA, M.G. Nicotine effects on alveolar macrophage respiration and adenosine triphosphatase activity. Archives of Environmental Health 22(3): 362-365, March 1971.

(73) MIKULICICH, G. Electrocardiographic changes in experimental anaphylactic reactions. Journal of Allergy 22(3): 249-263, May 1951.

(74) NEHER, G.H. Nicotine-induced depression of lymphocyte growth. Toxicology and Applied Pharmacology 27(2): 253-258, February 1974.

(75) NORMAN, V. An overview of the vapor phase, semivolatile and nonvolatile components of cigarette smoke. In: Recent Advances in Tobacco Science. Volume 3. Tobacco Smoke: Its Formation and Composition. Thirty-first Tobacco Chemists Research Conference. Greensboro, North Carolina, October, 5-7, 1977, pp. 27-58.

(75a) NORMAN-TAYLOR, W., DICKINSON, V.A. Dangers for children in smoking families. Community Medicine: 32-33, April 21, 1972.

(76) NULSEN, A., HOLT, P.G., KEAST, D. Cigarette smoking, air pollution, and immunity: A model system. Infection and Immunity 10(6): 1226-1229, December 1974.

(77) NYMAND, G. Maternal smoking and immunity. Lancet 2(7893): 1379-1380, December 7, 1974. (Letter)

(78) O'CONNELL, E.J., LOGAN, G.B. Parental smoking in childhood asthma. Annals of Allergy 32: 142-145, March 1974.

(79) PAINTAL, I.S., MININA, R.J. Tobacco smoking—a probable cause of eosinophilia. Indian Practitioner 28(5): 243-245, May 1975.

(80) PANAYOTOPOULOS, S., GOTSIS, N., PAPAZOGLOU, N., CONCOURIS, L. Antigenic study of nicotiana tabacum and research on precipitins against tobacco antigens in the serum of smokers and nonsmokers. Allergologia et Immunopathologia 2(1): 111-114, January/February 1974.

(81) PATON, W.D.M. The mechanism of histamine release. In: Wolstenholme, G.E.W., O'Connor, C.M. (Editors). Histamine. Boston, Little, Brown and Co., 1956, pp. 59-73.

(82) PAVIA, D., SHORT, M.D., THOMSON, M.L. No demonstrable long term effects of cigarette smoking on the mucociliary mechanisms of the human lung. Nature 226: 1228-1231, June 27, 1970.

(83) PESHKIN, M.M., LANDAY, L.H. Cutaneous reactions to tobacco antigen in allergic and nonallergic children with the direct and indirect (local passive transfer) methods of testing. Journal of Allergy 10: 241-245, 1939.

(84) PIMM, P., SHEPHARD, R.J., SILVERMAN, F. Physiological effects of acute passive exposure to cigarette smoke in asthmatics. Proceedings of the Federation of American Societies for Experimental Biology, 61st Annual Meeting, Chicago, Illinois, April 1-8, 1977, 36: 606, 1977. (Abstract)

(85) PIPES, D.M. Allergy to tobacco smoke. Annals of Allergy 28(3): 277-282, July/August 1945.

(86) POPESCU, I. GR., PAUN, R., MOLNER, C., OLARU, C., GHEORGHIU, T., IOTA, C.G. Contributions to the study of tobacco allergy. Revue Roumaine de Medecine Interna 1(5): 427-436, 1964.

(87) POWELL, J.R., THIERCELIN, J.-F., VOZEH, S., SANSOM, L., RIEGELMAN, S. The influence of cigarette smoking and sex on theophylline disposition. American Review of Respiratory Disease 116: 17-23, 1977.

(88) PRATT, S.A., FINLEY, T.N., SMITH, M.H., LADMAN, A.J. A comparison of alveolar macrophages and pulmonary surfactant (?) obtained from the lungs of human smokers and nonsmokers by endobronchial lavage. Anatomical Record 163: 497-508, 1969.

(89) REGLAND, B., CAJANDER, S., WIMAN, L.-G., FALKMER, S. Scanning electron microscopy of the bronchial mucosa in some lung diseases using bronchoscopy specimens. Scandinavian Journal of Respiratory Diseases 57: 171-182, 1976.

(90) REYNOLDS, H.Y., NEWBALL, H.H. Analysis of proteins and respiratory cells obtained from human lungs by bronchial lavage. Journal of Laboratory and Clinical Medicine 84(4): 559-573, October 1974.

(91) ROSEN, F.L. Studies in tobacco allergy. Journal of the Medical Society of New Jersey 51(3): 109-114, March 1954.

(92) ROSEN, F.L., LEVY, A. Bronchial asthma due to allergy to tobacco smoke in an infant. Journal of the American Medical Association 144: 620-621, 1950.

(93) ROSZMAN, T.L. Effect of nicotine and water soluble condensate from whole smoke in the *in vitro* secondary antibody response. Proceedings of the University of Kentucky Tobacco and Health Research Institute, Tobacco and Health Workshop Conference, Lexington, Kentucky, March 26-28, 1973, pp. 530-541.

(94) ROSZMAN, T.L., ELLIOTT, L.H., ROGERS, A.S. Suppression of lymphocyte function by products derived from cigarette smoke. American Review of Respiratory Disease 111(4): 453-457, 1975.

(95) ROSZMAN, T.L., ROGERS, A.S. The immunosuppressive potential of products derived from cigarette smoke. American Review of Respiratory Disease 108(5): 1158-1163, November 1973.

(96) SAMITZ, M.H., MORI, P., LONG, C.-F. Dermatological hazards in the cigar industry. Industrial Medicine and Surgery 18(10): 434-439, October 1949.

(97) SCHACHTER, J., Allergy Statistics: Allergic Conditions in the United States. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Institute of Allergy and Infectious Diseases, DHEW Publication No. (NIH) 75-757, 1975, 2 pp.

(98) SCHOEN, I., PIZER, M. Eosinophilia apparently related to cigarette smoking. New England Journal of Medicine 270(25): 1344-1347, June 18, 1964.

(99) SELYE, H. The Mast Cells. Washington, Butterworths, 1965, pp. 132-216.

(100) SILVERMAN, N.A., POTVIN, C., ALEXANDER, J.C., JR., CHRETIEN, P.B. *In vitro*lymphocyte reactivity and T-cell levels in chronic cigarette smokers. Clinical and Experimental Immunology 22(2): 285-292, November 1975.

(101) SOUTAR, C.A. Distribution of plasma cells and other cells containing immunoglobulin in the respiratory tract of normal man and class of immunoglobulin contained therein. Thorax 31(2): 158-166, April 1976.

(102) SPEER, F. Tobacco and the nonsmoker. A study of subjective symptoms. Archives of Environmental Health 16(3): 443-446, March 1968.

(103) SUCIU-FOCA, N., MOLINARO, A., BUDA, J., REEMTSMA, K. Cellular immune responsiveness in cigarette smokers. Lancet 1: 1062, May 25, 1974. (Letter)

(104) SULZBERGER, M.B. Studies in tobacco hypersensitivity. I. A comparison between reactions to nicotine and to denicotinized tobacco extract. Journal of Immunology 24(1): 85-91, 1933.

(105) SULZBERGER, M.B., FEIT, E. Studies in tobacco hypersensitivity. II. Thromboangiitis obliterans with positive urticarial skin reactions and negative reagin findings. Journal of Immunology 24(5): 425-432, 1933.

(106) THOMAS, W.R., HOLT, P.G., KEAST, D. Antibody production in mice chronically exposed to fresh cigarette smoke. Experientia 30(12): 1469-1470, December 15, 1974.

(107) THOMAS, W.R., HOLT, P.G., KEAST, D. Cellular immunity in mice chronically exposed to fresh cigarette smoke. Archives of Environmental Health 27(6): 372-375, December 1973.

(108) THOMAS, W.R., HOLT, P.G., KEAST, D. Development of alterations in the primary immune response of mice by exposure to fresh cigarette smoke. International Archives of Allergy and Applied Immunology 46(4): 481-486, 1974.

(109) THOMAS, W.R., HOLT, P.G., KEAST, D. Humoral immune response of mice with long-term exposure to cigarette smoke. Archives of Environmental Health. 30(2): 78-80, February 1975.

(110) THOMAS, W.R., HOLT, P.G., KEAST, D. Recovery of immune system after cigarette smoking. Nature 248(5446): 358-359, March 22, 1974.

(*111*) TOMIOKA, H., ISHIZAKA, K. Mechanisms of passive sensitization. II. Presence of receptors for IgE on monkey mast cells. Journal of Immunology 107(4): 971-978, October 1971.

(*112*) TOWNLEY, R.G., RYO, U.Y., KOLOTKIN, B.M., KANG, B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. Journal of Allergy and Clinical Immunology 56(6): 429-442, December 1975.

(*113*) TRASOFF, A., BLUMSTEIN, G., MARKS, M. The immunologic aspect of tobacco in thromboangiitis obliterans and coronary artery disease. Journal of Allergy 7: 250-253, 1936.

(*114*) TULEBAEV, R.K., MOSHKEVICH, V.S. Allergicheskie zabolevaniya verkhnikh dykhatel, nykh pytei u rabochikh tabachnogo proizvodstva (Allergic diseases of the upper respiratory tract in tobacco production workers). Zhurnal Ushnykh Nosovykh I Gorlovykh Boleznei (4): 12-14, 1975.

(*115*) VON PIRQUET, C. Allergie, Muenchener Medizinische Wochenschrift. 53: 1457, 1906. In: Gell, P.G.H., Coombs, R.R.A. (Editors). Clinical Aspects of Immunology. Philadelphia, F.A. Davis Co., 1963, pp. 40-41.

(*116*) VOS-BRAT, L.C., RUEMKE, P. Immunoglobuline concentraties, PHA reacties van lymfocyten in vitro (Immunoglobulin concentrations, PHA reactions of lymphocytes in vitro, and some antibody titers of healthy smokers). Jaarboek Karkeronderzoek Kankerbestruding 19: 49-53, 1969.

(*117*) WALDMAN, R.H., BOND, J.O., LEVITT, L.P., HARTWIG, E.C., PRATHER, E.C., BARATTA, R.L., NEILL, J.S., SMALL, P.A., JR. An evaluation of influenza immunization. Influence of route of administration and vaccine strain. Bulletin of the World Health Organization 41: 543-548, 1969.

(*118*) WANNER, A., HIRSCH, J.A., GREENELTCH, D.E., SWENSON, E.W., FORE, T. Tracheal mucous velocity in beagles after chronic exposure to cigarette smoke. Archives of Environmental Health 27: 370-371, December 1973.

(*119*) WARR, G.A., MARTIN, R.R. Concanavalin-A agglutination of human pulmonary alveolar macrophages from nonsmokers and cigarette smokers: A comparison. Life Sciences 18(10): 1177-1184, May 15, 1976.

(*120*) WARR, G.A., MARTIN, R.R. In vitro migration of human alveolar macrophages: Effects of cigarette smoking. Infection and Immunology 8(2): 222-227, August 1973.

(*121*) WARR, G.A., MARTIN, R.R., HOLLEMAN, C.L., CRISWELL, B.S. Classification of bronchial lymphocytes from nonsmokers and smokers. American Review of Respiratory Disease 113(1): 96-100, January 1976.

(*122*) WEARY, P.E., WOOD, B.T. Allergic contact dermatitis from tobacco smoke residues. Journal of the American Medical Association 208(10): 1905-1906, June 9, 1969.

(*123*) WEHNER, A.P., OLSON, R.J., BUSCH, R.H. Increased life span and decreased weight in hamsters exposed to cigarette smoke. Archives of Environmental Health 31(3): 146-153, May/June 1976.

(*124*) WESTCOTT, F.H., WRIGHT, I.S. Tobacco allergy and thromboangiitis obliterans. Journal of Allergy 9: 555-564, 1938.

(*125*) WHITEHEAD, R.H., HOOPER, B.E., GRIMSHAW, D.A., HUGHES, L.E. Cellular immune responsiveness in cigarette smokers. Lancet 1(7868): 1232-1233, June 15, 1974.

(*126*) WIDE, L., BENNICH, H., JOHANSSON, S.G.O. Diagnosis of allergy by an in-vitro test for allergen antibodies. Lancet 2: 1105-1107, November 25, 1967.

(*127*) WINGERD, J., SPONZILLI, E.E. Concentrations of serum protein fractions in white women: Effects of age, weight, smoking, tonsillectomy, and other factors. Clinical Chemistry 23(7): 1310-1317, 1977.

(*128*) YEATES, D.B., ASPIN, N., LEVISON, H., JONES, M.T., BRYAN, A.C. Mucociliary tracheal transport rates in man. Journal of Applied Physiology 39(3): 487-495, September 1975.

(*129*) ZDICHYNEC, B. Zmeny v bilem krevnim obraze u dlouhodobych kuraku. (Na Zaklade srovnani souboru nemocnych s transmuralnim srdecnim infarktem a nemocnych bez priznaku koronarni choroby v predchorobi) (The change of the white blood cells count in long-term smokers. [Basis for the comparison of patients with transmural myocardial infarct and patients without symptoms of coronary disease]). Vnitrni Lekarstvi 17(4): 327-330, April 1971.

(*130*) ZUSSMAN, B.M. Atopic symptoms caused by tobacco hypersensitivity. Southern Medical Journal 61(11): 1175-1179, 1968.

(*131*) ZUSSMAN, B.M. Tobacco sensitivity in the allergic population. Journal of Asthma Research 11(4): 159-168, 1974.

11. INVOLUNTARY SMOKING.

CONTENTS

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Introduction

The effects of smoking on the smoker have been extensively documented in other chapters of this report. This chapter will review the effects of tobacco smoke on the nonsmoker, an area in which there has been increasing concern in the past several years (*66a, 76, 77*). This topic has been referred to as "passive smoking" or "secondhand" smoking as well as "involuntary smoking." The term involuntary smoking will be used to mean the inhalation by the nonsmoker of tobacco combustion products from smoke-filled atmospheres. This type of exposure is, in a sense, "smoking" because it provides exposure to many of the same constituents of tobacco smoke that voluntary smokers experience. It is also "involuntary" because the exposure occurs as an unavoidable consequence of breathing in a smoke-filled environment.

The chemical constituents found in an atmosphere filled with tobacco smoke are derived from two sources—mainstream and sidestream smoke. Mainstream smoke emerges from the tobacco product while being drawn through the tobacco during puffing. Sidestream smoke rises from the burning cone of tobacco. For several reasons, mainstream and sidestream smoke contribute different concentrations of many substances to the atmosphere: different amounts of tobacco are consumed in the production of mainstream and sidestream smoke; the temperature of combustion for tobacco is different during puffing than while smouldering; and certain substances are partially absorbed from the mainstream smoke by the smoker. The amount of a substance absorbed by the smoker depends on the characteristics of the substance and the depth of inhalation by the smoker.

When the smoker does not inhale the smoke into his lungs, the smoke he exhales contains less than half its original amount of water-soluble volatile compounds, four-fifths of the original nonwater-soluble compounds and particulate matter, and almost all of the carbon monoxide (*25*). When the smoker inhales the mainstream smoke, he exhales into the atmosphere less than one-seventh of the amount of volatile and particulate substances that were originally present in the smoke, and he also reduces the exhaled CO to less than half its original concentration (*26*). As a result, different concentrations of substances are found in exhaled mainstream smoke depending on the tobacco product, composition of the tobacco, and degree of inhalation by the smoker.

The effects of cigarette smoke on the environment and on the nonsmoker in the environment will be examined by reviewing data on the constituents of cigarette smoke measured under various conditions and on the absorption of these constituents by the nonsmoker. The physiologic effects of this "involuntary smoking" will then be considered.

Constituents of Tobacco Smoke and Their Absorption by the Nonsmoker

Brunnemann, et al. (*14*) have recently presented a compilation of the levels of some of the important substances in mainstream cigarette smoke and the ratio of sidestream to mainstream levels for these substances (Table 1). The actual amount of the substance and the mainstream-to-sidestream ratio will vary with different types of tobacco tested and the method used to burn the cigarette, but Table 1 gives values generally consistent with those found by others (*23*, *45*, *50*). Many of the substances, including nicotine, carbon monoxide, and ammonia, are found in much higher concentrations in sidestream smoke than in mainstream smoke. Thus, the total smoke exposure of nonsmokers is quantitatively much smaller than the exposure of smokers, but the smoke nonsmokers inhale may be qualitatively richer in certain compounds than mainstream smoke. This qualitative

TABLE 1.—Constituents of Cigarette Smoke.[1] Ratio of sidestream smoke (SS) to mainstream smoke (MS)

A. GAS PHASE	MS	SS/MS		MS	SS/MS
Carbon Dioxide	20–60 mg	8.1	Nitrogen Oxides (NO_x)		
Carbon Monoxide	10–20 mg	2.5	Ammonia	80 μg	73
Methane	1.3 mg	3.1	Hydrogen cyanide	430 μg	0.2
Acetylene	27 μg	0.8	Acetonitrile	120 μg	3.9
Propane Propene	0.5 mg	4.1	Pyridine	32 μg	10
Methylchloride	0.65 mg	2.1	3-Picoline	24 μg	13
Methylfuran	20 μg	3.4	3-Vinylpyridine	23 μg	28
Propionaldehyde	40 μg	2.4	Dimethylnitrosamine	10–65 μg	52
2-Butanone	80–250 μg	2.9	Nitrospyrrolidine	10–35 μg	27
Acetone	100–600 μg				

B. PARTICULATE PHASE	MS	SS/MS		MS	SS/M
"Tar"	1–40 mg	1.7	Quinoline	1.7 μg	11
Water	1–4 mg	2.4	Methylquinolines	0.7 μg	11
Toluene	108 μg	5.6	Aniline	360 ng	30
Stigmasterol	53 μg	0.8	2-Naphthylamine	2 ng	39
Total Phytosterols	130 μg	0.8	4-Aminobiphenyl	5 ng	31
Phenol	20–150 μg	2.6	Hydrazine	32 ng	3
Catechol	130–280 μg	0.7	N'-Nitrosonornicotine	100–500 ng	5
Napthalene	2.8 μg	16	NNK[2]	80–220 ng	10
Methylnaphthalene	2.2 μg	28	Nicotine	1–2.5 mg	2
Pyrene	50–200 μg	3.6			
Benzo(*a*)pyrene	20–40 μg	3.4			

[1]Nonfilter cigarette
[2]NNK = 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (tobacco specific carcinogenic nitrosamine)
SOURCE: Adapted from Brunnemann (*14*).

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
Anderson and Dalhamn (*3*).				
Room 80 m^3	6.4 air changes per hour	46 cig & 3 pipefuls	4.5 ppm CO 377 mg/m^3 nicotine	COHb .6%
Bridge and Corn (*13*).				
Party room 145 m^3	7.0 air changes per hour	50 cig & 17 cigars in 1.5 hr	7.0 ppm CO	
Party room 101 m^3	10.6 air changes per hour	63 cig & 10 cigars in 1.5 hr	9.0 ppm CO	
Brunnemann, et al. (*16*).				
Box .4 m^3	none	10 cig in 1 hr	2.7 ng/l dimethylnitrosamine	
	1.5 liters/min	10 cig in 1 hr	2.9 ng/l dimethylnitrosamine	
Small room 20 m^3	none	100 cig in 1 hr	.33 ng/l dimethylnitrosamine	
	none	100 cig in 1 hr	.23 ng/l dimethylnitrosamine	
	some	100 cig in 1 hr	1.85 ng/l dimethylnitrosamine	

TABLE 2.—Measurement of constituents of tobacco smoke in experimenta

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level constit
DeRouane and Verduyn (*27*).			
House 50 m³	closed	3 cig in 34 min	7.5 pp
Dublin (*28*).			
Conference room 138 m³	12.0 air changes per hour	2 cig	32.5 p
Harke (*36*).			
Room 57 m³	none	42 cig in 18 min	50 pp .560 n
	7.2 air changes per hour	42 cig in 18 min	10 pp .12 m
	8.4 air changes per hour	42 cig in 18 min	< 10 < .1
	none	9 cigars in 35 min	60 pp 1.04 n
	7.2 air changes per hour	9 cigars in 35 min	20 pp .42 m

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
Harke (*36*).				
Room 57 m^3 (Cont.)	none	9 pipes in 40 min	10 ppm CO .52 mg/m^3 nicotine	
	7.2 air changes per hour	9 pipes in 40 min	< 10 ppm CO < .1 mg/m^3 nicotine	
Room 170 m^3	none	105 cig	30 ppm CO	Smokers 7.5% COHb Nonsmokers 2.1% COHb
	1.2 air changes per hour	107 cig	5 ppm CO	Smokers 5.8% COHb Nonsmokers 1.3% COHb
	2.3 air changes per hour	101 cig	75 ppm CO	Smokers 5.0% COHb Nonsmokers 1.6% COHb
Harke, et al. (*38*).				
Room 38.2 m^3	none	30 cig	.51 mg/m^3 nicotine .65 mg/m^3 acetaldehyde .46 mg/m^3 acrolein	
	none	15 cig	.27 mg/m^3 nicotine .29 mg/m^3 acetaldehyde .23 mg/m^3 acrolein	
	none	10 cig	.13 mg/m^3 nicotine .19 mg/m^3 acetaldehyde .16 mg/m^3 acrolein	

TABLE 2.—Measurement of constituents of tobacco smoke in experimenta

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level constit
Harke, et al. (*38*).			
Room 38.2 m³ (Cont.)	none	5 cig	.06 mg
			.13 mg
			.07 mg
Room 170 m³	none	150 cig	58 ppr
		by machine	.72 mg
		in 34 min	.53 mg
			.39 mg
	none	102 cig	28 ppr
		by machine	.18 mg
		in 2 hr	.10 mg
			.09 mg
	2.4 air changes per hour	102 cig	8 ppm
		by machine	.10 mg
		in 2 hr	.5 mg
			.04 mg
	none	108 cig	24.5 p
		by 11 smokers	.14 mg
		in 2 hr	1.0 mg
			.06 mg

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
Harke, et al. (*40*).				
Mid-size European car, engine off, in wind tunnel at 50 km/hr wind speed	none	9 cig	30 ppm CO	
	air jets open and blower off	6 cig	20 ppm CO	
	air jets open and blower on	6 cig	10 ppm CO	
Mid-size European car, engine off, in wind tunnel at zero km/hr wind speed	none	9 cig	110 ppm CO	
	none	6 cig	80 ppm CO	
	air jets open and blower on	6 cig	8-10 ppm CO	
Harmsen and Effenberger (*43*).				
Room 98 m^3	none	62 cig in 2 hr	80 ppm CO, 5,200 $\mu g/m^3$ nicotine	
Hoegg (*45,46*).				
Sealed test chamber 25 m^3	none	4 cig	12.2 ppm CO, 2.28 mg/m^3 TPM	
		8 cig	25.6 ppm CO, 5.39 mg/m^3 TPM	
		16 cig	47.0 ppm CO, 11.41 mg/m^3 TPM	
		24 cig	69.8 ppm CO, 16/65 mg/m^3 TPM	

TABLE 2.—Measurement of constituents of tobacco smoke in experimenta

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level constit
Jermini, et al. (*47*).			
Box 30 m³	none	3 cig by machine	.13 pp
			.22 pp
			.011 p
			.041 p
			.013 p
			.023 p
			.45 pp
			.24 pp
			.015 p
			.10 pp
			.17 pp
			.52 pp
			.067 p
			.008 p
			.020 p
			.032 p
			.38 pp
			.10 pp
			.006 p
			.043 p
Lawther and Commins (*52*).			
Room 15 m³	1 air change per hour	7 cig	20 pp
			3 mg/

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
McNall (*57*).				
Home 425 m³	3 air changes per hour	12 cig in 1 hr	1.1 mg/m³ TPM	
	.5 air changes per hour	35 cig in 1 hr	2.7 mg/m³ TPM	
Russell, et al. (*65,66*).				
Room 43 m³	none	80 cig & 2 cigars per hr	38 ppm CO	Smokers 9.6% COHb, 1,236 ng/ml urinar nicotine Nonsmokers 2.6% COHb, 80 ng/ml urinary nicotine
Seppanen (*70*).				
Room 37.5 m³	none	126 cig by smokers in 1/5 hr	30 ppm CO	Smokers 9.1% COHb Nonsmokers 2.2% CO
Srch (*78*).				
Car, engine off, 2.09 m³	none	10 cig in 1 hr	90 ppm CO	Smokers 10% COHb Nonsmokers 5% COH

TABLE 2.—Measurement of constituents of tobacco smoke in experimental conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	Measure of absorption
Weber, et al. (*79,80,81,82*).				
Box 30 m^3	none	5 cig	12 ppm CO .19 ppm NO .02 ppm NO_2 .23 ppm CH_2O .05 ppm acrolein	
	none	10 cig	24 ppm CO .36 ppm NO .04 ppm NO_2 .46 ppm CH_2O .11 ppm acrolein	

[1]cig = cigarettes, — = unknown, TPM = total particulate matter.

difference in smoke exposure makes the quantification of the involuntary smoking exposure in terms of "cigarette equivalents" confusing and inaccurate. It requires that involuntary smoking be evaluated as a separate problem not subject to simple extrapolation of our understanding of dose-response relationships for cigarette smoking. A more comprehensive review of the chemistry of tobacco smoke is provided in the Chapter on Constituents of Tobacco Smoke in this report.

A number of investigators have attempted to measure the levels of some of the substances in cigarette smoke encountered in experimentally controlled (Table 2) and everyday (Table 3) situations. The type and amount of tobacco product burned, size of the room, amount and type of ventilation or filtration, duration of the smoking, as well as background atmospheric contamination, have all been shown to influence the measured concentrations and absorption by the nonsmoker. A number of substances have been the subject of particular investigative attention.

Carbon Monoxide

Carbon monoxide is one of the major combustion products of cigarettes; mainstream smoke contains 1.5 to 5.5 volumes percent of CO, with levels in sidestream smoke up to three times as high (see Chapter on Constituents of Tobacco Smoke). Carbon monoxide produced by cigarette smoking represents a minor part of the total atmospheric burden of CO but, as can be seen from Tables 2 and 3, it can contribute substantially to the levels found in enclosed spaces. The major determinants of the CO levels in these situations are size of the space in which the smoking occurs (dilution of CO), the number and type of tobacco products smoked (CO production), and the amount and effectiveness of ventilation.

The type of tobacco product smoked is important as a determinant of CO exposure because it has been found that mainstream smoke from regular and small cigars contains more CO per puff and per gram of tobacco burned than that from filter or nonfilter cigarettes (*15*). This greater production of CO by cigars was confirmed by Harke (*36*). He measured the CO produced by 42 cigarettes, 9 cigars, and 9 pipefuls of tobacco, each product evaluated separately but under the same room conditions. The cigars produced the highest CO level (60 ppm).

Carbon monoxide is a gas, does not settle out of the atmosphere in an enclosed space, and is not removed by most of the standard air filtration systems. As a result, the reduction of CO levels requires the replacement of contaminated air with uncontaminated air. Jones and Fagan (*51*) calculated the levels of CO that would result in a 3,000 cubic-foot room populated by 25 smokers when the ventilation was

TABLE 3.—Measurement of constituents of tobacco smoke under natural conditions.[1]

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	
			Smoking section	Other control section
Brunnemann and Hoffmann (*16*).			dimethylnitrosamine	
Train 1 (Bar Car)			.13 ng/l	
Train 2 (Bar Car)			.11 ng/l	
Bar			.24 ng/l	
Cano, et al. (*19*).				
Submarines 66 m^3	yes	157 cig per day	< 40 ppm CO, 32 ug/m^3 nicotine	
		94–103 cig per day	< 40 ppm CO, 15–35 ug/m^3 nicotine	
Chappel and Parker (*20*).				
General public places		—	3.5 ppm CO	2.0 ppm CO
Government offices	—	—	2.5 ppm CO	2.5 ppm CO
Restaurants	—	—	4.0 ppm CO	2.5 ppm CO
Night clubs and taverns	—	—	13.0 ppm CO	3.0 ppm CO

TABLE 3.—Measurement of constituents of tobacco smoke under natural conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	
			Smoking section	Other control section
Cuddeback, et al. (*24*).				
Tavern 1	6 air changes per hour	—	12.5 ppm CO .33 mg/m³ TPM	—
Tavern 2	none	—	17 ppm CO .98 mg/m³ TPM	—
Elliott and Rowe (*30*).				
Arenas	—	—	14.3 ppm CO .367 mg/m³ TPM	3 ppm CO .068 mg/m³ TPM
Galuskinova (*33*).				
Restaurant	—	—	.0002 - .0046 mg/m³ benzopyrene	
Godin, et al. (*35*).				
Ferry boat compartments			18.4 ± 8.7 ppm CO	3.0 ± 2.4 ppm CO
Theater			3.4 ± 0.8 ppm CO	1.4 ± 0.8 ppm CO

TABLE 3.—Measurement of constituents of tobacco smoke under natural conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	
			Smoking section	Other control section
Harke (*37*).				
Office Building	air conditioned	—	< 5 ppm CO	
Office Building	not air conditioned	--	< 5 ppm CO	
Room 78.3 m^3	...	3 smokers	15.6 ppm CO	
Harke and Peters (*41*).				
Automobile	35 km/hr speed, no ventilation.	4 cig	24.3 ppm CO	
	80 km/hr speed, no ventilation.	4 cig	12.1 ppm CO	
	30 km/hr speed, no ventilation.	4 cig	21.4 ppm CO	
	30 km/hr speed, air jets open.	4 cig	15.7 ppm CO	
	3 km/hr speed, air jets open & blower on.	4 cig	12.0 ppm CO	
Hinds and First (*44*).	—	--	nicotine:	
Commuter train			.0049 mg/m^3	
Commuter bus			.0063 mg/m^3	
Bus waiting room			.001 mg/m^3	
Airline waiting room			.0031 mg/m^3	
Restaurant			.0052 mg/m^3	
Cocktail lounge			.0103 mg/m^3	
Student lounge			.0028 mg/m^3	

TABLE 3.—Measurement of constituents of tobacco smoke under natural conditions.[1]–continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	
			Smoking section	Other control section
Lefcoe and Inculet (*55*).				
House	—	1 cig	48 x 10^6 particles per cubic foot	.9 x 10^6 particles per cubic foot
Szadkowski, et al. (*75*).				
Offices	—	—	2.7 ppm CO	
Sebben, et al. (*68*).				
Night clubs	—	—	13.4 ppm CO	9.2 ppm CO
Restaurants	—	—	8–28 ppm CO	—
Bus	—	—	7.3 ppm CO	6.2 ppm CO
Slavin and Hertz (*71*).				
Conference room	8 air changes per hour	—	8 ppm CO	1-2 ppm CO
	6 air changes per hour	—	10 ppm CO	1-2 ppm CO

TABLE 3.—Measurement of constituents of tobacco smoke under natural conditions.[1]—continued

Reference, location, and dimensions	Ventilation	Amount of tobacco burned	Level of constituent	
			Smoking section	Other control section
Seiff (*69*).				
Intercity bus	15 air changes per hour	23 cig burning continuously	33 ppm CO	
		3 cig burning continuously	18 ppm CO	
U.S. Dept. Transportation, et al. (*60*).				
Airplane flights:				
Overseas - 100% filled	15–20 air changes per hr		2–5 ppm CO, < .120 mg/m³ TPM	
Domestic - 66% filled			2 ppm CO, < .120 mg/m³ TPM	

[1]cig = cigarettes, — = unknown, TPM = total particulate matter.

varied (Figure 1). They assumed that the smokers would smoke four cigarettes per hour and that each cigarette would produce 74 mg of CO. They then repeated the same calculations for 25 nonsmokers and extrapolated that the room filled with smokers would require a rate of ventilation 10 times higher (1000 cu ft/min versus 100 cu ft/min) than the room with the nonsmokers in order to keep the CO concentration below the Ambient Air Quality Standards set by the Environmental Protection Agency (9 ppm CO) (*31*). These data generate some concern due to the current trend toward more tightly sealed buildings with recirculation and filtration of the air rather than the more energy-costly intake and warming or cooling of uncontaminated outside air. As air conditioning systems become more self-contained the problem of meeting the Ambient Air Quality Standards for CO may become more complex.

Examination of Table 2 reveals that under conditions of heavy smoking and minimal ventilation even the threshold limit value for an 8-hour industrial exposure to CO (50 ppm) (*1*) may be exceeded, but the addition of even modest amounts of ventilation results in a rapid drop in the CO levels. Harke (*40*) also showed that in small enclosed unventilated spaces (an automobile) the CO level is determined more by the number of cigarettes being smoked at one time than by the cumulative number of cigarettes that have been smoked and that the CO level decreases rapidly once the smoking stops.

The level of smoking in these experimental conditions was generally far heavier than is common in everyday situations. Indeed, when levels are measured in everyday situations (Table 3), they are found to be lower than those in the experimental situation. However, cigarette smoking can produce CO levels well above the Ambient Air Quality Standard (9 ppm) in these everyday stiuations.

One must be careful when using the levels recorded in Table 3 as measures of individual exposure because the CO levels were usually measured at points several feet from the nearest smoker. Individuals might be exposed to higher or lower levels depending on their distance from someone actively smoking (*28, 52*). In addition, it is the CO absorbed by the body that causes the harmful effects, not that which is measured in the atmosphere. This absorption can vary from individual to individual, depending on factors such as duration of exposure and cardio-respiratory status.

Several investigators have tried to determine the amount of carbon monoxide absorbed in involuntary smoking situations by measuring changes in carboxyhemoglobin levels in nonsmokers exposed to cigarette smoke-filled environments. Anderson and Dalhamn (*3*) found no change in the COHb levels of nonsmokers in a well-ventilated room where the CO level was 4.5 ppm. When Harke (*36*) studied nonsmokers under similar conditions (good ventilation and less than 5 ppm CO), he found an increase in COHb level from 1.1 to 1.6 percent; without

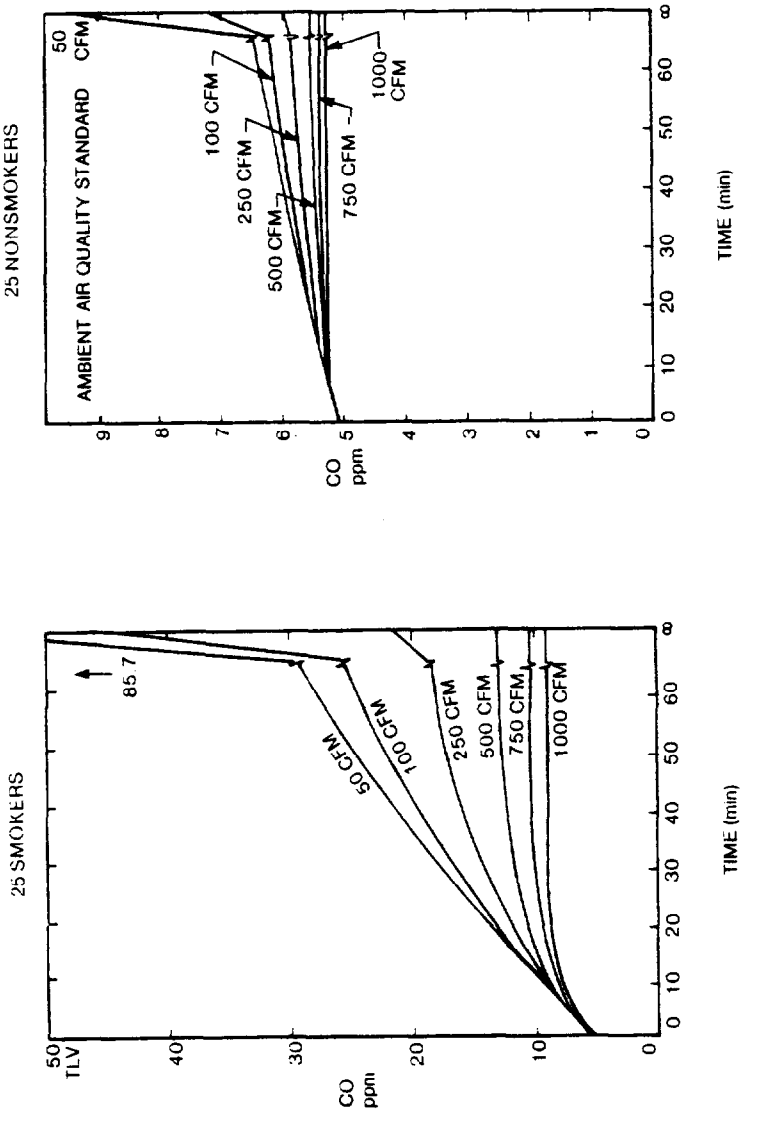

FIGURE 1.—Calculated buildup of CO under varying conditions of ventilation and smoking. Calculated for a room 3000 ft³ with 25 smokers on the left and for 25 nonsmokers on the right. TLV is the threshold limit value for CO (50 ppm). CFM is ventilation in cubic feet per minute.

SOURCE: Jones, R.N. (*51*).

TABLE 4.—Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for nonsmokers by location.

Location	Nonsmokers		No. of nonsmokers	Percent of nonsmokers with COHb >1.5%
	Median	Range		
Anchorage	1.5	0.6–3.2	152	56
Chicago	1.7	1.0–3.2	401	74
Denver	2.0	0.9–3.7	744	76
Detroit	1.6	0.7–2.7	1,172	42
Honolulu	1.4	0.7–2.5	503	39
Houston	1.2	0.6–3.5	240	30
Los Angeles	1.8	1.0–3.0	2,886	76
Miami	1.2	0.4–3.0	398	33
Milwaukee	1.2	0.5–2.5	2,720	26
New Orleans	1.6	1.0–3.0	159	59
New York	1.2	0.6–2.5	2,291	35
Phoenix	1.2	0.5–2.5	147	24
St. Louis	1.4	0.9–2.1	671	35
Salt Lake City	1.2	0.6–2.5	544	27
San Francisco	1.5	0.8–2.7	660	61
Seattle	1.5	0.8–2.7	535	55
Vermont, New Hampshire	1.2	0.8–2.1	959	18
Washington, D.C.	1.2	0.6–2.5	850	35

SOURCE: Stewart, R.D. (74).

ventilation the CO levels rose to 30 ppm and the COHb level increased from .9 to 2.1 percent in 2 hours. Russell, et al. (*65*) found that COHb levels increased from 1.6 to 2.6 percent in nonsmokers present in a smoke-polluted room where the CO level was measured at 38 ppm; however, he cautioned that nearly all persons in the room felt that the conditions were worse than those experienced in most social situations.

Aronow (*4*) exposed 10 patients with coronary artery disease to the smoke from 15 cigarettes smoked by 3 volunteers over 2 hours in a 30.8 m^3 room. He reported that the COHb levels increased in the nonsmokers from a baseline of 1.26 percent to 1.77 percent when the room was ventilated at 11.4 air changes per hour and from 1.30 percent to 2.28 percent when the ventilation was turned off.

Stewart, et al. (*74*) measured COHb levels in a group of nonsmoking blood donors from several cities and found that 45 percent exceeded the Clean Air Act's Quality Standard of 1.5 percent, with the 90 percent range as high as 3.7 percent for individual cities (Table 4).

These levels represent the total body burden of CO for the nonsmoker due to endogenous production as well as to all forms of environmental exposure (industrial and automobile as well as smoking). They are also the levels from which any increase would occur

when the nonsmoker encounters an environment in which smoking has raised the ambient CO levels.

Nicotine

Nicotine in the atmosphere differs from CO in that it tends to settle out of the air with or without ventilation, thereby decreasing its atmospheric concentration, whereas the CO level will remain constant until the CO is removed. The concentrations of both substances are decreased substantially by ventilation. As can be seen from data in Tables 2 and 3, under conditions of adequate ventilation, neither exceeds the maximum threshold limit values for industrial exposure (nicotine, 500 $\mu g/m^3$; CO, 50 ppm) (*1*); whereas in conditions without ventilation, smoking produces very high concentrations of both nicotine (up to 1,040 $\mu g/m^3$) and CO (110 ppm).

Nicotine in the environment is of concern because nicotine absorbed by cigarette smokers is felt to be one factor contributing to the development of atherosclerotic cardiovascular disease. Several researchers have attempted to measure the amount of nicotine absorbed by nonsmokers in involuntary smoking situations. Cano, et al. (*19*) studied urinary excretion of nicotine by persons on a submarine. Despite very low levels measured in the air (15 to 32 $\mu g/m^3$), nonsmokers showed a small rise in nicotine excretion; however, the amount excreted was still less than 1 percent of the amount excreted by smokers. Harke (*36*) measured nicotine and its main metabolite, cotinine, in the urine of smokers and nonsmokers exposed to a smoke-filled environment and reported that nonsmokers excreted less than 1 percent of the amount of nicotine and cotinine excreted by smokers. He concluded that at this low level of absorption nicotine is unlikely to be a hazard to the nonsmoker.

Russell and Feyerabend (*66*) examined the plasma and urinary nicotine values for smokers and nonsmokers under conditions of severe tobacco smoke pollution (CO 38 ppm). They demonstrated a rise in the plasma nicotine in nonsmokers to 90 ng/ml and in urinary nicotine to 80 ng/ml—values which are substantially below those for urinary nicotine found in smokers (1236 ng/ml).

Other Substances

In two studies environmental levels of the experimental carcinogen benzo(*a*)pyrene were measured. Galuskinova (*33*) found levels of benzo(*a*)pyrene from 2.82 to 14.4 $\mu g/m^3$ in smoky restaurants, but it is not clear how much of this was due to cooking and how much was due to smoking. In a study of the concentration of benzo(*a*)pyrene in the atmosphere of airplanes (*60*), only a fraction of a microgram per cubic meter was detected. The effect of chronic exposure to very low levels of this carcinogen has not been established for humans.

Brunnemann and Hoffmann (*16*) measured the levels of dimethylnitrosamine in a small room under very heavy experimental smoking and found levels of this potent carcinogen of .23 to 2.7 ng/l. When levels were measured under ambient conditions in two train bar-cars and in one bar, levels from .11 to .24 ng/l were measured. The authors state that these levels would result in the nonsmoker inhaling air containing the same quantity of nitrosamine in 1 hour as there is in the mainstream smoke of 5 to 30 cigarettes. However, it is not clear that the absorption of nitrosamine from environmental conditions is equivalent to the absorption by smoking, and it is also not established that nitrosamines can act as carcinogens at these levels delivered by inhalation.

Acrolein, acetaldehyde, and a number of other irritating substances have been measured in experimental smoking conditions (*38*, *47*, *79*, *80*, *81*, *82*) and may contribute to the eye irritation experienced in these conditions. Acrolein was the only substance that exceeded the threshold limit values even under conditions of very heavy smoke pollution.

Effects of Tobacco Smoke on the Nonsmoker

General Population

The effect of involuntary smoking on an individual is determined not only by the qualitative and quantitative aspects of the smoke-filled environment but also by the characteristics of the individual. Reactions may vary with age as well as with the sensitivity of an individual to the components of tobacco smoke. The possible effects range from minor eye and throat irritations experienced by most people in smoke-filled rooms to the anginal attacks in some persons with coronary artery disease.

In 1975, a national probability sample of U.S. telephone households was asked to agree or disagree with the statement, "It is annoying to be near a person who is smoking cigarettes" (*59*). Of "never smokers," 77.0 percent of the males and 80.5 percent of the females agreed with the statement; of current smokers, 35.o percent of the males and 34.5 percent of the females also agreed with the statement.

Speer (*72*) assessed the nature of this annoyance by interviewing 250 nonallergic patients about their reaction to cigarette smoke; 69.2 percent reported eye irritation, 31.6 percent headache, 29.2 percent nasal symptoms, and 25.2 percent cough.

Two government-sponsored studies have attempted to evaluate the degree of minor irritation due to cigarette smoke experienced by bus and plane passengers. The U.S. Department of Transportation (*69*) studied the environment on two ventilated buses—one with simulated unrestricted smoking and another with simulated smoking limited to the rear 20 percent of the seats. In one bus, lighted cigarettes were

placed at every other seat (23 cigarettes) to simulate a bus filled with smokers. In the other bus, cigarettes were placed only in the rear 20 percent of the bus (5 cigarettes) to simulate a bus where smoking was limited to the rear 20 percent of the seats. When smoking was limited, the CO level at the driver's seat was 18 ppm (ambient air 13 ppm), compared to the level of 33 ppm (ambient air 7 ppm) measured in the unrestricted smoking situation. Four of the six subjects seated in the bus reported eye irritation during the unrestricted smoking simulation. None of the six subjects, including those seated in the rear 20 percent of the bus, reported any eye irritation in the restricted smoking situation.

Several Federal agencies (*60*) cooperated to survey the symptoms experienced by travelers on both military and commercial aircraft. They distributed a questionnaire to passengers on 20 military and 8 commercial flights; 57 percent of the passengers on the military flights and 45 percent of the passengers on the commercial flights were smokers. The planes were well ventilated and CO levels were always below 5 ppm, with low levels of other pollutants as well. In spite of the low level of measurable pollution, over 60 percent of the nonsmoking passengers and 15 to 22 percent of the smokers reported being annoyed by the other passengers' smoking. These feelings were even more prevalent among those nonsmokers who had a history of respiratory disease. Seventy-three percent of the nonsmoking passengers on the commercial flights and 62 percent of the nonsmoking passengers on the military flights suggested that some remedial action be taken; 84 percent of those suggesting remedial action felt that segregating the smokers from nonsmokers would be a satisfactory solution.

Weber, et al. (*80*) found an increasing frequency of reported eye, nose, and throat irritation with increasing concentrations of smoke in a sealed chamber. Eye and nose irritation was much more frequent than throat or respiratory irritation, and self-reported eye irritation was very clearly related to objective signs such as tear flow, eye closing, and eye rubbing. The authors felt that acrolein was the major offending substance, but high concentration of other substances were also present. Artho and Koch (*10*) have reported 11 unpleasant smelling constituents in the volatile and 50 in the semivolatile phase of cigarette smoke.

The eye and nose irritation experienced by nonsmokers in a smoke-filled environment is influenced by the humidity of the air as well as by the concentration of irritating substances found in the atmosphere. Johansson and Ronge (*48, 49*) have shown that eye and nose irritation due to cigarette smoke is maximal in warm, dry air and decreases with a small rise in relative humidity. A change from acceptable to unpleasant was reported at 4.7 mg/m^3 of particulate matter for nonsmokers, and eye irritation was noted at 9 mg/m^3 for both smokers and nonsmokers. The authors concluded that a ventilation rate of 12 m^3

/hr/cig was necessary to avoid eye irritation and 50 m^3/hr/cig was necessary to avoid unpleasant odors.

The effects of cigarette smoking on the cardiovascular system of the smoker are reviewed in the Chapter on Cardiovascular Diseases. The response of the nonsmoker to cigarette smoke will be examined here. Harke and Bleichert (*39*) studied 18 adults (11 smokers and 7 nonsmokers) in a 170 m^3 room in which 150 cigarettes were smoked or allowed to burn in ashtrays for 30 minutes. They noted that the subjects who smoked during the experiment had a significant lowering of skin temperature and a rise in blood pressure. Nonsmokers who were exposed to the same smoke-contaminated environment showed no change in either of these parameters. Luquette, et al. (*56*) performed a similar experiment with 40 children exposed alternately to smoke-contaminated and clean atmospheres, but otherwise they were under identical experimental conditions. They found that exposure to the smoke was associated with increases in heart rate (5 beats per minute) and in systolic (4 mm Hg) and diastolic (5 mm Hg) blood pressure. The differences in results between these studies may be due, in part, to the age of the subjects, i.e., children may be more sensitive to the cardiovascular effects of involuntary smoking than adults; or, the increase in heart rate and blood pressure may be due to a difference between children and adults in the psychologic response to being in a smoke-filled atmosphere.

Rummel, et al. (*64*) examined this question with a group of 56 students exposed to cigarette smoke. They found a slight increase in systolic blood pressure on exposure to smoke for the entire group. When the group was divided into those who were indifferent to cigarette smoke and those who expressed a dislike for smoke, both groups had a rise in systolic blood pressure on exposure to smoke. However, the "dislike" group also had a significantly higher heart rate at the start of the study and during the entire course of the study, suggesting that psychological factors may play a role in the physiologic response to involuntary smoking.

Several authors have found small decrements in the exercise time until exhaustion (*5*), ventilation-V_{O2} max (*62*), and an increase in heart rate with exercise (*34*) after exposure to low levels of carbon monoxide. These effects are more pronounced in older than in younger populations (*5, 34*).

Pimm, et al. (*61*) examined the effect of exposure to machine-produced smoke on ventilatory function in healthy adults. They were able to show no significant changes in subdivisions of lung volume, maximum expiratory flow-volume curves, and single-breath nitrogen washout curves following exposure.

Schilling, et al. (*67*) examined the presence of self-reported symptoms and pulmonary function tests (FVC, $FEV_{1.0}$, PEF, MEF_{50}, and MEF_{25}) in 376 families with 816 children aged 1 to 17. The data did

not show any significant association between parental smoking habits and either symptoms or pulmonary function tests in spouses or children.

In summary, a substantial proportion of the normal population experiences irritation and annoyance on being exposed to cigarette smoke. The eyes and nose are the areas most sensitive to irritation, and the level of irritation increases with increasing levels of smoke contamination. Healthy nonsmokers exposed to cigarette smoke have little or no physiologic response to the smoke, and what response does occur may be due to psychological factors. There probably is a slight reduction in the maximum exercise capacity in older nonsmokers exposed to levels of CO occasionally found in involuntary smoking situations.

Effects of Carbon Monoxide in Psychomotor Tests

There has been some concern over the effects of relatively low levels of carbon monoxide on psychomotor functions (the ability to perceive and react to stimuli), especially on those functions related to driving an automobile. Yabroff, et al. (*85*) recently reviewed this topic extensively. They concluded that "experimenters have found some performance tasks associated with driving affected by low levels of carboxyhemoglobin, some as low as 2 percent. However, disagreement exists regarding the levels at which particular tasks are affected. These tasks include:

1. Vigilance—both visual and acoustical—needed for defensive driving.
2. Color vision and discrimination, especially important in discerning taillight or brake light usage and traffic lights.
3. Brightness discrimination, important to driving as a clue used in distance estimation.
4. Peripheral vision, used in surveying the environment, signs, and other traffic.
5. Glare recovery, which is the ability to recover visual acuity after being subjected to bright lights of another motor vehicle at night or in going from bright sunshine into a shaded area (e.g., a tunnel).
6. Speech linkage"(*85*).

A number of authors have tested driving ability directly. Ray and Rockwell (*63*) found that as COHb increased time estimates were shorter, distance estimates were longer, and taillight discrimination and determination of velocity change in the lead car took longer. There were also slight changes in normal driving and cornering. Weir and Rockwell (*84*) also found slight deterioration in driving performance; measurements of visual acuity showed that drivers required more time to retrieve visual information and spent less time looking outside the forward direction (20 degrees x 20 degrees visual angle). These changes were noted at 6 to 8 percent COHb and are similar to those

found in drivers under low alcohol concentrations. The combined effect of alcohol and CO has been studied and no additional impairment due to CO could be demonstrated for tests of coordination or cognitive function (*58*). When actual driving skills were tested (*83*), significant interactions between CO and alcohol occurred for tasks which demanded higher information processing such as curve negotiation and car following (at 12 percent COHb).

In summary, it is possible to demonstrate changes in psychomotor function at levels of CO found in involuntary smoking conditions, but these effects generally are measurable only at the threshold of stimuli perception. Effects of CO on driving performance and interactive effects of CO and alcohol have been demonstrated only for levels of COHb above those found in involuntary smoking conditions.

Special Populations

The above studies examined the effects of involuntary smoking on relatively healthy populations. An exposure that is harmless for someone who is healthy may have a very different effect on someone with heart or lung disease or hypersensitivity to substances found in smoke. Children are also a group in which effects may differ, due to their greater ventilation per body weight. This section will review the evidence on the effects of involuntary smoking for each of these special populations.

Cardiovascular Disease

Carbon monoxide, which has 230 times the affinity of oxygen for hemoglobin, impairs oxygen transport in two ways. First, it competes with oxygen for hemoglobin binding sites. Second, it increases the affinity of the remaining hemoglobin for oxygen, thereby requiring a larger gradient in PO_2 between the blood and tissue to deliver a given amount of oxygen. Carbon monoxide also binds to other heme-containing pigments, most notably myoglobin, for which it has an even greater affinity than for hemoglobin under conditions of low PO_2. The significance of this binding is unclear but may be important in tissues such as heart muscle, which have both high oxygen requirements and large amounts of myoglobin.

In healthy individuals, the levels of COHb due to involuntary smoking are probably functionally insignificant, with small changes demonstrable only under extreme exertion. In individuals with a limited cardiovascular reserve, however, any reduction in the oxygen-carrying capacity of the blood may be of greater importance.

Ayres, et al. (*11, 12*) exposed a group of patients to various concentrations of CO (COHb 9 percent), and found that they had lower arterial and mixed venous PO_2's, decreased lactate extraction, and decreased coronary sinus PO_2.

Aronow and Isbell (*9*) and Anderson, et al. (*2*) have shown a decrease in the mean duration of exercise before onset of pain in patients with angina pectoris exposed to low levels of carbon monoxide (50 and 100 ppm). Carboxyhemoglobin levels were significantly elevated (2.9 percent after 50 ppm; 4.5 percent after 100 ppm), and the systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate (a measure of cardiac work) were all significantly lower at the onset of angina pectoris.

In a continuation of this work, Aronow, et al. (*6, 8*) studied eight patients with angiographically demonstrated coronary artery disease (> 75 percent obstruction of at least one coronary artery) during two separate cardiac catheterizations. During the first, each patient smoked three cigarettes; during the second, each patient inhaled carbon monoxide until the maximal coronary sinus COHb level equaled that produced by smoking during the first catheterization. Smoking increased the systolic and diastolic blood pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and coronary sinus, arterial, and venous CO levels. No changes were noted in left ventricular contractility (dp/dt), aortic systolic ejection period, or cardiac index; decreases were found in stroke index and coronary sinus, arterial, and venous PO_2. When carbon monoxide was inhaled, increased LVEDP and coronary sinus, arterial, and venous CO levels were noted; there were no changes in systolic and diastolic blood pressure, heart rate, or systolic ejection period; and decreases in left ventricular dp/dt, stroke index, cardiac index and coronary sinus, arterial and venous PO_2 were found. These data suggest that carbon monoxide has a negative ionotropic effect on myocardial tissue resulting in the decreased contractility (dp/dt) and stroke index. When the positive effect of nicotine on contractility and heart rate is added by smoking, the net effect is increased cardiac work for the same cardiac output.

Aronow (*4*) also examined the effect of involuntary smoking on patients with angina pectoris. Ten patients (two smokers and eight nonsmokers) were exercised after a control exposure to uncontaminated air, after exposure to 15 cigarettes smoked over 2 hours in a well ventilated (30.8 m^3) room, and after exposure to 15 cigarettes smoked over 2 hours in an unventilated (30.8 m^3) room. He reported that the carboxyhemoglobin levels rose from 1.25 percent in the control situation to 1.77 percent after exposure in the ventilated room, and to 2.28 percent in the unventilated room. He found that the mean time of exercise until onset of angina decreased 22 percent after exposure in the ventilated room and 38 percent after exposure in the unventilated room. The patients also had onset of angina at a lower heart rate and systolic blood pressure. He also noted that the patients had an elevation in their heart rate and systolic and diastolic blood pressures. He attributed this to the possible absorption of nicotine (no nicotine

levels were measured). The very low levels of nicotine absorption documented under these conditions (see the previous section) make it unlikely that nicotine would be responsible for these physiologic changes. Another explanation would be the anxiety or aggravation induced by the smoke-filled room resulting in a stress response (*78*). The combination of elevated blood pressure and pulse at the start of exercise and the elevation in carboxyhemoglobin levels resulted in a greater decline in exercise time to produce angina for the measured level of carboxyhemoglobin than had been shown for carbon monoxide exposure alone.

In summary, there is evidence that elevations in carboxyhemoglobin levels capable of being produced by involuntary smoking can reduce the exercise duration required to induce angina in some patients with coronary artery disease.

Chronic Obstructive Lung Disease

Patients with chronic lung disease represent a second group who are limited in their ability to exercise and who might be particularly susceptible to involuntary smoking exposures. Aronow, et al. (*7*) exercised 10 patients with hypoxic chronic lung disease (PO_2 less than 70 torr) before and after a 1-hour exposure to 100 ppm CO (COHb increased from 1.43 percent to 4.08 percent). There was a significant reduction in the mean exercise time, from 218.5 seconds to 146.6 seconds, until marked dyspnea. There was no difference in exercise mean systolic or diastolic blood pressure, heart rate, product of systolic blood pressure times heart rate/100, or arterial P_{O2}, P_{CO2}, or pH before or after CO exposure. The mechanism for this earlier induction of dyspnea remains unclear because decreased oxygen transport to the exercising tissues should have been reflected in a shift to anaerobic metabolism and the development of acidosis.

Hypersensitivity

The evidence for possible immunologic reactions to tobacco smoke is reviewed in the allergy chapter of this report; the existence of a true tobacco allergy has not been clearly established. It does seem clear, however, that those patients with a history of allergies to other substances are more likely to report the irritating effects of tobacco smoke (*32*, *72*).

Children

Children have a higher incidence of respiratory infections than adults and may be more susceptible to air pollutants than adults due to their greater minute ventilation per body weight. Several researchers have investigated the effects of parental smoking on the health of children. Cameron, et al. conducted two telephone surveys of Detroit families to

determine the relationship between children's respiratory illness and parental smoking habits. In the first survey (*17*), they found a statistically significant relationship between the prevalence of children's respiratory infection and parental smoking habits only when all children under 16 were considered but not when only those under 9 or under 5 were considered. In a larger survey of the same city (*18*), they found a relationship between parental smoking and prevalence of respiratory illness in the 10- to 16-year age group and in the birth to 5-year age group. Neither study was controlled for smoking by the children, which might be a factor in the 10- to 16-year age group, or for socioeconomic status, which has an effect on both smoking habits and illness. However, the data suggested a higher prevalence of respiratory disease in families where there are smokers than in nonsmoking families.

Colley, et al. (*21*) also found a relationship between parental smoking habits and the prevalence of respiratory illness in the children. However, an even stronger relationship was found between parental cough and phlegm production and respiratory infections in children. They postulated that this latter relationship resulted from the greater infectivity of these parents due to their cough and phlegm production. The relationship between parental cigarette smoking and respiratory infection in their children would then occur because cigarette smoking caused the parents to cough and produce phlegm and would not be indicative of a direct effect of cigarette smoke-filled air on the children. Lebowitz and Burrows (*53*) found a similar relationship, but Schilling, et al. (*67*) did not.

Harlap and Davies (*42*) studied infant admissions to Hadassah Hospital in West Jerusalem and found a relationship between admissions for bronchitis and pneumonia in the first year of life and maternal smoking habits during pregnancy. Data on maternal smoking habits after the birth of the child were not obtained, but it can be assumed that most of the mothers who smoked during pregnancy continued to smoke during the first year of the infant's life. A relationship between infant admission and maternal smoking habits was demonstrable only between the sixth and ninth months of infant life and was more pronounced during the winter months. Mothers who smoke during pregnancy are known to have infants with a lower average birth weight than the infants of nonsmoking mothers. The relationship between maternal smoking and their infants' admission to the hospital found in this study was greater for low birth-weight infants, but the same relationship was found for normal birth-weight infants (Table 5) (*42*). Harlap and Davies (*42*) demonstrated a dose-response relationship for maternal smoking and infant admission for bronchitis and pneumonia; however, they also found a relationship between maternal smoking and infant admissions for poisoning and injuries. This may indicate a bias in the study due to relationships

TABLE 5.—Admission rates (per 100 infants) by diagnosis, birth weight, and maternal smoking.

Diagnosis	Birth weight (g)						Total (including unknown)	
	<2,999		3,000–3,499		3,500+			
	S (297)	NS (2,326)	S (415)	NS (4,098)	S (264)	NS (3,195)	S (986)	NS (9,686)
Bronchitis and pneumonia	19.2	12.3	9.6	8.2	12.1	9.0	13.1	9.5
All other	22.6	19.9	14.5	14.6	15.2	13.3	16.9	15.5
Total	41.8	32.2	24.1	22.8	27.3	22.3	30.0	24.9

NOTE. — S = Smokers; NS = Nonsmokers. Absolute numbers in parentheses.
SOURCE: Harlap and Davies (*42*).

which may exist between smoking and factors such as parental neglect or socioeconomic class. In addition, hospital admission rates may not be an accurate index of infant morbidity.

Colley, et al. (*22*) and Leeder, et al. (*54*) studied the incidence of pneumonia and bronchitis in 2,205 children over the first 5 years of life in relation to the smoking habits of both parents. They found that a relationship between parental smoking habits and respiratory infection in children occurred only during the first year of life (Table 6). They also showed a relationship between parental cough and phlegm production and infant infection (Table 6) which was found to be independent of the effect of parental smoking habits. The relationship between parental smoking and infant infection was greater when both parents smoked and increased with increasing number of cigarettes smoked per day. The relationship persisted after controlling for social class and birth weight.

Thus, respiratory infections during the first year of life are related to parental smoking habits independently of parental symptoms, social class, and birth weight. Because of the dose-response relationship between parental smoking and infant respiratory infection established by Colley, et al. (*22*), it is reasonable to suspect that cigarette smoke in the atmosphere of the home may be the cause of these infections; however, other factors such as parental neglect may also play a role.

Summary

1. Tobacco smoke can be a significant source of atmospheric pollution in enclosed areas. Occasionally, under conditions of heavy smoking and poor ventilation, the maximum limit for an 8-hour work exposure to carbon monoxide (50 ppm) may be exceeded. The upper limit for CO in ambient air (9 ppm) may be exceeded even in cases where ventilation is adequate. For an individual located close to a cigarette that is being smoked by someone else, the pollution exposure

TABLE 6.—Pneumonia and bronchitis in the first 5 years of life, by parents' smoking habit and morning phlegm.

Year of followup	Annual incidence of pneumonia and bronchitis per 100 children (Absolute numbers in parentheses)									
	Both nonsmokers		One smoker		Both smokers		Both ex-smokers or one ex-smoker or smoking habit changed		All	
	N	O/B	N	O/B	N	O/B	N	O/B	N	O/B
1	7.6	10.3	10.4	14.8	15.3	23.0	8.2	13.2	10.1	16.7
	(343)	(29)	(424)	(128)	(339)	(139)	(546)	(129)	(1,652)	(425)
2	8.1	8.3	7.1	15.5	8.7	9.2	6.5	10.7	7.4	11.3
	(322)	(36)	(365)	(129)	(286)	(152)	(599)	(159)	(1,572)	(476)
3	6.9	8.1	10.5	9.4	7.9	11.0	8.2	11.6	8.4	10.6
	(305)	(37)	(353)	(107)	(242)	(154)	(661)	(173)	(1,561)	(471)
4	8.0	11.1	7.5	10.8	7.6	11.6	8.2	9.1	7.9	10.3
	(287)	(36)	(306)	(102)	(236)	(121)	(695)	(187)	(1,524)	(446)
5	6.7	14.7	5.6	9.4	3.9	10.6	6.4	7.3	5.9	9.1
	(285)	(34)	(267)	(107)	(208)	(132)	(737)	(219)	(1,497)	(492)

NOTE.—*N* = neither with winter morning phlegm; *O/B* = one or both with winter morning phlegm.
SOURCE: Colley, J.R.T. (*22*).

may be greater than would be expected from atmospheric measurements.

2. Carbon monoxide, at levels occasionally found in cigarette smoke-filled environments, has been shown to produce slight deterioration in some tests of psychomotor performance, especially attentiveness and cognitive function. It is unclear whether these levels impair complex psychomotor activities such as driving a car. The effects produced by CO may become important when added to factors such as fatigue and alcohol which are known to have an effect on the ability to operate a motor vehicle.

3. Unrestricted smoking on buses and planes is reported to be annoying to the majority of nonsmoking passengers, even under conditions of adequate ventilation.

4. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life, and this may be due to their being exposed to cigarette smoke in the atmosphere.

5. Levels of carbon monoxide which can be reached in cigarette smoke-filled environments have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. These levels of CO also have been shown to reduce the exercise time until onset of dyspnea in patients with hypoxic chronic lung disease.

Recommendations

There has been a long-term research interest in the health effects of voluntary smoking, and substantial relevant data have accumulated. Attention to involuntary smoking is of recent vintage, and only limited information regarding the health effects of such exposure upon the nonsmoker is available. Therefore, research is needed to define these effects.

The initial research priorities with respect to involuntary smoking should be focused on those populations which might be considered at particular risk of negative health effects based on the information now available; namely, children, patients with coronary artery disease, patients with hyperactive airways, and patients with chronic lung diseases. In addition, the potential effects of involuntary smoking on psychomotor performance merit priority attention because of their possible importance in certain circumstances (e.g., driving). More specifically:

1. Prospective studies are needed to define the relationship between parental smoking and the prevalence of respiratory illness and symptoms and pulmonary function status in children. Care should be taken to consider such confounding factors as socioeconomic status and the smoking habits of the children.

2. Further in-depth studies are needed on patients with demonstrable coronary artery disease to assess the effects of carefully-defined carbon monoxide and involuntary smoking exposures upon angina and other indicators of myocardial ischemia and performance.

3. The clinical (symptomatic) and physiologic responses to involuntary smoking exposure should be investigated in patients with demonstrably hyperactive airways ("asthmatics") and chronic lung diseases.

Involuntary Smoking: References

(1) AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS. TLVs® threshold limit values for chemical substances in workroom air adopted by the American Conference of Government Industrial Hygienists for 1973. Journal of Occupational Medicine 16(1): 39-49, January 1974.

(2) ANDERSON, E.W., ANDELMAN, R.J., STRAUCH, J.M., FORTUIN, N.J., KNELSON, J.H. Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. A study of ten patients with ischemic heart disease. Annals of Internal Medicine 79(1): 46-50, July 1973.

(3) ANDERSON, G., DALHAMN, T. The risks to health of passive smoking. Lakartidningen 70: 2833-2836, August 15, 1973.

(4) ARONOW, W.S. Effects of passive smoking on angina pectoris. New England Journal of Medicine 299(1): 21-24, 1978.

(5) ARONOW, W.S., CASSIDY, J. Effect of carbon monoxide on maximal treadmill exercise. A study in normal persons. Annals of Internal Medicine 83: 496-499, 1975.

(6) ARONOW, W.S., CASSIDY, J., VANGROW, J.S., MARCH, H., KERN, J.C., GOLDSMITH, J.R., KHEMKA, M., PAGANO, J., VAWTER, M. Effect of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. Circulation 50(2): 340-347, August 1974.

(7) ARONOW, W.S., FERLINZ, J., GLAUSER, F. Effect of carbon monoxide on exercise performance in chronic obstructive pulmonary disease. American Journal of Medicine 63: 904-908, 1977.

(8) ARONOW, W.S., GOLDSMITH, J.R., KERN, J.C., JOHNSON, L.L. Effects of smoking cigarettes on cardiovascular hemodynamics. Archives of Environmental Health 28(6): 330-332, June 1974.

(9) ARONOW, W.S., ISBELL, M.W. Carbon monoxide effect on exercise-induced angina pectoris. Annals of Internal Medicine 79(3): 392-395, September 1973.

(10) ARTHO, A., KOCH, R. Caracterisation olfactive des composes de la fumee de cigarettes (Characterization of the olfactory properties of the cigarette smoke components). Annales du Tabac (Section 1-11): 37-45, 1973.

(11) AYRES, S.M., GIANNELLI, S., JR., MUELLER, H. Myocardial and systemic responses to carboxyhemoglobin. Annals of New York Academy of Sciences 174: 268-293, 1970.

(12) AYRES, S.M., MUELLER, H.S., GREGORY, J.J., GIANNELLI, S., JR., PENNY, J.L. Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHb). Archives of Environmental Health 18: 699-709, 1969.

(13) BRIDGE, D.P., CORN, M. Contribution to the assessment of exposure of nonsmokers to air pollution from cigarette and cigar smoke in occupied areas. Environmental Research 5: 192-209, 1972.

(14) BRUNNEMANN, K.D., ADAMS, J.D., HO, D.P.S., HOFFMANN, D. The influence of tobacco smoke on indoor atmospheres. II. Volatile and tobacco specific nitrosamines in main- and sidestream smoke and their contribution to indoor pollution. Proceedings, 4th Joint Conference on Sensing of Environmental Pollutants, New Orleans, Louisiana, 1977. American Chemical Society, 1978, pp. 876-880.

(15) BRUNNEMANN, K.D., HOFFMANN, D. Chemical studies on tobacco smoke. XXIV. A quantitative method for carbon monoxide and carbon dioxide in cigarette and cigar smoke. Journal of Chromatographic Science 12(2): 70-75, February 1974.

(16) BRUNNEMANN, K.D., HOFFMANN, D. Chemical studies on tobacco smoke. LIX. Analysis of volatile nitrosamines in tobacco smoke and polluted indoor environments. In: Walker, F.A., Castegnaro, M., Griciute, L., Lyle, R.E. (Editors). Environmental Aspects of N-Nitroso Compounds. Lyon (IARC Scientific Publication No. 19), 1978, pp. 343-356.

(17) CAMERON, P., KOSTIN, J.S., ZAKS, J.M., WOLFE, J.H., TIGHE, G., OSELETT, B., STOCKER, R., WINTON, J. The health of smokers' and nonsmokers' children. Journal of Allergy 43(6): 336-341, June 1969.

(18) CAMERON, P., ROBERTSON, D. Effect of home environment tobacco smoke on family health. Journal of Applied Psychology 57(2): 142-147, 1973.

(19) CANO, J.P., CATALIN, J., BADRE, R., DUMAS, C., VIALA, A., GUILLERME, R. Determination de la nicotine par chromatographie en phase gazeuse. II.- Applications (Determination of nicotine by chromatography in the gaseous phase. II—Applications). Annales Pharmaceutiques Francaises 28(11): 633-640, 1970.

(20) CHAPPELL, S.B., PARKER, R.J. Smoking and carbon monoxide levels in enclosed public places in New Brunswick. Canadian Journal of Public Health 68: 159-161, 1977.

(21) COLLEY, J.R.T. Respiratory symptoms in children and parental smoking and phlegm production. British Medical Journal 2: 201-204, April 27, 1974.

(22) COLLEY, J.R.T., HOLLAND, W.W., CORKHILL, R.T. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. Lancet 2(7888): 1031-1034, November 2, 1974.

(23) CORN, M. Characteristics of tobacco sidestream smoke and factors influencing its concentration and distribution in occupied spaces. In: Rylander, R. (Editor). Environmental Tobacco Smoke Effects on the Non-Smoker. Report from a Workshop. Geneva, University of Geneva, 1974, pp. 21-36.

(24) CUDDEBACK, J.E., DONOVAN, J.R., BURG, W.R. Occupational aspects of passive smoking. American Industrial Hygiene Association Journal 37(5): 263-267, 1976.

(25) DALHAMN, T., EDFORS, M.-L., RYLANDER, R. Mouth absorption of various compounds in cigarette smoke. Archives of Environmental Health 16(6): 831-835, June 1968.

(26) DALHAMN, T., EDFORS, M.-L., RYLANDER, R. Retention of cigarette smoke components in human lungs. Archives of Environmental Health 17(5): 746-748, November 1968.

(27) DEROUANE, A., VERDUYN, G. Etude de quelques facteurs influencant la pollution de l'air a l'interieur des batiments (Study of some factors affecting air pollution inside buildings). Tribune du Cebedeau 27: 482-488, 1974.

(28) DUBLIN, W.B. Secondary smoking: A problem that deserves attention. Pathologist 26(9): 244-245, September 1972.

(29) DUBLIN, W. B. Unwilling smoking. California Medicine 117(1): 76-77, July 1972.

(30) ELLIOTT, L.P., ROWE, D.R. Air quality during public gatherings. Journal of the Air Pollution Control Association 25(6): 635-636, June 1975.

(31) ENVIRONMENTAL PROTECTION AGENCY. National primary and secondary ambient air quality standards. Federal Register 36(84-Part II): 8186-8201, April 30, 1971.

(32) EPSTEIN, N. The effects of tobacco smoke pollution on the eyes of the allergic nonsmoker. In: Steinfield, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH) 77-1413, 1977, pp. 337-345.

(33) GALUSKINOVA, V. 3,4-Benzpyrene determination in the smoky atmosphere of social meeting rooms and restaurants. A contribution to the problem of the noxiousness of so-called passive smoking. Neoplasma 11(5): 465-468, 1964.

(34) GLINER, J.A., RAVEN, P.B., HORVATH, S.M., DRINKWATER, B.L., SUTTON, J.C. Man's physiologic response to long-term work during thermal and pollutant stress. Journal of Applied Physiology 39(4): 628-632, October 1975.

(35) GODIN, G., WRIGHT, G., SHEPHARD, R.J. Urban exposure to carbon monoxide. Archives of Environmental Health 25(5): 305-313, November 1972.

(36) HARKE, H.-P. The problem of 'passive smoking.' Muenchener Medizinische Wochenschrift 112(51): 2328-2334, December 18, 1970.

(37) HARKE, H.-P. Zum Problem des Passivrauchens. I. Ueber den Einfluss des Rauchens auf die CO-Konzentration in Bueroraeumen (The problem of passive smoking. I. The influence of smoking on the CO concentration in office rooms). Internationales Archiv fuer Arbeitsmedizin 33(3): 199-206, 1974.

(38) HARKE, H.-P., BAARS, A., FRAHM, B., PETERS, H., SCHULTZ, C. The problem of passive smoking. The concentration of smoke constituents in the air of large and small rooms as a junction of the member of cigarettes smoked and of time. Internationales Archiv fuer Arbeitsmedizin 29: 323-339, 1972.

(39) HARKE, H.-P., BLEICHERT, A. Zum Problem des Passivrauchens (On the problem of passive smoking). Internationales Archiv fuer Arbeitsmedizin 29: 312-322, 1972.

(40) HARKE, H.-P., LIEDL, W., DENKER, D. Zum Problem des Passivrauchens. II. Untersuchungen Ueber den Kohlenmonoxidgehalt der Luft im Kraftfahrzeug durch das Rauchen von Zigaretten (The problem of passive smoking. II Investigations of CO level in the automobile after cigarette smoking). Internationales Archiv fuer Arbeitsmedizin 33(3): 207-220, 1974.

(41) HARKE, H.-P., PETERS, H. Zum Problem des Passivrauchens. III. Ueber den Einfluss des Rauchens auf die Co-Konzentration im Kraftfahrzeug bei Fahrten im Stadtgebiet (The problem of passive smoking. III. The influence of smoking on the CO concentration in driving automobiles). Internationales Archiv fuer Arbeitsmedizin 33(3): 221-229, 1974.

(42) HARLAP, S., DAVIES, A.M. Infant admissions to hospital and maternal smoking. Lancet 1(7857): 529-532, March 30, 1974.

(43) HARMSEN, H., EFFENBERGER, E. Tobacco smoke in transportation vehicles, living and working rooms. Archiv fuer Hygiene und Bakteriologie 141(5): 383-400, 1957.

(44) HINDS, W.C., FIRST, M.W. Concentrations of nicotine and tobacco smoke in public places. New England Journal of Medicine 292(16): 844-845, April 17, 1975.

(45) HOEGG, U.R. Cigarette smoke in closed spaces. Environmental Health Perspectives 2: 117-128, October 1972.

(46) HOEGG, U.R.E. The significance of cigarette smoke in confined spaces. Thesis. University of Cincinnati, Division of Graduate Studies, Department of Environmental Health. 1972, 137 pp. (Abstract)

(47) JERMINI, C., WEBER, A., GRANDJEAN, E. Quantitative Bestimmung verschiedener Gasphasenkomponenten des Nebenstromrauches von Zigaretten in der Raumluft als Beitrag zum Problem des Passivrauchens (Quantitative determination of various gas-phase components of the side-stream smoke of cigarettes in the room air as a contribution to the problem of passive-smoking). International Archives of Occupational and Environmental Health 36(3): 169-181, 1976.

(48) JOHANSSON, C.R. Tobacco smoke in room air—an experimental investigation of odour perception and irritating effects. Building Services Engineer 43: 254-262, March 1976.

(49) JOHANSSON, C.R., RONGE, H. Akuta irritation seffekter av tobaksrok i rumsluft (Acute irritation effects of tobacco smoke in the room atmosphere). Nordisk Hygienisk Tidskrift 46: 45-50, February 1965.

(50) JOHNSON, W.R., HALE, R.W., NEDLOCK, J.W., GRUBBS, H.J., POWELL, D.H. The distribution of products between mainstream and sidestream smoke. Tobacco Science 175(21): 43-46, October 12, 1973.

(51) JONES, R.M., FAGAN, R. Application of mathematical model for the buildup of carbon monoxide from cigarette smoking in rooms and houses. American Society of Heating, Refrigeration and Air Conditioning Engineers Journal: 49-53, August 1974.

(52) LAWTHER, P.J., COMMINS, B.T. Cigarette smoking and exposure to carbon monoxide. Annals of the New York Academy of Sciences 174: 135-147, October 5, 1970.

(53) LEBOWITZ, M.D., BURROWS, B. Respiratory symptoms related to smoking habits of family adults. Chest 69(1): 48-50, January 1976.

(54) LEEDER, S.R., CORKHILL, R., IRWIG, L.M., HOLLAND, W.W., COLLEY, J.R.T. Influence of family factors on the incidence of lower respiratory illness during the first year of life. British Journal of Preventive and Social Medicine 30(4): 203-212, December 1976.

(55) LEFCOE, N.M., INCULET, I.I. Particulates in domestic premises. II. Ambient levels and indoor-outdoor relationships. Archives of Environmental Health 30(12): 565-570, December 1975.

(56) LUQUETTE, A.J., LANDISS, C.W., MERKI, D.J. Some immediate effects of a smoking environment on children of elementary school age. Journal of School Health 40(10): 533-536, December 1970.

(57) MCNALL, P.E. Practical methods of reducing airborne contaminants in interior spaces. Archives of Environmental Health 30(11): 552-556, November 1975.

(58) MEDICAL COLLEGE OF WISCONSIN. Exposure of humans to carbon monoxide combined with ingestion of ethyl alcohol and the comparison of human performance when exposed for varying periods of time to carbon monoxide. Milwaukee, Medical College of Wisconsin, Department of Environmental Medicine, 1974, 39 pp.

(59) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1976, 23 pp.

(60) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. DEPARTMENT OF TRANSPORTATION, FEDERAL AVIATION ADMINISTRATION. Health aspects of smoking in transport aircraft U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Institute for Occupational Safety and Health, Division of Technical Services, December 1971, 85 pp.

(61) PIMM, P.E., SILVERMAN, F., SHEPHARD, R.J. Physiological effects of acute passive exposure to cigarette smoke. Archives of Environmental Health 33(4): 201-213, July/August 1978.

(62) RAVEN, P.B., DRINKWATER, B.L., HORVATH, S.M., RUHLING, R.O., GLINER, J.A., SUTTON, J.C., BOLDUAN, N.W. Age, smoking habits, heat stress, and their interactive effects with carbon monoxide and peroxyacetylnitrate on man's aerobic power. International Journal of Biometeorology 18(3): 222-232, October 1974.

(63) RAY, A.M., ROCKWELL, T.H. An exploratory study of automobile driving performance under the influence of low levels of carboxyhemoglobin. Annals of the New York Academy of Sciences 174: 396-408, October 5, 1970.

(64) RUMMEL, R.M., CRAWFORD, M., BRUCE, P. The physiological effects of inhaling exhaled cigarette smoke in relation to attitude of the nonsmoker. Journal of School Health 45(9): 524-529, November 1975.

(65) RUSSELL, M.A.H., COLE, P.V., BROWN, E. Absorption by non-smokers of carbon monoxide from room air polluted by tobacco smoke. Lancet 1(7803): 576-579, March 17, 1973.

(66) RUSSELL, M.A.H., FEYERABEND, C. Blood and urinary nicotine in non-smokers. Lancet 1(7900): 179-181, January 25, 1975.

(66a) RYLANDER, R. (Editor). Environmental Tobacco Smoke Effects on the Non-Smoker. Report from a Workshop. Geneva, University of Geneva, 1974, 90 pp.

(67) SCHILLING, R.S.F., LETAI, A.D., HUI, S.L., BECK, G.J., SCHOENBERG, J.B., BOUHUYS, A. Lung function, respiratory disease, and smoking in families. American Journal of Epidemiology 106(4): 274-283, 1977.

(68) SEBBEN, J., PIMM, P., SHEPHARD, R.J. Cigarette smoke in enclosed public facilities. Archives of Environmental Health 32(2): 53-58, March/April 1977.

(69) SEIFF, H.E. Carbon monoxide as an indicator of cigarette-caused pollution levels in intercity buses. U.S. Department of Transportation, Federal Highway Administration, Bureau of Motor Carrier Safety, April 1973, 11 pp.

(70) SEPPANEN, A. Smoking in closed space and its effect on carboxyhaemoglobin saturation of smoking and nonsmoking subjects. Annals of Clinical Research 9(5): 281-283, October 1977.

(71) SLAVIN, R.G., HERTZ, M. Indoor air pollution: A study of the Thirtieth Annual Meeting of the American Academy of Allergy. Paper presented at the American Academy of Allergy, Thirtieth Annual Meeting, San Diego, California, February 15-19, 1975, 4 pp.

(72) SPEER, F. Tobacco and the nonsmoker. A study of subjective symptoms. Archives of Environmental Health 16(3): 443-446, March 1968.

(73) SRCH, M. Ueber die Bedeutung des Kohlenoxyds beim Zigarettenrauchen im Personenkraftwageninnern (The significance of carbon monoxide in cigarette smoke in passenger car interiors). Deutsche Zeitschrift fuer die Gesamte Gerichtliche Medizin 60(3): 80-89, 1967.

(74) STEWART, R.D., BARETTA, E.D., PLATTE, L.R., STEWART, E.B., KALBFLEISCH, J.H., VAN YSERLOO, B., RIMM, A.A. Carboxyhemoglobin levels in American blood donors. Journal of the American Medical Association 229(9): 1187-1195, August 26, 1974.

(75) SZADKOWSKI, D., HARKE, H.-P., ANGERER, J. Kohlenmonoxidbelastung durch Passivrauchen in Bueroraeumen (Body burden of carbon monoxide from passive smoking in offices). Innere Medizin 3(6): 310-313, 1976.

(76) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

(77) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 77-8704, 1977, 235 pp.

(78) WAITE, C.L. Letter to the editor. New England Journal of Medicine 299(16): 897, October 19, 1978.

(79) WEBER, A., FISCHER, T., SANCIN, E., GRANDJEAN, E. La pollution de l'air par la fumee de cigarettes: Effets physiologiques et irritations (Air pollution due to cigarette smoke: Physiological and irritating effects). Sozial- und praeventiv-medizin/Medecine Sociale et Preventive 21(4): 130-132, July/August 1976.

(*80*) WEBER, A., JERMINI, C., GRANDJEAN, E. Irritating effects on man of air pollution due to cigarette smoke. American Journal of Public Health 66(7): 672-676, July 1976.

(*81*) WEBER-TSCHOPP, A., FISCHER, T., GRANDJEAN, E. Objektive und subjektive physiologische Wirkungen des Passivrauchens (Physiological and psychological effects of passive smoking). International Archives of Occupational and Environmental Health 37(4): 277-288, September 6, 1976.

(*82*) WEBER-TSCHOPP, A., JERMINI, C., GRANDJEAN, E. Luftverunreinigung und Belaestigung durch Zigarettenrauch (Air pollution and irritations due to cigarette smoke). Sozial- und Praeventiv-Medizin/Medecine Sociale et Preventive 21(2/3): 101-106, March–June 1976.

(*83*) WEIR, F.W., JOHNSON, D.F., ANGLEN, D.M., ROCKWELL, T.H., NEUHARDT, J.B., HARSHMAN, D.J., BALASUBRAMANIAN, K.N. The interactive effects of carbon monoxide and alcohol on driving skills. Columbus, Ohio State University, January 1975, 112 pp.

(*84*) WEIR, F.W., ROCKWELL, T.H., MEHTA, M.M., JOHNSON, D.F., ANGLEN, D.M., ATTWOOD, D.A., HERRIN, G.D., SAFFORD, R.R. An investigation of the effects of carbon monoxide on humans in the Driving Task. Columbus, Ohio State University Research Foundation, RF Projects 3141,3332, January 1973, 170 pp.

(*85*) YABROFF, I., MEYERS, E., FEND, V., DAVID, N., ROBERTSON, M., WRIGHT, R., BRAUN, R. The role of atmospheric carbon monoxide in vehicle accidents. Stanford Research Institute, Menlo Park, California, February 1974, 96 pp.

12. INTERACTIONS OF SMOKING WITH DRUGS, FOOD CONSTITUENTS, AND RESPONSES TO DIAGNOSTIC TESTS.

Food and Drug Administration

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Metabolism

Most drugs are metabolized in the liver, and metabolizing enzymes can occur in the soluble, mitochondrial, or microsomal fractions. The most common routes of drug metabolism involve oxidation, reduction, hydrolysis, and conjugation (*34*).

Mechanisms of Tobacco-Drug Interactions

Cigarette smoke is a complex mixture of noxious materials. Only a few of its components have been studied with respect to modifying drug disposition in animal, tissue, or enzyme systems. In this regard, polycyclic aromatic hydrocarbons (PAHs), nicotine, cadmium, and some pesticides have been reported to be enzyme inducers, and carbon monoxide (CO), nicotine, cadmium, some pesticides, hydrogen cyanide, and acrolein have been reported to be enzyme inhibitors (*23*).

The buccal and pulmonary bioavailability of most inhaled materials in cigarette smoke is relatively high. Dalhamn, et al. (*9*) found 86 to 99 percent retention of several components of cigarette smoke (acetaldehyde, isoprene, acetone, acetonitrile, toluene, and particulate matter) while CO absorption was only 54 percent. Mitchell (*38*) determined that appreciable retention of cigarette smoke occurs regardless of depth of inhalation. There was a mean retention of 37 percent of smoke in the buccal cavity, 82 percent during short inhalation (5 sec), and 97 percent during long inhalation (30 sec).

Aryl Hydrocarbon Hydroxylase

Aryl hydrocarbon hydroxylase (AHH), sometimes referred to as benzpyrene hydroxylase, is a mixed-function oxidase enzyme found in human and animal tissues. An extensive literature and many reviews cover the subject (*5*, *13*, *49*). AHH activity in many tissues is increased markedly by a variety of foreign compounds present in tobacco smoke, including most of the PAHs. Many carcinogens are biotransformed by AHH into reactive intermediates, such as epoxides, which can elicit cell transformation, mutagenicity, and cytotoxicity.

Inducers of microsomal oxidase enzymes can be classified according to their effects on various components of the enzyme system. The simplest categorization includes phenobarbital and many other drugs as stimulators of cytochrome P-450, while methylcholanthrene and PAHs produce an increase of a modified form of cytochrome P-450, namely cytochrome P-448 or cytochrome P_1-450. A summary of the primary biochemical and pharmacological differences between the two main classes of inducers is provided in Table 1. Steroids form a third group of compounds that can induce liver microsomal enzyme activity under certain conditions. These data, derived entirely from animal systems, led the authors to expect that, to the degree to which PAH constitutes the main enzyme inducer in cigarette smoke, only some

TABLE 1.—Differences between hepatic effect of phenobarbital and polycyclic hydrocarbons

Characteristic	Phenobarbital	Polycyclic aromatic hydrocarbons
Onset of effects	8-12 hr	3-6 hr
Time of maximum effect	3-4 hr	24 hr
Liver enlargement	Marked	Slight
Protein synthesis	Large increase	Small increase
Phospholipid synthesis	Marked increase	No effect
Liver blood flow	Increase	No effect
Ligandin content	Increase	Slight increase
Biliary flow	Increase	No effect
Enzyme components		
Cytochrome P-450	Increase	No effect
Cytochrome P-448	No effect	Increase
$NADPH_2$-cytochrome C reductase	Increase	No effect
Substrate specificity		
N-Demethylation of ethylmorphine and meperidine	Increase	No effect
N-Demethylation of 3-methyl-4-methyl-aminobenzene	Increase	Increase
Aliphatic hydroxylation of hexobarbital and pentobarbital	Increase	No effect
Aromatic hydroxylation of benzo(a)pyrene and zoxazolamine	Inrease	Large increase
4-Hydroxylation of biphenyl	Increase	Increase
2-Hydroxylation of biphenyl	Slight increase	Increase
Dehalogenation of halothane	Increase	No effect
Glucuronidation of bilirubin	Increase	Increase
Sulfoxidation of chlorpromazine	Increase	No effect

SOURCE: Jusko, W. (*23*).

drug disposition pathways will be modified by use of tobacco. Unlike phenobarbital, which affects diverse aspects of liver function, including blood and biliary flow, the actions of PAHs seem to be limited to the induction of selected drug-metabolizing enzymes (*5*, *13*, *27*, *28*, *42*, *49*).

Studies with human tissues demonstrate a correlation between cigarette smoking, increased AHH activity, and enhanced biotransformation of numerous—but selected—drugs that share both the P-450 and P-448 mixed-function oxidase pathways. Kapitulnik, et al. (*25*) found strong correlations between AHH activity in autopsied human livers and the metabolism rates of drugs, including hydroxylation of antipyrine, hexobarbital, and zoxazolamine. The hydroxylation of coumarin and the O-dealkylation of 7-ethoxycoumarin correlated more poorly. Nebert, et al. (*41*) and Welch, et al. (*65*) found significantly

higher levels of placental AHH in women with a history of cigarette smoking. The latter investigators also found an increase in aminoazo dye N-demethylase activity in placentas from smokers. Placental tissues show an excellent correlation between zoxazolamine and benzo(a)pyrene (BP) hydroxylation. The largest activities were found in cigarette smokers (*24*), although the stimulation of O-dealkylation of 7-ethoxycoumarin was less marked while oxidative aromatization (by steroid hydroxylase) of Δ^4-androstene-3,17-dione to estradiol and estrone was not affected. Much of these data show various degrees of correlation of drug and AHH activity and reflect the presence of several distinct monooxygenase systems.

Other than liver, human tissues which metabolize benzo(a)pyrene include lung, skin, lymphocytes, and some fetal tissues (*51*). The presence of inducible AHH activity in almost every animal tissue indicates the ubiquitous distribution of this enzyme (*50*). The liver is the most active tissue per unit weight in hydroxylating BP. Futhermore, its large size and blood flow, relative to other organs, make it the most dominant and important organ in BP-induced drug metabolism. Thus, most changes in drug biotransformation in response to smoking are presumed to occur in the liver. Welch, et al. (*64, 66*) were able to rule out much of an effect of intestinal metabolism in the enhanced first-pass metabolism of phenacetin. However, the potential for alteration of drug disposition via induction of drug metabolism in other major perfusion sites such as the kidney should not be ignored. Several animal studies have shown that PAHs are effective inducers of renal drug metabolism in rats and rabbits (*21, 63*).

The data obtained from animal systems reflecting the physiological and substrate specificity of PAH induction somewhat parallel the role of cigarette smoking in altering drug disposition in man. The selective increase in aliphatic hydroxylation of various drugs in smokers (antipyrine, pentazocine), which does not occur in animals, may either reflect species differences or be caused by the myriad other compounds in smoke capable of inducing oxidative enzymes. Alternatively, a rate-limiting process other than enzymatic activity (protein binding, blood flow) may control disposition of these drugs. For example, the rate of aromatic hydroxylation of phenytoin is saturable and is appreciably dependent on diffusion of free drug from plasma in man, while animals generally form different ring-hydroxylated metabolites and exhibit product inhibition in overall biotransformation of the metabolite (*22*).

The absence of an effect of smoking on liver size appears to be common in man and animals. Lewis, et al. (*30*) examined body organ weights in relation to smoking habits in 172 autopsied subjects. Mean liver weights were 1111 g/m^2bsa in male nonsmokers versus 980 g/m^2bsa in heavy smokers. On the other hand, the nonsmokers tended to have lighter kidneys and lungs than the smokers.

Microsomal Enzyme Systems Which Catalyze Drug Metabolism

Mueller and Miller (*39, 40*) first described the metabolism of a foreign compound by hepatic microsomes. They showed that the microsomal fraction of a liver homogenate catalyzed both the reductive splitting of the azo linkage and the oxidative N-demethylation of aminoazo dyes. The reactions required nicotinamide-adenine dinucleotide phosphate (NADP), nicotinamide-adenine dinucleotide (NAD), and molecular oxygen. A wide variety of oxidative reactions are known to occur in microsomes: deamination, 0-, N-, and S-dealkylation, expoxidation, hydroxylation of alkyl and aryl hydrocarbons, formation of alkyl derivatives, N-hydroxylation, N- and S-oxidation and dehalogenation. Azo- and nitro-reductase activities are also found in hepatic microsomes. The reactions are visualized more simply as different kinds of hydroxylation reactions (*3, 14, 16*): aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, deamination, sulfoxidation, and N-oxidation. (See Mannering (*35*) for a thorough discussion of the microsomal enzyme systems which catalyze drug metabolism.)

Drug Metabolizing Systems of the Hepatic Endoplasmic Reticulum

The microsomal drug metabolizing system is thought of as a mixed function oxidase mechanism whereby nicotinamide-adenine dinucleotide phosphate reductase (NADPH) reduces a component in microsomes which then reacts with molecular oxygen to form an "active oxygen" intermediate. The "active oxygen" is then transferred to the drug. Gillette (*15*) formulated the overall reaction as follows:

1. $NADPH + A + H^+ \rightarrow AH_2 + NADP^+$
2. $AH_2 + 0_2 \rightarrow$ "active oxygen"
3. "Active oxygen" + drug $\rightarrow$ oxidized drug + A + H_2O

In sum: $NADPH + O_2 +$ drug $= NADP^+ + H_2 +$ oxidized drug.

Key enzymes in the overall reactions are nicotinamide-adenine dinucleotide phosphate reductase (NADPH)-cytochrome C reductase, the flavin enzyme involved in the oxidation of NADPH, cytochrome P-450, which in its reduced form is generally considered to be A, and NADPH cytochrome P-450 reductase, which functions in the reduction of oxidized cytochrome P-450.

This mechanism requires that equivalent amounts of NADPH, oxygen, and substrate be utilized in the reaction. Stoichiometric relationships have been obtained for the hydroxylation of phenylalanine by hepatic microsomes (*26*) and the hydroxylation of 17-hydroxyprogesterone by adrenal microsomes (*8*). Trimethylamine has been reported to stimulate NADPH oxidation by an amount equivalent to the amount of trimethylamine oxide formed (*2*), and hexobarbital was found to increase NADPH oxidation in accordance with stoichiometric expectations (*62*). However, in several studies (*14, 15, 16, 17*) Gillette and coworkers found that some drugs had no effect on NADPH

oxidation, whereas others had more of an effect than could be accounted for by the metabolism of the drug. Microsomes contain enzymes which oxidize NADPH and utilize molecular oxygen in the absence of drugs, greatly complicating the analysis. Whether or not a drug stimulates or depresses NADPH oxidation would seem to depend upon whether or not it stimulates or depresses cytochrome P-450 reductase activity; this, in turn, would seem to depend upon whether the drug combines with cytochrome P-450 as a type I or as a type II compound (*17, 18, 19*) as discussed below. Ernster and Orrenius (*10*) demonstrated a 1:1:1 stoichiometry of oxygen utilization, NADPH disappearances, and formaldehyde formation from the oxidative demethylation of aminopyrine. However, Estabrook and Cohen (*11*) found that stoichiometry did not support the basic assumption of a mixed function oxidase reaction, that a mole of NADPH be oxidized for each mole of formaldehyde formed; two moles of nicotine-adenine dinucleotide phosphate (NADP) were formed per mole of formaldehyde, suggesting that the reaction is more complex than anticipated. Sasame, as cited in Mannering (*37*), did not find a stoichiometric relationship between NADPH and hexobarbital oxidation; the amount of NADPH oxidized was about 50 percent greater than the amount of hexobarbital metabolized.

Figure 1 shows the electron transfer system involving cytochrome P-450 as conceived by Omura, et al. (*43, 48*).

The first description of the microsomal system responsible for drug metabolism (*39, 40*) included a role of nicotinamide-adenine dinucleotide reductase (NADH) as well as NADPH. From time to time since then, NADH has been implicated in reactions involving drug metabolism (*6, 42, 62*). Using the mechanism of peroxidase action as a model, Estabrook and Cohen (*11*) suggested a way in which NADH might contribute to the reaction (Figure 2). NADPH may serve as an electron donor, via a respiratory chain, direct to cytochrome P-450 with an associated branched pathway to cytochrome b_5, the only cytochrome other than cytochrome P-450 found in microsomes. In this way, cytochrome b_5 might serve as a second electron donor to cytochrome P-450 and thus satisfy the requirement of two electrons for the overall reaction.

Sih and coworkers (*57, 58*) question the function of NADPH as solely to provide the reducing equivalents for cytochrome P-450 via the electron transfer system as shown in Figure 1. Mannering (*35*) discusses the three lines of evidence leading to the scheme given in Figure 3, which visualizes a dual role of NADPH in the oxidation of corticosteroids by mitochondria of the adrenal cortex.

Much of the speculation regarding the components of the microsomal drug metabolizing system existed because attempts to solubilize cytochrome P-450 in active form had failed, and it was necessary to employ crude microsomal preparations. In various studies (*7, 31, 32, 33*)

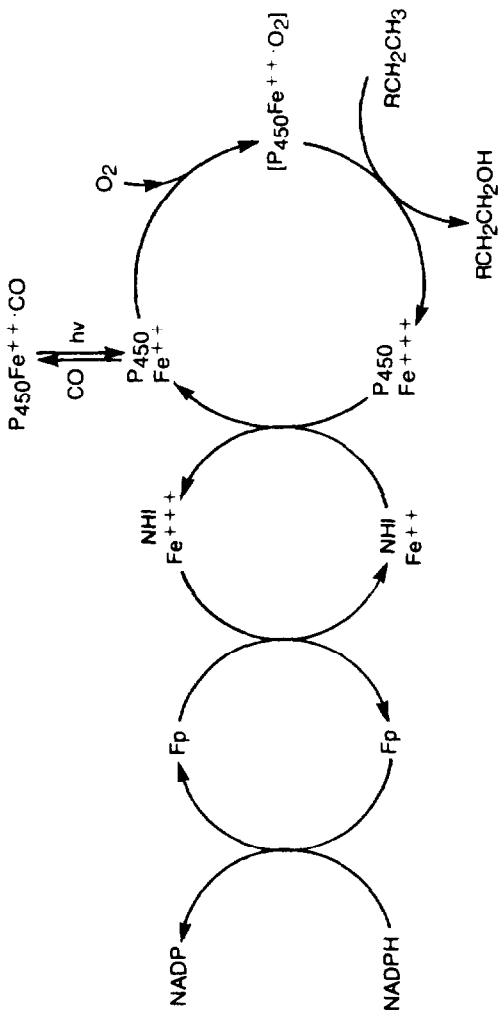

FIGURE 1.—Proposed electron transfer system employed in the microsomal metabolism of drugs. F_p = flavoprotein (in the liver, cytochrome C reductase; in the adrenal, adrenodoxin reductase); NHIP = non-heme iron protein (in the adrenal, adrenodoxin)
SOURCE: Omura, T. (*43,48*).

Coon and Lu and their associates did much toward solving this problem.

Solubilization of hepatic microsomes from the rabbit with a mixture of glycerol, dithiothreitol, and sodium deoxycholate in a potassium citrate buffer produced an extract which was resolved into a fraction

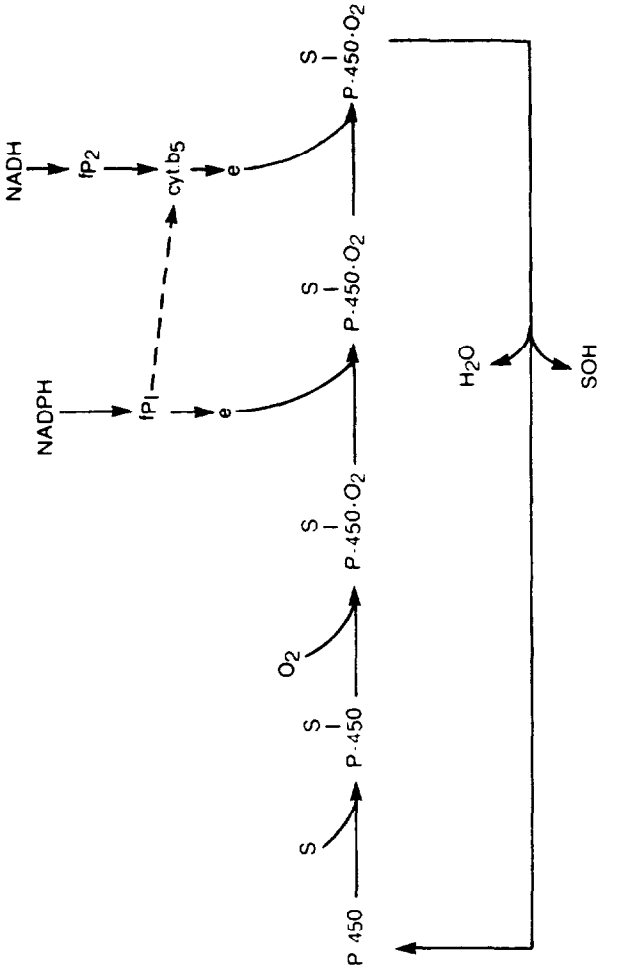

FIGURE 2.—Scheme showing how NADH and cytochrome b_5 might contribute to the electron transfer system employed in the microsomal metabolism of drugs

SOURCE: Estabrook, R. (*11*).

containing cytochrome P-450, a fraction containing a NADPH reductase, and a fat soluble, heat stable fraction. All three fractions were necessary for the maximal oxidation of drugs (benzphetamine, aminopyrine, ethylmorphine, hexobarbital, norcodeine, p-nitroanisole) or for the ω-hydroxylation of lurate. The criterion for the solubilization of cytochrome P-450 was that it remained in the supernatant fraction

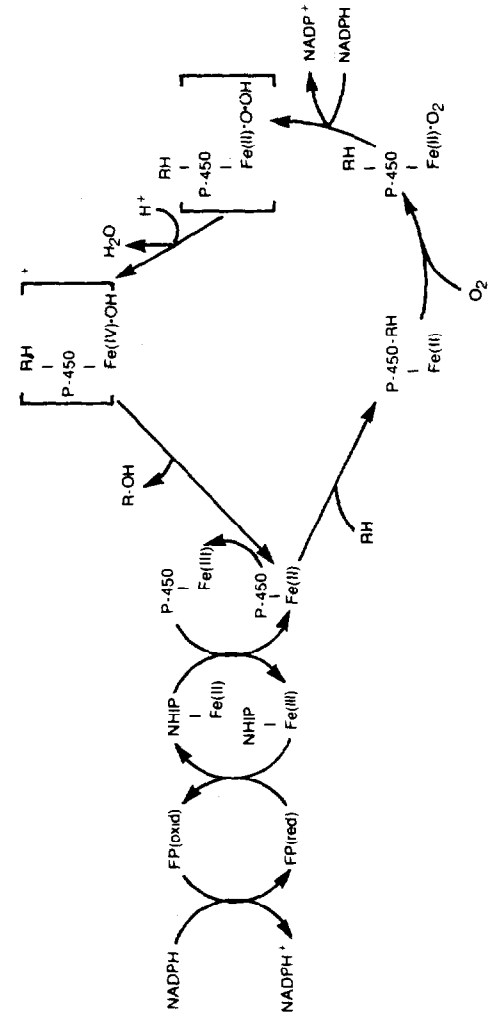

FIGURE 3.—Scheme illustrating a proposed dual role of NADPH in the oxidation of corticosteroids by mitochondria on the adrenal cortex. FP = flavoprotein (adrenodoxin); NHIP = non-heme iron protein (adrenodoxin reductase)

SOURCE: Sih, C. (*57,58*)

of the preparation after centrifugation at 105,000 × g for 2 hours. These fractions may provide the opportunity for purification and identification of the components of the system.

Both NADH and NADPH can act as the electron donor in the reduction of nitro compounds. The reaction is presumed to proceed to the primary amine through the formation of nitroso and hydroxyl-

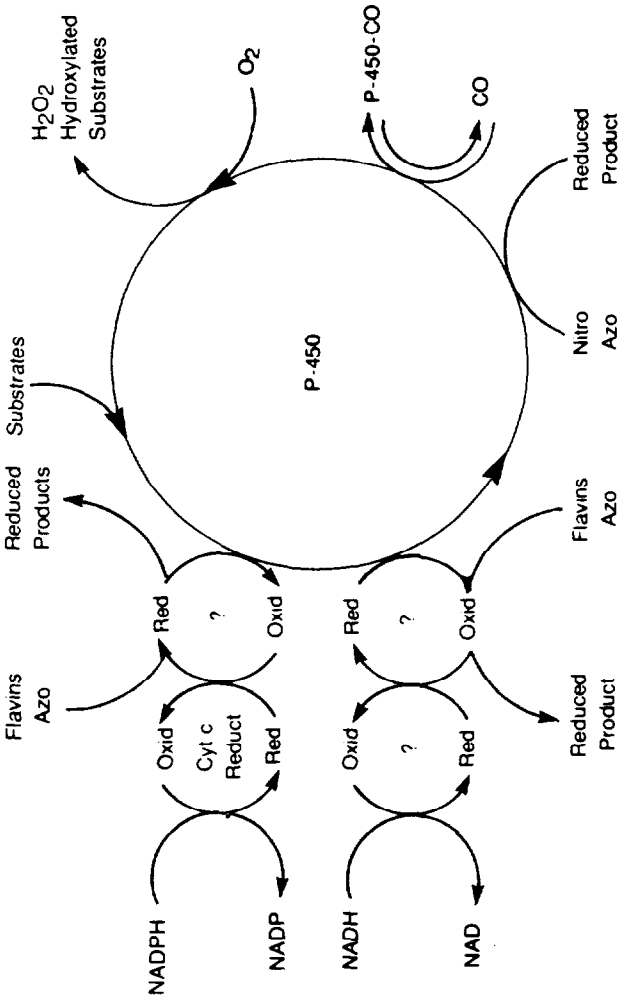

FIGURE 4.—Scheme showing how the microsomal electron transfer system might function in both the oxidation and reduction of drugs
SOURCE: Gillette, J.R. (*19*).

amine derivates. Nitroreductase is active only under anaerobic conditions. Sensitivity to oxygen may be due in part to the auto-oxidation of the hydroxylamine intermediate (*19*). In studies which employed p-nitrobenzoate as a substrate, Gillette, et al. (*19*) concluded that the reduction was mediated by cytochrome P-450. These investigators proposed an electron transport system which would explain both the oxidative and the reductive function of the microsomal drug-metabolizing system (Figure 4).

Cytochrome P-450

Cytochrome P-450, earlier referred to as the CO-binding pigment, was first described by Klingenberg (*29*), Garfinkel (*12*), and Omura and Sato (*44, 45, 46, 47*). It is found in abundance not only in hepatic microsomes, but also in the microsomes and mitochondria from the adrenal cortex where it functions in the hydroxylation of steroids (*11, 48*), although not in the oxidation of most drugs. Lesser amounts are found in the kidney and intestinal mucosa (*37*). The presence of cytochrome P-450 has also been reported in mitochondria from the corpus luteum (*67*).

Factors concerning cytochrome P-450 include (*35*): (1) its spectral characteristics; (2) its conversion to cytochrome P-420 by a wide variety of compounds, such as phospholipase A, sodium deoxycholate and urea; and (3) its concentration in hepatic microsomes, which is influenced by various drugs, varies with age and sex, and is reported to rise after fasting. Drugs and other foreign compounds bind to hepatic cytochrome P-450 to produce different spectra of two general types, type I and type II. Type I compounds give a different spectrum with a λ max in the general range of 385-390 mμ and λ min in the equally broad range of 418-427 mμ; the λ max and min given by type II compounds are 425-435 and 390-405 mμ, respectively (*54*). Thus, with opposing λ max and λ min, type I and type II spectra are approximate mirror images of each other. Figure 5 presents type I (hexobarbital) and type II (aniline) spectra.

Compounds that induce microsomal drug metabolism tend to be type I compounds, such as aminopyrine, 3,4 benzpyrene, coumarin, DDT, ethylmorphine, hexobarbital, and progesterone; one exception is nicotine, a type II compound, which is reported to be an inducing agent. Mannering (*35*) presents a thorough discussion of the significance of the binding of cytochrome P-450 to compounds.

Cytochrome P_1-450 (P-448, P-446, High Spin P-450, Type a P-450)

The mechanism by which phenobarbital and many other drugs stimulate the synthesis of the microsomal drug metabolizing system has long been considered to be different from the mechanism whereby PAHs produce their inductive effects (*36*). This early assumption was based on the knowledge that drugs such as phenobarbital induce the increased metabolism of a much larger number of drugs and other foreign substances than do the PAHs such as 3-methylcholanthrene (3-MC) or 3,4-benzpyrene (BP). Attempts to measure some of the differences between the two inductive processes led to the conclusion that PAHs cause the synthesis of a modified cytochrome P-450. For lack of a more suitable nomenclature for the microsomal hemoproteins, the hemoprotein cytochrome was named P_1-450 (*37, 55, 59, 60, 61*).

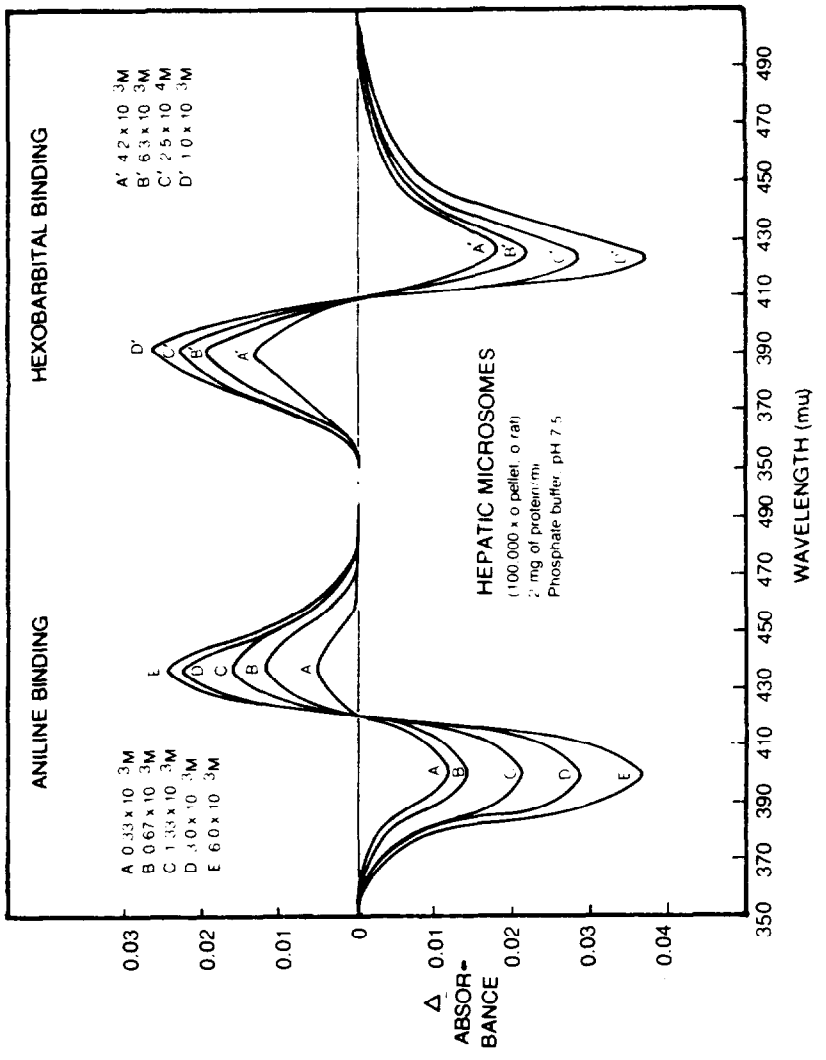

FIGURE 5.—Type I and type II binding spectra given by different concentrations of typical type I and type II compounds (hexobarbital, type I; aniline, type II)
SOURCE: Mannering, G. (*55*).

Because Alvares, et al. (*1*) observed a λ max at 448 mμ, cytochrome P_1-450 is sometimes called cytochrome P-448.

Although it is agreed that the administration of PAHs affect microsomal hemoprotein, there is much controversy as to whether the change reflects the formation or revelation of a new molecular species of hemoprotein, or is simply an alteration in the relative amounts of

interconvertible forms of a single hemoprotein. One view, based on indirect measurements as cited in Mannering (*35*), is that cytochrome P-450 and cytochrome P_1-450 are similar but separate entities, each of which can exist in two interconvertible forms.

Direct comparison of cytochrome P-450 and cytochrome P_1-450 was made possible through solubilization and partial purification of the microsomal hemoproteins from phenobarbital and 3-MC treated rats (unpublished observations of Fujita and Mannering as cited in Mannering (*35*)). The absolute spectrum of soluble purified cytochrome P_1-450 is shown in Figure 6, and some properties of cytochromes P-450 and P_1-450 in Table 2. The absolute spectra of the two hemoproteins are very much alike, but there are differences. The Soret peaks at 448 mμ and 450 mμ (reduced + CO) shown by cytochrome P_1-450 and cytochrome P-450, respectively, accord with what was expected from spectral studies employing microsomes. The Soret peak at 414 mμ rather than at 418 mμ (reduced hemoprotein) also distinguishes cytochrome P_1-450 from cytochrome P-450.

Particularly to be noted is the absence of a peak at about 395 mμ. Putatively, a peak at 395 mμ characterizes the form of the P-450 hemoprotein that results when PAHs are administered (*20, 53*). The most likely explanation for the peak at 395 mμ is that 3,4-benzpyrene, a type I compound (*53*), or a metabolite, binds with hemoprotein to produce a type I spectrum. The PAH or its metabolite binds more avidly than most type I compounds and is not lost during preparation of the microsomes. However, the loss of 3-MC or its metabolite occurs when the hemoprotein is solubilized.

Further evidence for the existence of two molecular species of P-450 hemoprotein was obtained by comparing the cytochrome P-420 derived from cytochromes P-450 and P_1-450 (*56*). When hepatic microsomes from untreated rats were incubated under nitrogen at 4°C for 24 hours with 0.07% steapsin, about 25 percent of the P-450 hemoprotein was solubilized as P-420 hemoprotein. After desalting and concentrating the clear solution to about one-fourth its volume, an aggregate of cytochrome P-420 was formed consisting of microtubules with globular substructures (*56*). Microsomes from rats that had received 3-MC, when treated in the same manner, also yielded aggregates; but only small numbers of the tubular structures were seen, their presence possibly due to the existence of some residual cytochrome P-450 in the microsomes. Aggregates of cytochrome P-420 showed both type I and type II binding with drugs, but aggregates of cytochrome P_1-420 bound only with type II compounds. On the basis of heme content, the molar absorbency of cytochrome P-420 was determined to be 110 $mM^{-1}cm^{-1}$, whereas that of cytochrome P_1-420 was 134 $mM^{-1}cm^{-1}$. Disc electrophoresis of aggregates solubilized with 8 M urea disclosed differences in the ionic mobilities of the two P-420 hemoproteins.

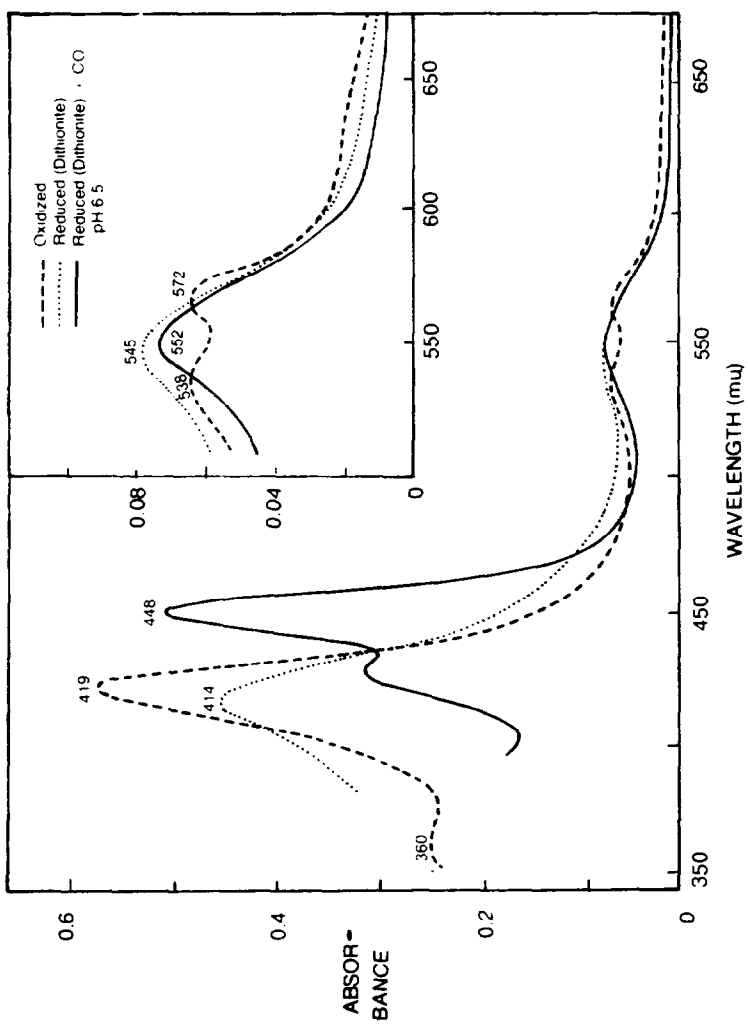

FIGURE 6.—Absolute spectra of solubilized microsomal P–450 hemoprotein (cytochrome P_1–450) from livers of rats treated with 3–MC (Fujita and Mannering, unpublished results). The hemoprotein was solubilized by treating microsomes with Triton N–101 and fractionating the supernatant on a DEAE cellulose column. The preparation was free of cytochrome b_5, but contained a small amount of P–420 hemoprotein. Table 2 summarizes the spectral properties of solubilized cytochromes P–450 and P_1–450

SOURCE: Mannering, G. (*35*).

In summary, the preponderance of evidence leads to the following conclusions:

TABLE 2.—**Absorption peaks and molar extinction coefficients of absolute spectra of soluble cytochromes P-450 and P_1-450**[a]

Conditions		Cytochrome P-450[b] max (mu)	Cytochrome P-450[b] ($mM^{-1}cm^{-1}$)	Cytochrome $P_1$450[c] max (mu)	Cytochrome $P_1$450[c] ($mM^{-1}cm^{-1}$)
Oxidized		360	49.2	360	45.7
	Soret	418	104.2	419	120.3
		537	12.9	537	13.5
		568	12.3	568	13.4
Reduced	Soret	418	86.0	414	90.1
		545	14.9	545	16.4
Reduced + CO		423	65.8	423	60.0
	Soret	450	89.1	448	108.0
		548	13.9	551	15.4

[a]The hemoprotein were solubilized by treating microsomes with Triton N-101 and fractionating the supernatant on a DEAE celluclose column (Fujita and Mannering, unpublished observations). The preparations were free of cytochrome b_5, but they contained small amounts of P-420. The absolute spectrum of cytochrome P_1-450 is shown in Figure 7.

[b]The preparation contained 3.24 mu moles of P-450 hemoprotein/mg of protein, an increase of 4.3-fold over that contained in the microsomes from which the preparation was obtained. Recovery of hemoprotein was 15.5%.

[c]The preparation contained 4.42 mu moles of P-450 hemoprotein/mg of protein, an increase of 3.5-fold over that contained in the microsomes from which the preparation was obtained. Recovery of hemoprotein was 13.9%.

SOURCE: Mannering, G. (*55*).

1. The administration of polycyclic aromatic hydrocarbons (PAHs) causes the biosynthesis of cytochrome P_1-450, a molecular species of cytochrome P-450 not normally detectable in appreciable amounts of microsomes from untreated or phenobarbital-treated animals. This does not exclude the possibility that small amounts of cytochrome P_1-450 may be found in untreated animals; in fact, this can be expected to be the case. PAHs or other substances capable of inducing the synthesis of cytochrome P_1-450 may be present in the diet or atmosphere or may be produced by the intestinal flora. Early recognition of an exogenous inductive effect on the metabolism of a foreign substance was made by Brown, et al. (*4*) and by Reif, et al. (*52*) who observed that rancid diets contained oxidized steroids which stimulated the N-demethylation of aminoazo dyes.

2. Both cytochrome P-450 and cytochrome P_1-450 exist in their own interconvertible forms.

3. Cytochrome P_1-450 does not form as a result of the combination of native cytochrome P-450 with PAHs or their metabolites.

Mechanisms of Induction of Drug Metabolism Enzymes

Gelboin (*13*) has discussed mechanisms of induction of drug metabolism enzymes. Significant highlights of this discussion are as follows:

1. The stimulatory effect of PAHs and drugs on certain liver microsomal enzymes appears not to be mediated through the endocrine

system, as the stimulation of at least the aryl hydrocarbon hydroxylase (AHH) is observed in adrenalectomized and hypophysectomized rats.

2. The inducer acts directly on the target tissue.

3. The half-life of induced AHH activity is 3.3 ± 1.2 hours.

4. Results of studies in cell culture have suggested the following sequence of events in microsomal enzyme induction:

a. Upon addition of the inducer to the culture medium, it is rapidly incorporated, within several minutes, into the cell. This has been shown by the use of radioactive inducer and fluorescence microscopy (Miller and Gelboin, unpublished observations cited in Gelboin (*13*)). After incorporation, there appears to be a rapid interaction between inducer and receptor site which is followed by a period of RNA synthesis. This stage of enzyme induction involving RNA synthesis is sensitive to actinomycin-D inhibition. This early RNA synthesis phase is independent of translation, since it occurs in the presence of inhibitors of protein synthesis.

b. Then follows the protein synthesis stage which is sensitive to inhibitors of protein synthesis. This stage can proceed in the absence of the RNA synthesis stage and can occur in the presence of actinomycin-D. It seems to be a polymerization of amino acid into polypeptide chains.

c. The next step appears to be an assembly process of the newly-made polypeptide chains. This is independent of protein synthesis and may persist for up to two hours. This entire process results in the appearance of increased levels of AHH. The specific protein, made and assembled in the microsomes, may be either the hydroxylase or another protein which may activate by an allosteric mechanism an inactive form of the hydroxylase. All of these events appear before there are gross changes in either protein or RNA synthesis. This suggests that the RNA and protein, which are required to be synthesized, are very small percentages of total cell RNA and protein and that many of the gross changes of RNA and protein synthesis may be subsequent to, and parallel, but not directly responsible for, the appearance of the early increases of enzyme level.

Thus, the various studies on the effect of methylcholanthrene (MC) on nuclear RNA metabolism have shown that: (1) MC causes an increase in the uptake of orotic acid into nuclear RNA which suggests increased RNA synthesis; (2) MC increases the amount of RNA in liver cell nuclei; (3) RNA isolated from the liver cell nuclei of MC treated rats has greater stimulatory activity in an E. coli phenylalanine-incorporating system; and (4) the administration of MC *in vivo* stimulates RNA polymerase activity of either isolated liver nuclei or isolated chromatin. These effects of MC suggest an alteration in genetic transcription.

TABLE 3.—Summary of effects of methylcholanthrene or phenobarbital on gene-action system

Microsomes	Nucleus
Increases of: 1. Specific enzymes and protein (MC, PB) 2. Amino acid incorporation (MC, PB) a. More mRNA (PB) b. More sensitive to added mRNA (PB) 3. Effects prevented by: a. Puromycin (MC, PB) b. Actinomycin-D (MC, PB) c. Ethionine (MC, PB)	Increases of: 1. Orotic acid-^{14}C incorporation into RNA (MC) 2. RNA/DNA ratio (MC) 3. Messenger RNA content (MC) 4. Stimulation of RNA polymerase (MC, PB)
Inhibitions of: 1. NADPH cytochrome C reductase degradation (PB) 2. b_5 degradation (PB)	
Changes in: 1. Special properties of P-450 (MC) 2. Phospholipid metabolism (MC) 3. Kinetic behavior of hydroxylase (MC)	

SOURCE: Gelboin, H. (*15*).

Table 3 shows a summary of the effects of MC and phenobarbital (PB) on various aspects of nuclear and microsomal metabolism.

Summary

The pervasiveness of tobacco use in our society and the frequency of altered disposition and pharmacological effects of many common drugs in smokers make it apparent that cigarette smoking should be considered as one of the primary sources of drug interactions in man. Most of the experimental work in man, animals, and tissues involving enzyme systems indicates that the dominant effect of smoking is enhanced drug disposition caused by induction of hepatic microsomal enzymes. The primary causal agents are probably the polynuclear aromatic hydrocarbons which are potent and persistent in tissues. While several of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, the selectivity of this enhancement in activity is unpredictable. The effects of cigarette smoke on other potential rate-limiting disposition processes for drugs are largely unexplored.

Metabolism: References

(1) ALVARES, A.P., SCHILLING, G., LEVIN, W., KUNTZMAN, R. Studies on the induction of CO-binding pigments in liver microsomes by phenobarbital and 3-methylcholanthrene. Biochemical and Biophysical Research Communications 29(4): 521-526, June 1967.

(2) BAKER, J.R., CHAYKIN, S. The biosynthesis of trimethylamine-N-oxide. Journal of Biological Chemistry 237(4): 1309-1310, April 1962.

(3) BRODIE, B.B., AXELROD, J., COOPER, J.R., GAUDETTE, L., LA DU, B.N., MITOMA, C., UNDENFRIEND, S. Detoxification of drugs and other foreign compounds by liver microsomes. Science 121: 603-604, April 22, 1955.

(4) BROWN, R.R., MILLER, J.A., MILLER, E.C. The metabolism of methylated aminoazo dyes. IV. Dietary factors enhancing demethylation in vitro. Journal of Biological Chemistry 209: 211-222, 1954.

(5) CONNEY, A.H. Pharmacological implications of microsomal enzyme induction. Pharmacological Reviews 19(3): 317-366, 1967.

(6) CONNEY, A.H., BROWN, R.R., MILLER, J.A., MILLER, E.C. The metabolism of methylated aminoazo dyes. VI. Intracellular distribution and properties of the demethylase system. Cancer Research 17: 628-633, July 1957.

(7) COON, M.J., LU, A.Y.H. Fatty acid ω-oxidation in a soluble microsomal enzyme system containing P-450. In: Gillette, J.R., Conney, A.H., Cosmides, G.J., Estabrook, R.W., Fouts, J.R., Mannering, G.J. (Editors). Microsomes and Drug Oxidations. New York, Academic Press, 1969 pp. 151-166.

(8) COOPER, D.Y., ESTABROOK, R.W., ROSENTHAL, O. The stoichiometry of C_{21}hydroxylation of steriods by adrenocortical microsomes. The Journal of Biological Chemistry 238(4): 1320-1322, April 1963.

(9) DALHAMN, T., EDFORS, M.L., RYLANDER, R. Retention of cigarette smoke components in human lungs. Archives of Environmental Health 17: 746-748, November 1968.

(10) ERNSTER, L., ORRENIUS, S. Substrate-induced synthesis of the hydroxylating enzyme system of liver microsomes. Federation Proceedings 24: 1190-1199, September/October 1965.

(11) ESTABROOK, R.W., COHEN, B. Organization of the microsomal electron transport system. In: Gillette, J.R., Conney, A.H., Cosmides, G.J., Estabrook, R.W., Fouts, J.R., Mannering, G.J. (Editors). Microsomes and Drug Oxidations. New York, Academic Press, 1969, pp. 95-105.

(12) GARFINKEL, D. Studies on pig liver microsomes. I. Enzymic and pigment composition of different microsomal fractions. Archives of Biochemistry and Biophysics 77: 493-509, 1958.

(13) GELBOIN, H.V. Mechanisms of induction of drug metabolism enzymes. In: La Du, B.N., Mandel, H.G., Leong Way, E. (Editors). Fundamentals of Drug Metabolism and Drug Disposition. Baltimore, Williams and Wilkins, 1972, pp. 279-307.

(14) GILLETTE, J.R. Biochemistry of drug oxidation and reduction by enzymes in hepatic endoplasmic reticulum. Advances in Pharmacology 4: 219-261, 1966.

(15) GILLETTE, J.R. Metabolism of drugs and other foreign compounds by enzymatic mechanisms. Progress in Drug Research 6: 13-71, 1963.

(16) GILLETTE, J.R., BRODIE, B.B., LA DU, B.N. The oxidation of drugs by liver microsomes: On the role of TPNH and oxygen. Journal of Pharmacology and Experimental Therapeutics 119: 532-540, November 1957.

(17) GILLETTE, J.R., CONNEY, A.H., COSMIDES, G.J., ESTABROOK, R.W., FOUTS, J.R., MANNERING, G.J. (Editors). Microsomes and Drug Oxidations. Academic Press. New York, 1969, 547 pp.

(18) GILLETTE, J.R., GRAM, T.E. Cytochrome P-450 reduction in liver microsomes and its relationship to drug metabolism. In: Gillette, J.R., Conney, A.H., Cosmides, G.J., Estabrook, R.W., Fouts, J.R., Mannering, G.J. (Editors). Microsomes and Drug Oxidations. New York, Academic Press, 1969, pp. 133-149.

(19) GILLETTE, J.R., KAMM, J.J., SASAME, H.A. Mechanism of p-nitrobenzoate reduction in liver: The possible role of cytochrome P-450 in liver microsomes. Molecular Pharmacology 4: 541-548, November 1968.

(20) HILDEBRANDT, A., REMMER, H., ESTABROOK, R.W. Cytochrome P-450 of liver microsomes – one pigment or many. Biochemical and Biophysical Research Communications 30(6): 607-612, August 1968.

(21) HOOK, J.B., HEWITT, W.R. Development of mechanisms for drug excretion. American Journal of Medicine 62: 497-506, April 1977.

(22) JUSKO, W.J. Bioavailability and disposition kinetics of phenytoin in man. In: Kellaway, P., Petersen, I. (Editors). Quantitative Analytic Studies in Epilepsy. New York, Raven Press, 1976, pp. 115-136.

(23) JUSKO, W.J. Role of tobacco smoking in pharmacokinetics. The Journal of Pharmacokinetics and Biopharmaceutics 6(1): 7-39, 1978.

(24) KAPITULNIK, J., LEVIN, W., POPPERS, P.J., TOMASZEWSKI, J.E., JERINA, D.M., CONNEY, A.H. Comparison of the hydroxylation of zoxazolamine and benzo(a)pyrene in human placenta: Effect of cigarette smoking. Clinical Pharmacology and Therapeutics 20(5): 557-564, November 1976.

(25) KAPITULNIK, J., POPPERS, P.J., CONNEY, A.H. Comparative metabolism of benzo(a)pyrene and drugs in human liver. Clinical Pharmacology and Therapeutics 21(2): 166-176, February 1977.

(26) KAUFMAN, S. The enzymatic conversion of phenylalanine to tyrosine. Journal of Biological Chemistry 226: 511-524, 1957.

(27) KLAASSEN, C.D. Biliary excretion of drugs: Role of ligandin in newborn immaturity and in the action of microsomal enzyme inducers. Journal of Pharmacology and Experimental Therapeutics 195(2): 311-319, November 1975.

(28) KLAASSEN, C.D. Biliary flow after microsomal enzyme induction. Journal of Pharmacology and Experimental Therapeutics 168(2): 218-223, April 1969.

(29) KLINGENBERG, M. Pigments of rat liver microsomes. Archives of Biochemistry and Biophysics 75: 376-386, 1958.

(30) LEWIS, G.P., JUSKO, W.J., COUGHLIN, L.L., HARTZ, S. Cadmium accumulation in man: Influence of smoking, occupation, alcoholic habit and disease. Journal of Chronic Diseases 25: 717-726, December 1972.

(31) LU, A.Y.H., COON, M.J. Role of hemoprotein P-450 in fatty acid ω-hydroxylation in a soluble enzyme system from liver microsomes. Journal of Biological Chemistry 243(6): 1331-1332, March 25, 1968.

(32) LU, A.Y.H., JUNK, K.W., COON, M.J. Resolution of the cytochrome P-450-containing ω-hydroxylation system of liver microsomes into three components. Journal of Biological Chemistry 244(13): 3714-3721, July 10, 1969.

(33) LU, A.Y.H., STROBEL, H.W., COON, M.J. Hydroxylation of benzphetamine and other drugs by a solubilized form of cytochrome P-450 from liver microsomes: Lipid requirement for drug demethylation. Biochemical and Biophysical Research Communications 36(4): 545-551, May 1969.

(34) MANDEL, H.G. Pathways of drug biotransformation: Biochemical conjugations. In: La Du, B.N., Mandel, H.G., Leong Way, E. (Editors). Drug Metabolism and Drug Disposition. Baltimore, Williams and Wilkins, 1972, pp. 149-186.

(35) MANNERING, G.J. Microsomal enzyme systems which catalyze drug metabolism. In: La Du, B., Mandel, H., Leong Way, E. (Editors). Drug Metabolism and Drug Disposition. Baltimore, Williams and Wilkins, 1972, pp. 206-252.

(36) MANNERING, G.J. Significance of stimulation and inhibition of drug metabolism in pharmacological testing. In: Burger, A. (Editor). Selected Pharmacological Testing Methods. New York, Marcel Dekker, 1968, pp. 51-119.

(37) MANNERING, G.J., SLADEK, N.E., PARLI, C.J., SHOEMAN, D.W. Formation of a new P-450 hemoprotein after treatment of rats with polycyclic hydrocarbons. In: Gillette, J.R., Conney, A.H., Cosmides, G.J., Estabrook, R.W., Fouts, J.R., Mannering, G.J. (Editors). Microsomes and Drug Oxidations. New York, Academic Press, 1969, pp. 303-330.

(38) MITCHELL, R.I. Controlled measurement of smoke-particle retention in the respiratory tract. American Review of Respiratory Diseases 95: 526-533, January 1962.

(39) MUELLER, G.C., MILLER, J.A. The metabolism of methylated aminoazo dyes. II. Oxidative demethylation by rat liver homogenates. Journal of Biological Chemistry 202: 579-587, 1953.

(40) MUELLER, G.C., MILLER, J.A. The reductive cleavage of 4-dimethylaminoazobenzene by rat liver: The intracellular distribution of the enzyme system and its requirement for triphosphopyridine nucleotide. Journal of Biological Chemistry 180: 1125-1136, 1949.

(41) NEBERT, D.W., WINKER, J., GELBOIN, H.V. Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. Cancer Research 29: 1763-1769, October 1969.

(42) NIES, A.S., WILKINSON, G.R., RUSH, B.D., STROTHER, J.T., McDEVITT, D.G. Effects of alteration of hepatic microsomal enzyme activity on liver blood flow in the rat. Biochemical Pharmacology 25: 1991-1993, January 1976.

(43) OMURA, T., SANDERS, E., ESTABROOK, R.W., COOPER, D.Y., ROSENTHAL, O. Isolation from adrenal cortex of a nonheme iron protein and a flavoprotein functional as a reduced triphosphopyridine nucleotide-cytochrome P-450 reductase. Archives of Biochemistry and Biophysics 117: 660-673, September 1966.

(44) OMURA, T., SATO, R. The carbon monoxide-binding pigment of liver microsomes. I. Evidence for its hemoprotein nature. Journal of Biological Chemistry 239(7): 2370-2378, July 1964.

(45) OMURA, T., SATO, R. The carbon monoxide-binding pigment of liver microsomes. II. Solubilization, purification, and properties. The Journal of Biological Chemistry 239(7): 2379-2385, July 1964.

(46) OMURA, T., SATO, R. Fractional solubilization of haemoproteins and partial purification of carbon monoxide-binding cytochrome from liver microsomes. Biochimica Biophysica Acta 71: 224-226, 1963.

(47) OMURA, T., SATO, R. A new cytochrome in liver microsomes. Journal of Biological Chemistry 237(4): 1375-1376, April 1962.

(48) OMURA, T., SATO, R., COOPER, D.Y., ROSENTHAL, O., ESTABROOK, R.W. Function of cytochrome P-450 of microsomes. Federation Proceedings 24: 1181-1189, September/October 1965.

(49) PARKE, D.V. Induction of the drug-metabolizing enzymes. In: Parke, D.V. (Editor). Enzyme Induction. Basic Life Sciences Series, Vol. 6, London, Plenum, 1975, pp. 207-271.

(50) PARLI, C.J., MANNERING, G.J. Induction of drug metabolism. IV. Relative abilities of polycyclic hydrocarbons to increase levels of microsomal 3-methyl 4-methylaminoazobenzene N-demethylase activity and cytochrome P_1-450. Molecular Pharmacology 6: 178-183, March 1970.

(51) PELKONEN, O. Metabolism of benzo(a)pyrene in human adult and fetal tissues. In: Freudenthal, R.I., Jones, P.W. (Editors). Carcinogenesis, Vol. 1: Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis. New York, Raven Press, 1976, pp. 9-21.

(52) REIF, A.E., BROWN, R.R., POTTER, V.R., MILLER, E.C., MILLER, J.A. Effect of diet on the antimycin titer of mouse liver. Journal of Biological Chemistry 209: 223-226, 1954.

(53) SCHENKMAN, J.B., GREIM, H., ZANGE, M., REMMER, H. On the problem of possible other forms of cytochrome P-450 in liver microsomes. Biochimica Biophysica Acta 171: 23-31, September 1969.

(54) SCHENKMAN, J.B., REMMER, H., ESTABROOK, R.W. Spectral studies of drug interaction with hepatic microsomal cytochrome. Molecular Pharmacology 3: 113-123, March 1967.

(55) SHOEMAN, D.W., CHAPLIN, M.D., MANNERING, G.J. Induction of drug metabolism. III. Further evidence for the formation of a new P-450 hemoprotein after treatment of rats with 3-methylcholanthrene. Molecular Pharmacology 5: 412-419, July 1969.

(56) SHOEMAN, D.W., VANE, F., MANNERING, G.J. Differences in the hepatic cytochrome P-420 obtained from normal and 3-methylcholanthrene (MC) treated rats. Federation Proceedings 29: 738, March/April 1970. (Abstract)

(57) SIH, C.J. Enzymatic mechanism of steroid hydroxylation. Science 163: 1297-1300, March 21, 1969.

(58) SIH, C.J., TSONG, Y.Y., STEIN, B. The roles of reduced nicotinamideadenine dinucleotide phosphate in steroid hydroxylation. Journal of the American Chemical Society 90(19): 5300-5302, September 11, 1968.

(59) SLADEK, N.E., MANNERING, G.J. Evidence for a new P-450 hemoprotein in hepatic microsomes from methylcholanthrene treated rats. Biochemical and Biophysical Research Communications 24(5): 668-674, December 1966.

(60) SLADEK, N.E., MANNERING, G.J. Induction of drug metabolism. I. Differences in the mechanisms by which polycyclic hydrocarbons and phenobarbital produce their inductive effects on microsomal N-demethylating systems. Molecular Pharmacology 5: 174-185, March 1969.

(61) SLADEK, N.E., MANNERING, G.J. Induction of drug metabolism. II. Qualitative differences in the microsomal N-demethylating systems stimulated by polycyclic hydrocarbons and by phenobarbital. Molecular Pharmacology 5: 186-199, March 1969.

(62) TRIVUS, R.H., SPIRTES, M.A. The stoichiometry of microsomal drug dependent NADPH oxidation. Federation Proceedings 24: 152, March/April 1965. (Abstract).

(63) UOTILA, P., MARNIEMI, J. Variable effects of cigarette smoking on aryl hydrocarbon hydroxylase, epoxide hydratase, and UDP-glucuronosyltransferase activities in rat lung, kidney, and small intestinal mucosa. Biochemical Pharmacology 25: 2323-2328, July 1976.

(64) WELCH, R.M., CAVALLITO, J., GILLESPIE, D.D. Effect of analgesics and exposure to cigarette smoke on the metabolism of acetophenetidin by rat tissues. Drug Metabolism and Disposition 1(1): 211-215, 1973.

(65) WELCH, R.M., HARRISON, Y.E., CONNEY, A.H., POPPERS, P.J., FINSTER, M. Cigarette smoking: Stimulatory effect on metabolism of 3,4-benzpyrene by enzymes in human placenta. Science 160: 541-542, May 3, 1968.

(66) WELCH, R.M., HUGHES, C.R., DeANGELIS, R.L. Effect of 3-methylcholanthrene pretreatment on the bioavailability of phenacetin in the rat. Drug Metabolism and Disposition 4(4): 402-406, July/August 1976.

(67) YOHRO, T., HORIE, S. Subcellular distribution of P-450 in bovine corpus luteum. Journal of Biochemistry 61(4): 515-517, June 1967.

Effects on Pharmacokinetics and Pharmacodynamics

The effects of smoking on the action of drugs have become a subject of an increasing number of investigations. Because the number of smokers in our population is significant, it is important to determine whether cigarette smoking alters the pharmacologic effects or the pharmacokinetics of drugs.

The mechanism of these alterations includes: stimulation or inhibition of biotransformation of drugs by the various constituents of tobacco smoke, alteration of physiological processes that control drug disposition, direct interference in the mechanism of drug action and modification of psychopharmacological behavior, such as drug consumption and pain threshold. Cigarette smoking may necessitate modification of drug therapy and alter organ function or responsiveness.

Extensive literature is being assembled on the interaction of tobacco smoke and drugs. Recently, Jusko prepared an excellent review (*28*) on the role of tobacco smoke in the pharmacokinetics and pharmacology of drugs in man and animals. Much of this discussion merely paraphrases the Jusko review.[1] Conney, et al. (*14*) have previously reviewed the interaction of smoking and biotransformation of drugs, and Jick (*27*) has addressed smoking and clinical drug effects.

Studies of tobacco smoking and nicotine have been closely associated for many years. Tobacco in the United States yields about 1.2 mg (range 0.1 to 2.2 mg) of nicotine per cigarette. Chronic nicotine inhalation produces various types of pharmacological stimulation. The assimilation of about 0.5 mg/kg/day of nicotine from tobacco smoke offers the potential for altering drug disposition. The extraction of nicotine from inhaled smoke by habitual smokers is nearly complete (*25*). The half-life of nicotine has been determined to be about one hour (*25*). Most studies in animals indicate that nicotine is an enzyme inducer, which will be described later.

The most common effect of tobacco smoke on drugs in man and animal is an increase in biotransformation rate consistent with induction in drug-metabolizing enzymes. The first observation of this type in man was made by Rottenstein, et al. (*65*), who found that intravenous injection of nicotine did not cause nausea in smokers, but in nonsmokers the same dose produced nausea and vomiting. Beckett and Triggs (*6*) subsequently reported that, following intravenous administration or inhalation of nicotine, the urinary excretion of nicotine by nonsmokers and smokers was 55 to 70 percent and 25 to 50 percent, respectively. The reduced recovery of nicotine in the smoker group was explained by an increased biotransformation of the nicotine. Nicotine had previously been reported to accelerate the biotransformation of meprobamate in mice (*88*) and of benzo(a)pyrene (BP) by rat

[1] Reproduced in part from (*28*) with permission of William J. Jusko and the Plenum Publishing Company.

Table 4.—Plasma levels of phenacetin in cigarette smokers and nonsmokers at various intervals after the oral administration of 900 mg of phenacetin

Subjects	Hours after phenacetin administration			
	1	2	3.5	5
	Phenacetin concentration in plasma, μg/ml			
Nonsmokers	0.81 ± 0.20[a]	2.24 ± 0.73	0.39 ± 0.13	0.12 ± 0.04
Smokers	0.33 ± 0.23	0.48 ± 0.28	0.09 ± 0.04	0.02 ± 0.01

[a]Each value represents the means ± S.E. for nine subjects.
SOURCE: Pantuck, E.J. (*55*).

liver microsomes (*92*). Welch, et al. (*87*) were the first to demonstrate that inhaled tobacco smoke increased the activity of the enzyme benzo(a)pyrene hydroxylase in rat lung. This study has stimulated studies of tobacco smoke as a source of drug interaction.

Phenacetin

Pantuck, et al. (*54, 55*) first reported that tobacco smoke could induce the metabolism of a therapeutic agent in man. Oral doses of 900 mg of phenacetin were administered to nonsmokers and smokers (smoked more than 15 cigarettes per day). By measuring the concentration of phenacetin in plasma it was determined that the phenacetin concentrations in the plasma of cigarette smokers were markedly lower than those in the nonsmokers (Table 4), but the average half-life of phenacetin (about 50 minutes) in both groups was not different. The lower plasma levels were not due to altered absorption of phenacetin, as the urinary excretion of its major metabolite, N-acetyl-p-aminophenol (APAP), was identical for both groups. The low plasma concentrations of phenacetin in smokers were thus presumed to be caused by increased metabolism of phenacetin by the enzymes either in the gastrointestinal tract or during the "first pass" through the liver. On a theoretical pharmacokinetic basis, an increased degree of "first pass" metabolism will cause a decrease in the area under the plasma level curve with little change in half-life (*21*).

Similar results were reported almost simultaneously by Welch, et al. (*83*) on the effect of cigarettes in rats. These workers demonstrated that the enzyme benzo(a)pyrene (BP) hydroxylase was inducible by 3-methylcholanthrene (3-MC) and caused lower plasma phenacetin levels in rats.

Phenacetin has since been extensively studied as a model drug to investigate various aspects of cigarette smoke-induced changes in biotransformation rate. Welch, et al. (*83, 86*) and Pantuck, et al. (*53*) exposed rats to cigarette smoke and observed marked increases in the rate of *in vitro* metabolism of phenacetin in liver, lung, and intestinal

homogenates. Similar effects were found when rats were pretreated with 3-MC or BP. Welch, et al. (*86*) examined the effects of 3-MC treatment of rats on the bioavailability of phenacetin and APAP in portal and peripheral plasma following oral and intravenous administration. Comparison of the plasma phenacetin concentration in portal blood of the control rats and those treated with 3-MC revealed almost identical plasma concentration of phenacetin. The results indicated that 3-MC treatment had little effect on the passage of phenacetin into the portal circulation, but did influence to a very marked extent the passage of phenacetin from the portal circulation into the general circulation. These results were interpreted by the authors to mean that the dominant effect of 3-MC treatment was induction of hepatic rather than intestinal enzyme activity. On this basis, they concluded that the reduced plasma phenacetin concentrations in smokers probably reflected an increased "first pass" metabolism by the liver. However, Kuntzman, et al. (*39*) have investigated the stimulation of intestinal BP hydroxylase in rats following exposure to cigarette smoke or exposure to BP. Their data showed that rats exposed to cigarette smoke or to pretreatment with BP enhanced the *in vivo* metabolism of phenacetin and stimulated enzymes in the intestinal mucosa to O-dealkylate phenacetin to APAP. Therefore, the question whether the stimulatory effect of cigarette smoking on the metabolism of phenacetin occurs in the gastrointestinal tract or in an additional first-pass increase in liver metabolism remains unanswered.

Antipyrine

Antipyrine is an analgesic often used as a "marker" for several hepatic microsomal drug-metabolizing systems in man and animals. Vestal, et al. (*80*) studied the effects of aging and cigarette smoking on the disposition of antipyrine in 307 healthy subjects. Determination of the half-life and metabolic clearance rate (MCR) of antipyrine revealed that young and middle-aged smokers metabolized antipyrine more rapidly than nonsmokers (Table 5). The half-life and the metabolic clearance rate were defined as: $t_{1/2} = 0.693/k_e$ where k_e = overall elimination constant, and $MCR = aVd \times k_e$ where aVd = apparent volume of distribution.

The half-life was 16.5 percent longer and the total clearance (Cl_T) rate was 18.5 percent less in the older subjects than in the younger. By old age (60 to 92 years), there was essentially no difference in the Cl_T between smokers and nonsmokers, although the Cl_T diminished with age in all smoking categories. Similar total clearance values were reported by Wilson, et al. (*89*) and found to be 46.0 ml/hr/kg in smokers and 36.5 ml/hr/kg in nonsmokers following administration of antipyrine to subjects in the 24- to 45-year age range.

Hart, et al. (*23*) found enhanced metabolism of antipyrine in cigarette smokers. These investigators found a mean half-life of 12.5

TABLE 5.—Effect of age and cigarette smoking on antipyrine metabolism. Data are from 307 healthy subjects

Age group (yr)	t1/2 (hr)	Smoking[a] group	No. of subjects	MCR (ml/hr/kg)
Young (18-39)	12.7 ± 0.50[b]	Nonsmoker	37	30.6 ± 1.24
		Moderate	27	37.3 ± 2.39
		Heavy	9	42.4 ± 4.24
Middle (40-59)	13.8 ± 0.47	Nonsmoker	102	28.0 ± 0.86
		Moderate	30	37.2 ± 2.27
		Heavy	18	36.8 ± 3.02
Old (60-92)	14.8 ± 0.65	Nonsmoker	67	28.2 ± 1.09
		Moderate	14	29.9 ± 2.85
		Heavy	3	15, 21, 28

[a]Nonsmoker: Did not smoke or smoked "once in a while," Moderate: Smoked less than 20 cigarettes/day, Heavy: Smoked more than 20 cigarettes/day.
[b]Mean ± SEM
SOURCE: Vestal, R.E. (*80*).

hours in 17 nonsmokers and 10.8 hours in 25 smokers, a smaller but significant difference. To determine whether this difference was due to tobacco consumption, eight smokers were restudied two months after they stopped smoking. The half-life of antipyrine had increased in six of the subjects, with an overall increase of about 23 percent. Welch, et al. (*84*) reported the mean half-life of antipyrine was 4.2 hours in epileptic patients treated with anti-convulsants for more than two months; whereas the mean half-life was found to be 12.6 hours in normal volunteers, three of whom were smokers. These data suggested that the anti-convulsant, phenytoin, may be a much stronger enzyme inducer than tobacco smoke. However, Kellermann and Luyten-Kellermann (*31*) found that the half-life of antipyrine was decreased 22 percent in normal subjects following 7 days on orally administrated phenobarbital. This shortening of the antipyrine half-life is almost identical in the report by Hart, et al. (*23*).

Kellerman, et al. (*31, 32, 33*) measured the half-life of antipyrine and the percent induction of BP hydroxylase by 3-MC in mitogen-stimulated lymphocytes from normal individuals. Resting lymphocytes had relatively little BP hydroxylase activity and the capacity to induce lymphocyte activity *in vitro* correlated with hepatic metabolism of various drugs in the same individual. The antipyrine half-life ranged from 7.7 to 16.2 hours and showed a high inverse correlation coefficient ($r = 0.923$) with the BP hydroxylase ratio. This indicated that antipyrine and BP share one or more common determinants that are responsible for the observed interindividual variation in the oxidation rates, and that antipyrine may serve as a useful predictor drug for

evaluating the drug- and carcinogen-metabolizing capacity of different individuals in the human population. The difference in the antipyrine half-life and the metabolic clearance rate between smokers and nonsmokers, however, was not large and, therefore, makes antipyrine an insensitive predicator for smoking effects.

Recently, Ambre, et al. (*3*) reported the antipyrine total clearance rate in patients with bronchogenic carcinoma, in patients with chronic lung disease, and in normal subjects. The mean antipyrine Cl_T values were 2.98 ± 0.68, 2.02 ± 0.67, and 2.14 ± 0.69 liters/hour, respectively. These results could not be reproduced by Tschanz, et al. (*74*), however. The latter group examined patients with lung cancer and a malignancy-free control group very well matched for age, sex, drug intake, smoking, and drinking habits. Their study took more blood samples than the Ambre study and the mean Cl_T values were determined to be 47.5 ± 0.9 in the cancer group and 55.7 ± 0.7 mg/kg/hr in the malignancy-free groups; this was a reversal of the earlier study. This topic should be investigated further, as an increase in antipyrine Cl_T in cancer patients would suggest a common factor in the observations of bronchogenic carcinoma, enhanced drug disposition, and inducibility of BP hydroxylase. This common factor may be a genetic susceptibility (*33*) to the multiple effects of exposure to polycyclic aromatic hydrocarbons (PAHs, PNAs).

Theophylline and Other Xanthines

Theophylline

Theophylline is of primary importance as a bronchodilator used to treat acute and chronic asthma or bronchitis. It is generally recognized that the therapeutic index of theophylline is narrow and the disposition rate among patients is widely variable. Jenne, et al. (*26*), Hunt, et al. (*24*), and Powell, et al. (*63*) have investigated the interaction of cigarette smoking and theophylline disposition. These investigators have found that the theophylline half-life ranged from about 4 to 6 hours in smokers to 7 to 9 hours in nonsmokers. Theophylline appears to be metabolized mainly in the liver, because only about 10 percent of the dose is excreted unchanged in the urine. Smokers exhibited a Cl_T of 100 ± 44 ml/min/1.73 m^2. This value was larger and more variable than 45 ± 13 ml/min/1.73 m^2 found for nonsmokers. A somewhat surprising finding was that four of the smokers who stopped smoking for three months had relatively little change in the Cl_T (*24*). This suggested that more than three months is needed for the effects of chronic tobacco use to dissipate. The average theophylline half-life of smokers who discontinued their habit for at least 2 months was intermediate between those of nonsmokers and smoker groups (*63*). Further studies by Jusko, et al. (*29*) showed that increased age offset the increased Cl_T of theophylline, as was observed earlier in the case of antipyrine. These investigators found mean Cl_T values for theophylline of 55.3

ml/min/1.73 m^2 in non/light smokers and 77.5 ml/min/1.73 m^2 in heavy smokers. When younger smokers (20 to 40 years) were compared to older smokers (40 or more years) the mean Cl_T values were found to be 106 and 61 ml/min/1.73 m^2, respectively.

The increased biotransformation rate of theophylline in smokers appears to be accompanied by a reduced toxicity during clinical use of this drug. Pfeifer and Greenblatt (*62*) studied the toxic effects of theophylline in 2,766 patients. The frequency of adverse reactions following administration of theophylline correlated negatively with the daily smoking habit. The data revealed a significant trend, with nonsmokers exhibiting 12.9 percent, light smokers (20 cigarettes/day) 10.8 percent, and heavy smokers (20 or more cigarettes/day) 7.0 percent incidence of adverse reactions to theophylline.

The dosing of patients on theophylline therapy is important because of the frequency of adverse reactions of the drug. The rate of elimination of a drug from the body (total body clearance) can be ascertained from the plasma half-life and apparent volume of distribution (aVd) for that drug. The aVd for theophylline does not appear to be altered in patients with a history of smoking; therefore, the shorter plasma half-life in smokers indicates that they have more rapid total body clearance of theophylline. Thus, when a multiple dose regimen (maintenance dose) is used, the steady-state plasma concentration achieved with a given dose will likely be lower in smokers than in nonsmokers. Although there appears to be considerable overlap in the theophylline clearance values, some heavy smokers may require as much as one and one half to two times the maintenance dose of nonsmokers. These large maintenance doses required by heavy smokers could result in toxicity if the patient discontinues smoking. Because specific information about the recovery of the drug-metabolizing enzymes following cessation of smoking is not available, clinical effects should be carefully monitored.

Lohman and Miech (*43*) have confirmed the inductive effect of 3-MC on theophylline metabolism by liver slices in rats.

Other Xanthines

Welch, et al. (*85*) and Parsons and Aldridge (*56*) reported that the biotransformation of caffeine in the rat was accelerated by PAHs in cigarette smoke. Welch, et al. (*85*) showed that benzpyrene, benzanthrene, dibenzanthracene, chrysene, and pyrene, which are potent inducers of the cytochrome P-448 system in liver microsomes, caused a marked increase in the plasma clearance of caffeine without altering its volume of distribution. On the other hand, phenanthracene and anthracene, generally considered very weak inducers of the liver microsomal cytochrome system, did not change the plasma clearance of caffeine. Following treatment with BP for three days, the Cl_T of caffeine in rats increased from 50.3 to 125.3 ml/hr. Moreover, the

subsequent elimination rates in rats of the caffeine metabolites, theophylline, paraxanthine, and theobromine, were greatly accelerated. A dose response study with BP indicated that a dose of 1 mg/kg or more of BP for 3 days was required for the enzyme induction in the rat and that 0.1 mg/kg had no significant effect. At the higher doses, BP proved to be a more potent inducer than phenobarbital (equivalent induction at 75 mg/kg). Thus, increased caffeine biotransformation may, in part, explain the tendency for smokers to consume more coffee than nonsmokers.

Other Drugs

Imipramine

The disposition of the tricyclic antidepressant, imipramine, has been reported to be affected by smoking. Perel, et al. (*60, 61*) gave 29 depressed patients daily doses of 3.5 mg/kg of imipramine and determined the mean steady-state plasma concentration of total imipramine and desmethyl imipramine to be 160 ng/ml in smokers and 290 ng/ml in nonsmokers. A strong correlation was also found between these plasma levels and the half-life of phenylbutazone administered to the same patients. These results implied that the pharmacokinetics of phenylbutazone may also be affected by smoking, but no direct evidence is available.

Glutethimide

The metabolism of glutethimide, a hypnotic, has been reported by Crow, et al. (*16*) to be altered by smoking. They measured plasma concentrations of glutethimide given at 8-hour intervals after attainment of steady-state. The mean area under the curve (0 to 8 hours after the dose) was determined to be 41 mg/liter-hour for four smokers and 26 mg/liter-hour for four nonsmokers. The half-life of glutethimide was not found to be significantly different between groups. These results suggested that the bioavailability was changed and that either the apparent volume of distribution of glutethimide (aV_G) was smaller or the fraction of drug absorbed was larger in smokers. The latter appeared unlikely because there was no difference in the rate of excretion of 4-hydroxy-2-ethyl-2 phenylglutaramide, an active metabolite, in the urine of smokers and nonsmokers. The presence of other active metabolites is a possible explanation for these results, since smokers also performed relatively poorly in a computer-generated tracking test designed for psychomotor response. The possible mechanism of this interaction is difficult to assess. Bennett (*7*) has pointed out a lack of firm data on the effects of smoking on most aspects of gastrointestinal secretion and mobility.

Vitamin C

Pelletier, et al. (*58, 59*) have reported that the vitamin C levels in serum and leukocytes were reduced in smokers. It is not clear whether reduced absorption or enhanced catabolism of the vitamin is the mechanism for the reduction in vitamin C, as studies to measure the bioavailability of vitamin C have not been conducted. The studies carried out by Pelletier, et al. (*58*) suggest that reduced absorption of vitamin C by smokers may be involved in reduced levels of vitamin C.

Bilirubin

Nymand (*52*) recently reported the effects of maternal smoking on neonatal hyperbilirubinemia. He observed that the biotransformation of bilirubin was enhanced in newborn infants of smoking mothers. The incidence of cases with serum bilirubin concentrations below 100 μM/liter was significantly higher in smokers than in nonsmokers. On the other hand, Conney, et al. (*15*) reported earlier that the serum bilirubin levels in newborn of 9 nonsmokers and of 14 smokers showed no difference in the serum bilirubin levels between the two groups of newborns. No differences in the serum bilirubin concentration have been observed between adult smokers and nonsmokers (*11*).

Substances Interfering with the Assay Procedure

In pharmacokinetic studies, the effect of exogenous chemicals on the data obtained with nonspecific assays is of particular concern. Beckett, et al. (*5*) found that the higher urinary excretion of amphetamine by smokers was explained by an amine which interfered with the assay. This interfering substance was subsequently identified as nicotine. Caution must be used in tobacco-drug studies, because the complex mixture of chemicals in tobacco smoke could present similar problems in drug assays carried out on biological samples from smokers.

Biotransformation of Drugs

Jusko (*28*) has compiled a list of drugs which have clearly been shown either to have enhanced biotransformation or to have had no effect on drug disposition in cigarette smokers. This list is given in Table 6. The majority of the studies of smoking and drug effects have investigated the drug disposition and clearance, with emphasis on the alterations in the metabolic rate rather than on the absorption or distribution process. Except for ethanol, all of the drugs in the list are biotransformed by microsomal oxidative pathways. Most interesting is the selectivity in the effects of smoking on drugs which undergo N-demethylation. This effect may be accounted for by differences in rate-limiting steps in the overall elimination of the drug. Other rate-limiting processes are plasma protein binding, metabolism in nonmicrosomal systems, and metabolism in nonhepatic tissue. Diazepam,

TABLE 6.—Summary of smoking effects on *in vivo*, biotransformation of drugs in man

Drug	Major biotransformation pathway Increased metabolic rate in smokers	Reference number
Nicotine	Hydroxylation to N of cyclic amine	(6)
Phenacetin	O-Dealkylation	(54,55)
Antipyrine	Aliphatic hydroxylation	(39,80,85)
Theophylline	N-demethylation, purine oxidation	(24,26,28,63)
Imipramine	N-demethylation	(60,61)
Pentazocine	Allylic hydroxylation	(30)
	Not affected by smoking	
Diazepam	N-demethylation	(37)
Meperidine	N-demethylation	(48)
Phenytoin	Aromatic hydroxylation	(64)
Nortriptyline	N-demethylation	(51)
Warfarin	Aromatic hydroxylation	(50,91)
Ethanol	Alcohol dehydrogenation	(79)

SOURCE: Jusko, W. (28).

phenytoin, and warfarin, which showed no difference in pharmacokinetics in smokers, are highly bound to plasma or protein and, for this reason, exhibit low total clearance rates. The plasma binding and diffusion of free drugs may not be altered significantly by tobacco smoke. Contrarily, meperidine and nortriptyline are drugs which exhibit very high total clearance rates, and hepatic blood flow may be the determining factor which is unaffected by smoking. The only generalization which can be made about these drugs is that the enhanced metabolism induced by tobacco smoking appears to be a selective process with several microsomal pathways being induced or unaffected.

Drug Effects in Man

The uncovering of differences in drug effects related to smoking has been attributed to the comprehensive in-hospital drug monitoring by the Boston Collaborative Drug Surveillance Program. Information has been obtained on drug efficacy and toxicity for all drugs administered to medical patients in this program. In addition to these data, an array of basic patient statistics, such as smoking habits, is obtained prior to admission. Several statistically significant findings that have emerged from this program are described by Jick (27).

TABLE 7.—Mean priming dose and maintenance dose of pentazocine for supplementation of nitrous oxide anesthesia

Group	No. of subjects	Mean (± SEM) priming dose (mg/kg)		Mean (± SEM) maintenance dose (μg/kg/72)	
Smokers	15	0.91 ± 0.11	P = 0.05	3.8 ± 0.4	P = 0.01
Nonsmokers	26	0.57 ± 0.13		2.5 ± 0.5	

SOURCE: Keeri-Szanto, M. (*30*).

Pentazocine

A number of clinical reports on the alteration of drug responses in smokers have been published. One of the first was the examination of pentazocine dosage requirements for supplementation of nitrous oxide anesthesia. Keeri-Szanto, et al. (*30*) found that smokers required larger priming and maintenance doses of pentazocine than did nonsmokers (see Table 7).

These results were correlated to plasma concentration of pentazocine, and the increased priming and maintenance doses were attributed to enhanced drug disposition in smokers. These findings have been confirmed by Vaughan, et al. (*77*) by examination of urinary pentazocine excretion in smokers and nonsmokers. The researchers determined that smokers metabolize 40 percent more pentazocine than nonsmokers.

Propoxyphene

The first drug to be evaluated in detail with respect to smoking in the Boston Collaborative Drug Surveillance Program was propoxyphene (*10*). Propoxyphene was rated ineffective by 10.1 percent of 335 nonsmokers, 15 percent of 347 light smokers, and 20.3 percent of 153 heavy smokers.

A summary of other observations of differences in drug effects in smokers and nonsmokers made by the Boston Collaborative Drug Surveillance Program (*27*) and by Jusko (*28*) is given in Table 8.

Although the disposition of some drugs (phenacetin, theophylline, and antipyrine) is known to be increased in smokers, the mechanisms of other drug/smoking interactions are not well established. An increased "first pass" metabolism is one possibility. A possible explanation for the reduced clinical effect of propoxyphene in smokers is decreased pain threshold. Seltzer, et al. (*69*) have found that deep pain tolerance is significantly diminished in white male and female cigarette smokers as compared to nonsmokers. In addition, two surveys (one conducted in the United States and the other in Australia) have

TABLE 8.—Modification of clinical drug effects by smoking: observations of the Boston Collaborative Drug Surveillance Program

Drug	Diminished effect observed	Incidence related to smoking habit (% patients)			Reference number
		Non	Light	Heavy	
Propoxyphene	Pain/headache efficacy	10.1	15.0	20.3	(9)
Chlorpromazine	Drowsiness	16	11	3	(72)
Diazepam	CNS depression	7.9	7.7	2.8	(10)
Chlordiazepoxide	None (CNS)	9.7	6.1	3.5	(10)
Phenobarbital	None (CNS)	5.9	9.3	4.8	(10)
Warfarin	No modification of anticoagulant needs	- -	- -	- -	(50)
Theophylline	Various adverse reactions	12.9	10.8	7.0	(28)

SOURCE: Jick, H. (27), Jusko, W. (28).

found that smokers tend to consume more analgesics than nonsmokers (19, 68).

Other Drugs

There are a few reported tobacco-drug interactions which do not involve enzyme induction. Vapaatalo, et al. (76) found that cigarette smoking somewhat reduced the diuretic effects of furosemide. This interaction was best explained by an increased secretion of the antidiuretic hormone caused by nicotine.

Kershbaum, et al. (35) reported that the stimulating effect of smoking on adrenocortical secretion could neutralize the suppressive effect of dexamethasone on plasma corticosteroid concentrations.

Beta-blockers such as propranolol have been used to modify nicotine-stimulated catecholamine effects such as increased pulse rate, blood pressure, and ventilatory function (12, 13, 20, 90, 93). Frankl and Soloff (20) reported that five subjects who received propranolol, followed by smoking, experienced significantly decreased cardiac output, significantly increased blood pressure, and significantly increased calculated systemic peripheral resistance compared to smoking without propanolol.

Absence of Smoking Effect

Alteration in drug disposition or pharmacological action in smokers generally received greater attention than those reports demonstrating no effect of tobacco smoke; it is equally important, however, from a

clinical and pharmacokinetic point of view to identify clearly those drugs which are not influenced by tobacco smoke.

Diazepam

A Boston Collaborative Drug Surveillance Program report (*9*) on the relationship to cigarette smoking of depression of the central nervous system during chronic diazepam therapy indicated that drug-attributed drowsiness became less common as the exposure to cigarette smoke increased. These findings were explained by the stimulation of diazepam metabolism by one or more of the constituents of cigarette smoke. Klotz, et al. (*37*) have reinvestigated the effects of age, smoking, and liver disease on diazepam disposition. They determined that an induction of the diazepam disposition would manifest itself by an increase in the plasma clearance or by a reduction in the $t_{1/2}$ of drug, yet no obvious differences between these values in smokers and nonsmokers were seen at any age. The authors concluded that cigarette smoking did not affect the disposition of diazepam and suggested that factors other than inferred changes in metabolism were involved in the greater incidence of side effects of diazepam in nonsmokers. These results suggest that further study of the effects of smoking and diazepam disposition is required.

Phenytoin

Phenytoin is subject to highly variable and dose-dependent elimination in patients, and its low therapeutic ratio requires careful patient monitoring for its use as an anticonvulsant. Rose, et al. (*64*) found that the only effect of tobacco smoke on disposition of phenytoin was an exacerbation of the inherent variability in its elimination, but the mean total clearance and $t_{1/2}$ values were similar in young, closely matched smokers and nonsmokers. No difference in the volume of distribution or the degree of plasma protein binding of phenytoin was observed between the two groups.

Warfarin

The Boston Collaborative Drug Surveillance Program found no difference in maintenance dosages of warfarin administered to hospitalized patients who were nonsmokers, light smokers, or heavy smokers (*49*). Similarly, Yacobi, et al. (*91*) have determined that nonsmokers, as well as smokers and patients taking barbiturates, have similar total clearance and plasma protein binding of warfarin. Recently Bachmann and Tarloff (*4*) have uncovered a species difference in the susceptibility of warfarin disposition to enzyme induction. They have found that pretreatment with benzo(a)pyrene decreased the duration of hypoprothrombinemia and shortened the $t_{1/2}$ of warfarin rate in rats.

Meperidine

Mather, et al. (*47*) have investigated the effects of cigarette smoking on meperidine disposition in surgical patients and volunteers. The mean total clearance value was determined to be 26.9 liters/hr/m^2 for smokers and 28.6 liter/hr/m^2 for nonsmokers.

Nortriptyline

Norman, et al. (*51*) dosed a group of 22 smokers and 31 nonsmokers with 150 mg/day of nortriptyline and determined steady-state plasma concentrations. Smokers achieved a mean plasma concentration of nortriptyline concentration of 191 ± 141 ng/ml, but nonsmokers had a level of 169 ± 92 ng/ml. This difference was not determined to be significant. Age, sex, and number of cigarettes smoked had no effect on the plasma nortriptyline concentrations achieved.

Ethanol

Smokers tend to consume more coffee, ethanol, and nonnarcotic analgesics than nonsmokers. Therefore the study by Vestal, et al. (*79*) on ethanol disposition and aging is of interest. The mean maximum biotransformation capacity (Vmax) for five cigarette smokers was determined to be 75.9 mg/kg/hr while 45 nonsmokers averaged 74.8 mg/kg/hr (*79*). It should be noted that ethanol metabolism differs markedly from that of other drug metabolism in that it is primarily oxidized by the cytosolic hepatic enzyme, alcohol dehydrogenase. Further studies on the effects of alcohol metabolism and smoking are needed, because Kopun and Propping (*38*), in a study using 19 identical and 22 fraternal sets of male twins, showed that regular alcohol consumption and heavy smoking correlated with an increased alcohol elimination rate. The number of individuals used in this study was somewhat limited.

Other Drugs

The rate of phenol red excretion was not altered by smoking after administration of the dye by various routes (*42*).

Hagedorn and Kostenbauder (*22*) found that cigarette smoke had no effect on the metabolism of prostaglandin F-2α in the isolated perfused rabbit lung, but administration of cigarette smoke was found to have a pronounced inhibitory effect on the metabolism of both nicotine and BP in this *in vitro* system (*44*, *48*).

Uotila and Hartiala (*75*) have reported that the covalent binding of BP was greatly enhanced by 3-methylcholanthrene pretreatment. The amount of polar metabolites in the perfusion fluid of 3-MC treated lung was increased. They suggested that this may indicate induction of pulmonary BP metabolizing enzyme, but additional studies are needed.

Mechanism of Tobacco-Drug Interaction

Tobacco smoke is a complex mixture of noxious materials (*66*). (See the Chapter on the Constituents of Tobacco Smoke.) The particulate phase consists of water-soluble materials such as nicotine, other alkaloids, and a myriad of organic substances. It also contains fat soluble polycyclic aromatic hydrocarbons (PAHs, PNAs) and more complex organic compounds. At least 48 major components have been identified (*70*) in the PAH fraction. To date only a few of the components of tobacco smoke have been examined with respect to modifying drug disposition in man or animal or their effects on tissue or enzyme systems.

The incomplete combustion of organic materials in tobacco yields PAH. Akin, et al. (*2*) separated cigarette smoke into the PAH-enriched fraction which comprised 0.4 percent of the weight of the crude condensate, but accounted for virtually all the carcinogenic potential. It has been estimated that a 20-cigarette-per-day smoker of unfiltered cigarettes would inhale about 0.7 μg/day of BP while filtered cigarettes would yield about 0.4 μg/day of BP. It has been reported in a number of studies that BP induces the microsomal enzyme benzpyrene hydroxylase (*14, 39, 86*). The characteristics of this enzyme system have been reviewed in the metabolism section of this chapter.

Other Pathophysiological Factors of Smoking

Tobacco smoking is associated with a number of pathophysiological changes which may not be directly related to any specific drug interaction, but do offer the potential for contributing to altered drug disposition. Smoking and nicotine have been shown to increase corticosteroid secretion (*36*). It is also known that chronic administration of steroids will accelerate drug disposition. Nicotine treatment has been shown to cause catecholamine release; this can result in mobilization of free fatty acids from adipose tissue (*34*). The release of free fatty acids could displace drugs from protein binding sites. Dales, et al. (*17*) examined serum chemistry levels in over 65,000 cigarette smokers and nonsmokers and found slightly lower serum albumin, uric acid, and creatinine concentration in smokers who were over 30 years old. This lower serum albumin may relate either to altered hepatic function or to changes in drug binding. In a similar study, Lellouch, et al. (*40*) reported that smokers had lower serum urea and uric acid concentration than nonsmokers. The lower values for creatinine, urea, and uric acid may reflect altered renal or hepatic function in smokers. BP is strongly bound to serum albumin (*45*) and is therefore capable of displacing ligands from similar protein binding sites.

There may be other physiological, biochemical, and behavorial differences in the smoker group. Smokers are a "self-selected" group which means that the unknown factors that cause individuals to smoke may be of importance in drug disposition. Studies have examined the

differences between smokers and nonsmokers. Seltzer, et al. (*67*) have reviewed several studies; the consensus was that smokers tend to be more energetic, restless, and extroverted than nonsmokers. On the other hand, smokers tend to possess more neurotic traits including greater psychological tension and more psychosomatic symptoms. In addition, smokers tend to be hospitalized more often than nonsmokers and are, as expected, beset with a higher incidence of specific disease such as hypertension, coronary artery disease, and lung problems. The self-selection biases are difficult to remove from pharmacokinetic studies of the effects of smoking.

In the future, it would be helpful if, after cessation of smoking, careful studies of the reversibility of the smoking effect were conducted. Present studies indicate that the induction of BP hydroxylase is not completely reversed following 2- to 3-month cessation of smoking (*24*).

Smoking and Drug Consumption

The relationship of smoking and drug disposition is complicated by the typical pattern that cigarette smokers tend to consume other drugs and chemicals more frequently than nonsmokers. Furthermore, smokers tend to ingest more coffee and alcohol than nonsmokers. Ferguson (*19*) found that smokers consumed more alcohol and nonnarcotic analgesics. Weitman, et al. (*81*) and Seltzer, et al. (*69*) examined the incidence of various types of drugs used in relation to tobacco smoking. In these studies, it was determined that smoking correlated highly with the use of other drugs. Smokers admitted to taking more cough medicine, aspirin-containing drugs, pain medications, prescription analgesics, barbiturates, sleeping pills, tranquilizers, diuretics, hormones, anemia medicine (iron), amphetamines, antibiotics, stomach medicines, and laxatives than nonsmokers. The only drugs taken by a larger percentage of nonsmokers were those for allergic conditions—antihistamines and asthma medicine. Great care must be used in carrying out pharmacokinetic studies of the effects of smoking. Because most studies do not or cannot control for many of the secondary differences between smoker and nonsmokers, care must be used in the interpretation of the results so that the reported associations between smoking and pharmacological action of drugs are not related to psychosomatic differences, drug ingestion patterns, and therapeutic need (threshold dose) of the two groups.

Studies of the effect of smoking on drug disposition usually attempt to quantitate smoke intake by vague descriptive categories such as nonsmokers/smokers, nonsmokers/light smokers/heavy smokers, or number of cigarettes smoked per day. These measures approximate only the potential exposure of man to the various chemicals in tobacco smoke. Factors such as cigarette brand, filters, degree of inhalation, duration of habit, respiratory rate, pharmacokinetics of the chemical in

man, and so forth, are unknowns in a study of this type. All of these factors sometimes make an investigation of the interaction of tobacco smoking and drugs extremely difficult to assess.

In the future, scientific reports describing the pharmacokinetics or clinical pharmacology of a drug should list and examine the smoking status of the subjects employed in the study. Smoking should be included as a basic characteristic of each subject in the same way as is age, race, body weight, and presence and type of disease. Monitoring subjects for intensity of tobacco use might be accomplished by determining of serum or urine thiocyanate (*26*). This substance possesses a long $t_{1/2}$ (about one week), which allows for an assessment of chronic smoking at a consumption rate which is most likely to affect drug disposition. Thiocyanate is relatively easy to assay and serum concentration has been reported to be proportional to the number of cigarettes smoked (*24*).

Marijuana

The subject of tobacco smoking and drug interaction needs to consider the interaction of drugs and marijuana smoking. It has been estimated that 13 million people in the United States now smoke marijuana (*1*).

Animal systems show mixed effects, with marijuana studies reporting induction and inhibition of the microsomal drug-metabolized enzymes. Paton and Pertwee (*57*) reported that cannabis extract prolonged pentobarbital sleeping time in mice and inhibited the aerobic metabolism of phenazone in mouse liver microsome preparation. Mitra, et al. (*50*) found that chronic treatment with Δ^9-tetrahydrocannabinol (THC) for 21 days (10 mg/kg/day) competitively inhibited N- and O-demethylase activity, but had no inhibitory effect on aniline hydroxylase activities. Siemens, et al. (*71*) found a prolonged pentobarbital sleeping time and a longer $t_{1/2}$ in rats pretreated with various cannabinoid compositions as well as pure Δ^9-THC.

Sofia and Barry (*72*) noted both enzyme inhibition and induction in mice following treatment with Δ^9-THC. Pretreatment with a single high dose of Δ^9-THC (20 mg/kg) increased the duration of the loss of the righting reflex after a dose of zoxazolamine and hexobarbital, and enhanced the duration of hexobarbital sleeping time. Berman and Bochantin (*8*) also found that chronic doses of Δ^9-THC (2.5 or 5.0 mg/kg daily for 4 days) increased liver microsomal dichlorinase activity (enzymes that metabolize methoxyflurane and halothane) in rats. Marcotte, et al. (*46*) have determined that analysis of the smoke condensate from cigarettes and from marijuana placed in a smoking machine gave 0.32 and 0.44 ng of BP/mg of PAH condensate, and 0.42 and 0.67 ng of 3-MC/mg of PAH condensate, respectively. These investigators found that exposure to the smoke of either marijuana or marijuana placebo (with the cannabinoid removed) maximally stimulated benzpyrene hydroxylase activity in rat lung tissue.

Similar types of diverse effects on drug disposition caused by marijuana have been found in man. Vessell and Passananti (*78*) found that oral doses (0.6 mg/kg/day) of Δ^9-THC for 7 days caused a slight increase in the antipyrine $t_{1/2}$. Dalton, et al. (*18*) examined the effects of smoking a marijuana cigarette containing 0, 150, and 500 μg/kg cannabidiol (a major cannabinoid constituent of *Cannabis sativa*) and found that cannabidiol did not alter secobarbital disposition.

Lemberger, et al. (*41*) found that chronic marijuana users eliminated Δ^9-THC from blood plasma with a $t_{1/2}$ of 28 hours compared to 57 hours in nonusers. The apparent volume of distribution did not significantly differ between the two groups.

Purified cannabinoid appears to inhibit the induction of the drug-metabolizing enzyme, but the marijuana smoke is generally inhaled; the chronic inhalation of marijuana smoke results in enzyme induction caused by the PAHs in the smoke. The multiple components in the smoke of a "joint" may play an additive or an inactive role in altering drug disposition as does tobacco smoking. Therefore, the chronic use of marijuana must be considered as a source of pharmacological drug interaction not only because of its psychoactive actions, but also because of its ability to stimulate or to inhibit the metabolic rate of susceptible drugs used in man.

Summary

Despite the warning "The Surgeon General Has Determined That Cigarette Smoking Is Dangerous To Your Health" on each pack of cigarettes, the use of tobacco is still "enjoyed" by one out of three adults in the United States. This extensive use of tobacco and the frequency of altered disposition and pharmacological effects of many drugs in smokers make it apparent that smoking of tobacco should be considered as one of the primary sources of drug interactions in man.

The majority of the *in vivo* and *in vitro* experimental work conducted to the present time indicates that the dominant effect of smoking is enhanced drug disposition caused by an induction of hepatic microsomal enzymes. The primary causal agent for this induction is probably the PAHs which are potent enzyme inducers and which are persistent in the tissues. Many other ingredients of tobacco smoke are capable of inducing (nicotine, cadmium, and insecticides) or inhibiting (carbon monoxide and hydrogen cyanide) drug-metabolizing enzymes. Inhibition of the drug-metabolizing enzymes is apparently overridden by the inducers in tobacco smoke, because presently there are no reports of diminished rates of drug metabolism in man or animals treated with tobacco smoke. Alteration of drug-transport processes can occur, as seen by the enhanced bioavailability of glutethimide by smokers, but this does not appear to be a common pathway. Diminished protein binding of drugs in smokers could occur, but there is no evidence for this at the present time. Factors such as the volume of

distribution of drugs in smokers and nonsmokers have been examined. The variability in drug disposition for antipyrine and theophylline was appreciable. There is evidence for genetic control of the degree of enzyme induction from smoking which may also be a common factor in the carcinogenicity of inhaled chemicals.

Reports of altered pharmacological or toxicological effects of drugs in smokers can sometimes be explained by induced metabolism of the drug (pentazocine, theophylline). On the other hand, smokers differ from nonsmokers in their pain threshold, psychosomatic characteristics, and drug consumption; the presence of substances, such as nicotine, which cause competing or additive pharmacological effects, may complicate the action of drugs used in treating pain or anxiety (propoxyphene, benzodiazepine, chlorpromazine).

In addition to the identification of a wider array of drugs, enzymatic pathways, and clinical effects which are altered by tobacco smoking, future studies should investigate the role of smoking in affecting other clearance processes. Even though it is known that some of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, the selectivity of this induction is unpredictable and the effects of smoking on other potential rate-limiting disposition processes, such as the effect of smoking on protein binding of various drugs, and the contribution of nonhepatic tissue such as kidney, lung, and intestine are largely unexplored.

Effects on Pharmacokinetics and Pharmacodynamics: References

(1) ABRAMOWICZ, M. (Editor). Marijuana. Medical Letter on Drug and Therapeutics 18(17): 69-70, August 13, 1976.

(2) AKIN, F.J., SNOOK, M.E., SEVERSON, R.E., CHAMBERLAIN, W.J., WALTERS, D.B. Identification of polynuclear aromatic hydrocarbons in cigarette smoke and their importance as tumorigens. Journal National Cancer Institute 57(1): 191-195, July 1976.

(3) AMBRE, J., GRAEFF, D., BURES, F., HAUPT D., DEASON, K. Antipyrine metabolism and bronchogenic carcinoma. Journal of Medicine 8(1): 57-70, 1977.

(4) BACHMANN, K., TARLOFF, J. Influence of 3, 4-benzo(a)pyrene on warfarin hypoprothrombinemia and disposition in the rat. Toxicology and Applied Pharmacology 42: 157-165, 1977.

(5) BECKETT, A.H., ROWLAND, M., TRIGGS, E.J. Significance of smoking in investigations of urinary excretion rates of amines in man. Nature 207(4993): 200-201, July 10, 1965.

(6) BECKETT, A.H., TRIGGS, E.J. Enzyme induction in man caused by smoking. Nature 216: 587, November 11, 1967.

(7) BENNETT, J.R. Progress Report. Smoking and the gastrointestinal tract. Gut 13: 658-665, 1972.

(8) BERMAN, M.L., BOCHANTIN, J.F. Effect of delta-9 tetrahydrocannabinol (marihuana) on liver microsomal dechlorinase activity: A preliminary report. Anesthesia and Analgesia 51(6): 929-932, November/December, 1972.

(9) BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM. Clinical depression of the central nervous system due to diazepam and chlorodiazepoxide in relation to cigarette smoking and age. New England Journal of Medicine 288(6): 277-280, February 8, 1973.

(10) BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM. Decreased clinical efficacy of propoxyphene in cigarette smokers. Clinical Pharmacology and Therapeutics 14(2): 259-263, 1973.

(11) BURNEY, S.W., BONUS, L. Cross-sectional assessment of laboratory variables in a healthy male population. II. Cigarette smoking and laboratory values. Aging and Human Development 3: 89-94, 1972.

(12) CARRUTHERS, M. Modification of the noradrenaline related effects of smoking by beta blockade. Psychological Medicine 6: 251-256, 1976.

(13) COFFMAN, J.D. Effect of propranolol on blood pressure and skin blood flow during cigarette smoking. Journal of Clinical Pharmacology 9(1): 39-44, January/February, 1969.

(14) CONNEY, A.H., PANTUCK, E.J., HSIAO, K.-C., KUNTZMAN, R., ALVARES, A. P., KAPPAS, A. Regulation of drug metabolism in man by environmental chemicals and diet. Federation Proceedings 36(5): 1647-1652, April 1977.

(15) CONNEY, A.H., WELCH, R., KUNTZMAN, R., CHANG, R., JACOBSON, M., MUNRO-FAURE, A.D., PECK, A.W., BYE, A., POLAND, A., POPPERS, P.J., FINSTER, M., WOLFF, J.A. Effects of environmental chemicals on the metabolism of drugs, carcinogens and normal body constituents in man. Annals of the New York Academy of Science 179: 155-172, 1971.

(16) CROW, J.W., LAIN, P., BOCHNER, F., SHOEMAN, D. W., AZARNOFF, D.L. Glutethimide and 4-OH glutethimide: Pharmacokinetics and effect on performance in man. Clinical Pharmacology and Therapeutics 22(4): 458-464, 1977.

(17) DALES, L.G., FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C. Cigarette smoking and serum chemistry tests. Journal of Chronic Disease 27: 293-307, 1974.

(18) DALTON, W.S., MARTZ, R., RODDA, B.E., LEMBERGER, L., FORNEY, R.B. Influence of cannabidiol on secobarbital effects and plasma kinetics. Clinical Pharmacology and Therapeutics 20(6): 695-700, 1976.

(19) FERGUSON, D. Smoking, drinking and non-narcotic analgesic habits in an occupational group. Medical Journal of Australia 1: 1271-1274, June 30, 1973.

(20) FRANKL, W.S., SOLOFF, L.A. The hemodynamic effects of propranolol hydrochloride after smoking. American Journal of Medical Sciences 254: 623-628, November 1967.

(21) GIBALDI, M., PERRIER, D. Pharmacokinetics. New York, Marcel Dekker, 1975, pp. 243-250.

(22) HAGEDORN, B., KOSTENBAUDER, H.B. Studies on the effect of tobacco smoke on the biotransformation of vasoactive substances in the isolated perfused rabbit lung. I. Prostaglandin $F_{2\alpha}$. Research Communications in Chemical Pathology and Pharmacology 18(3): 495-504, November 1977.

(23) HART, P., FARRELL, G.C., COOKSLEY, W.G.E., POWELL, L.W. Enhanced drug metabolism in cigarette smokers. British Medical Journal 2: 147-149, July 17, 1976.

(24) HUNT, S. N., JUSKO, W.J., YURCHAK, A.M. Effect of smoking on theophylline disposition. Clinical Pharmacology and Therapeutics 19(5) Part I: 546-551, 1976.

(25) ISAAC, P.F., RAND, M.J. Cigarette smoking and plasma levels of nicotine. Nature 236: 308-310, April 7, 1972.

(26) JENNE, J., NAGASAWA, H., McHUGH, R., MacDONALD, F., WYSE, E. Decreased theophylline half-life in cigarette smokers. Life Sciences 17(2): 195-198, 1975.

(27) JICK, H. Smoking and clinical drug effects. Medical Clinics of North America 58(5): 1143-1149, September 1974.

(28) JUSKO, W.J. Role of tobacco smoking in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 6(1): 7-39, 1978.

(29) JUSKO, W.J., KOUP, J.R., SCHENTAG, J.J., VANCE, J.W. Surveillance of factors affecting theophylline clearances in patients. American Pharmaceutical Association, Academy of Pharmaceutical Sciences Meeting, New Orleans, 1976, p. 145. (Abstract)

(30) KEERI-SZANTO, M., POMEROY, J.R. Atmospheric pollution and pentazocine metabolism. Lancet 1: 947-949, May 8, 1971.

(31) KELLERMANN, G., LUYTEN-KELLERMANN, M. Phenobarbital-induced drug metabolism in man. Toxicology and Applied Pharmacology 39: 97-104, 1977.

(32) KELLERMANN, G., LUYTEN-KELLERMANN, M., HORNING, M.G., STAFFORD, M. Correlation of aryl hydrocarbon hydroxylase activity of human lymphocyte cultures and plasma elimination rates for antipyrene and phenylbutazone. Drug Metabolism and Disposition 3(1): 47-50, 1975.

(33) KELLERMANN, G., LUYTEN-KELLERMANN, M., HORNING, M.G., STAFFORD, M. Elimination of antipyrine and benzo(a)pyrene metabolism in cultured human lymphocytes. Clinical Pharmacology and Therapeutics 20(1): 72-80, 1976.

(34) KERSHBAUM, A., OSADA, H., PAPPAJOHN, D.J., BELLET, S. Effect of nicotine on the mobilization of free fatty acids from adipose tissue in vitro. Experientia 25: 128, 1969.

(35) KERSHBAUM, A., PAPPAJOHN, D.J., BELLET, S. Smoking effect on dexamethasone suppression test. Clinical Research 17(2): 287, April 1969. (Abstract)

(*36*) KERSHBAUM, A., PAPPAJOHN, D.J., BELLET, S., HIRABAYASHI, M., SHAFIHA, H. Effect on smoking and nicotine on adrenocortical secretion. Journal of the American Medical Association 203 (4): 275-278, January 22, 1968.

(*37*) KLOTZ, U., AVANT, G.R., HOYUMPA, A., SCHENKER, S., WILKINSON, G.R. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. Journal of Clinical Investigation 55: 347-359, February 1975.

(*38*) KOPUN, M., PROPPING, P. The kinetics of ethanol absorption and elimination in twins and supplementary repetitive experiments in singleton subjects. European Journal of Clinical Pharmacology 11: 337-344, 1977.

(*39*) KUNTZMAN, R., PANTUCK, E.J., KAPLAN, S. A., CONNEY, A.H. Phenacetin metabolism: Effect of hydrocarbons and cigarette smoking. Clinical Pharmacology and Therapeutics 22(5): 757-764, 1977.

(*40*) LELLOUCH, J., SCHWARTZ, D., TRAN, M.H., BEAUMONT, J.L. The relationships between smoking and levels of serum urea and uric acid. Results of an epidemiological survey. Journal of Chronic Disease 22: 9-15, 1969.

(*41*) LEMBERGER, L., TAMARKIN, N.R., AXELROD, J., KOPIN, I.J. Delta-9-Tetrahydrocannabinol: Metabolism and disposition in long-term marihuana smokers. Science 173: 72-73, July 2, 1971.

(*42*) LEVINE, R.R., PELIKAN, E.W., KENSLER, C.J. The effect of cigarette smoking on the excretion of phenol red. Federation Proceedings 20: 414, 1961. (Abstract)

(*43*) LOHMAN, S.M., MIECH, R.P. Theophylline metabolism by the rat liver microsomal system. Journal of Pharmacology and Experimental Therapeutics 196(1): 213-225, 1976.

(*44*) LUBAWY, W.C., GRIFFITH, R.B., KOSTENBAUDER, H.B., PERRIER, D. An isolated perfused lung (IPL)-smoke system for studying the inhibition of benzo(a)pyrene (BAP) metabolism by smoke. Federation Proceedings 77: 970, 1977. (Abstract)

(*45*) MA, J.K.H., FU, P.P., LUZZI, L.A. Protein-binding of benzo(a)anthracene and benz(a)pyrene. Journal of Pharmaceutical Sciences 66(2): 209-213, February 1977.

(*46*) MARCOTTE, J., SKELTON, F.S., COTE, M.G., WITSCHI, H. Induction of aryl hydrocarbon hydroxylase in rat lung by marijuana smoke. Toxicology and Applied Pharmacology 33: 231-245, 1975.

(*47*) MATHER, L.E., TUCKER, G.T., PFLUG, A.E., LINDOP, M.J., WILKERSON, C. Meperidine kinetics in man: Intravenous injection in surgical patients and volunteers. Clinical Pharmacology and Therapeutics 17(1): 21-30, 1975.

(*48*) McGOVREN, J.P., LUBAWY, W.C., KOSTENBAUDER, H.B. Uptake and metabolism of nicotine by the isolated perfused rabbit lung. Journal of Pharmacology and Experimental Therapuetics 199(1): 198-207, 1976.

(*49*) MITCHELL, A.A. Smoking and warfarin dosage. New England Journal of Medicine 287(22): 1153-1154, November 1972.

(*50*) MITRA, G., PODDAR, M.K., GHOSH, J.J. In vivo and in vitro effects of Δ^9-tetrahydrocannabinol on rat liver microsomal drug-metabolizing enzymes. Toxicology and Applied Pharmacology 35: 523-530, 1976.

(*51*) NORMAN, T.R., BURROWS, G.D., MAGUIRE, K.P., RUBINSTEIN, G., SCOGGINS, B.A., DAVIES, B. Cigarette smoking and plasma nortriptyline levels. Clinical Pharmacology and Therapeutics, 21(4): 453-456, 1977.

(*52*) NYMAND, G. Maternal smoking and neonatal hyperbilirubinaemia. Lancet 2: 173, July 20, 1974.

(53) PANTUCK, E.J., HSIAO, K.-C., KAPLAN, S.A., KUNTZMAN, R., CONNEY, A.H. Effects of enzyme induction on intestinal phenacetin metabolism in the rat. Journal of Pharmacology and Experimental Therapeutics 191(1): 45-52, 1974.

(54) PANTUCK, E.J., HSIAO, K.-C., MAGGIO, A., NAKAMURA, K., KUNTZMAN, R., CONNEY, A.H. Effect of cigarette smoking on phenacetin metabolism. Clinical Pharmacology and Therapeutics 15(1): 9-17, 1974.

(55) PANTUCK, E.J., KUNTZMAN, R., CONNEY, A.H. Decreased concentration of phenacetin in plasma of cigarette smokers. Science 175: 1248-1250, March 17, 1972.

(56) PARSONS, W.D., ALDRIDGE, A. Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Federation Proceedings 35: 665, 1976. (Abstract)

(57) PATON, W.D.M., PERTWEE, R.G. Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. British Journal of Pharmacology 44: 250-261, 1972.

(58) PELLETIER, O. Vitamin C and cigarette smokers. Annals of New York Academy of Science 258: 156-168, 1975.

(59) PELLETIER, O., KEITH, M.O., Bioavailability of synthetic and natural ascorbic acid. Journal of the American Dietetic Association 64: 271-275, March 1974.

(60) PEREL, J.M., HURWIC, M.J., KANZLER, M.B. Pharmacodynamics of imipramine in depressed patients. Psychopharmacology Bulletin 11(4): 16-18, 1975.

(61) PEREL, J.M., SHOSTAK, M., GANN, E., KANTOR, S.J., GLASSMAN, A.H. Pharmacodynamics of imipramine and clinical outcome in depressed patients. In: Gottschalk, L.A., Merlis, S. (Editors). Pharmacokinetics of Psychoactive Drugs. New York, Spectrum Publications, 1976, pp. 229-241.

(62) PFEIFER, H.J., GREENBLATT, D.J. Clinical toxicity of theophylline in relation to cigarette smoking. Chest 73(4): 455-459, April 1978.

(63) POWELL, J.R., THIERCELIN, J.-F., VOZEH, S., SANSOM, L., RIEGELMAN, S. The influence of cigarette smoking and sex on theophylline disposition. American Review of Respiratory Disease 116: 17-23, 1977.

(64) ROSE, J.Q., BARRON, S.A., JUSKO, W.J. Phenytoin disposition in smokers and nonsmokers. American Pharmaceutical Association, Academy of Pharmaceutical Sciences Meeting. New York, 1977, p. 162. (Abstract)

(65) ROTTENSTEIN, H., PEIRCE, G., RUSS, E., FELDER, D., MONTGOMERY, H. Influence of nicotine on the blood flow of resting skeletal muscle and of the digits in normal subjects. Annals of the New York Academy of Sciences 90(1): 102-113, 1960.

(66) SCHUMACHER, J.N., GREEN, C.R., BEST, F.W., NEWELL, M.P. Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke. Journal Agricultural and Food Chemistry 25(2): 310-320, 1977.

(67) SELTZER, C.C. Constitution and heredity in relation to tobacco smoking. Annals of New York Academy of Sciences 142: 322-330, March 15, 1967.

(68) SELTZER, C.C., FRIEDMAN, G.D., SEIGELAUB, A.B. Smoking and drug consumption in white, black, and oriental men and women. American Journal of Public Health 64(5): 466-473, May 1974.

(69) SELTZER, C.C., FRIEDMAN, G.D., SIEGELAUB, A.B., COLLEN, M.F. Smoking habits and pain tolerance. Archives of Environmental Health 29: 170-172, September 1974.

(70) SEVERSON, R.F., SNOOK, M.E., ARRENDALE, R.F., CHORTYK, O.T. Gas chromatographic quantitation of polynuclear aromatic hydrocarbons in tobacco smoke. Analytical Chemistry 48(13): 1866-1871, November 1976.

(71) SIEMENS, A.J., KALANT, H., KHANNA, J.M., MARSHMAN, J., HO, G. Effect of cannabis on pentobarbital-induced sleeping time and pentobarbital metabolism in the rat. Biochemical Pharmacology 23: 477-488, 1974.

(72) SOFIA, R.D., BARRY, H. Interactions of chronic and acute Δ¹tetrahydrocannabinol pretreatment with zoxazolamine and barbiturates. Research Communications in Chemical Pathology and Pharmacology 5(1): 91-98, January 1973.

(73) SWETT, C., Jr., COLE, J.O., HARTZ, S.C., SHAPIRO, S., SLONE, D. Hypotension due to chlorpromazine. Relation to cigarette smoking, blood pressure, and dosage. Archives of General Psychiatry 34: 661-663, June 1977.

(74) TSCHANZ, C., HIGNITE, C.E., HUFFMAN, D.H., AZARNOFF, D.L. Metabolic disposition of antipyrine in patients with lung cancer. Cancer Research 37: 3881-3886, November 1977.

(75) UOTILA, P., HARTIALA, J. Drug and steroid metabolism in the isolated perfused rat lung. In: Duncan, W.A.M., Leonard, B.J. (Editors). Proceedings of the European Society of Toxicology. Excerpta Medica. Amsterdam 18: 201-202, 1977.

(76) VAPAATALO, H.I., NEUVONEN, P.J., TISSARI, A., MANSNER, R., PAASONEN, M.K. Effect of cigarette smoking on diuresis induced by furosemide. Annals of Clinical Research 3: 159-162, 1971.

(77) VAUGHAN, D.P., BECKETT, A.H., ROBBIE, D.S. The influence of smoking on the inter-subject variation in pentazocine elimination. British Journal of Clinical Pharmacology 3: 279-283, 1976.

(78) VESELL, E.S., PASSANANTI, G.T. Inhibition of drug metabolism in man. Drug Metabolism and Disposition 1(1): 402-410, 1973.

(79) VESTAL, R.E., McGUIRE, E.A., TOBIN, J.D., ANDRES, R., NORRIS, A.H., MEZEY, E. Aging and ethanol metabolism. Clinical Pharmacology and Therapeutics 21(3): 343-354, 1977.

(80) VESTAL, R.E., NORRIS, A.H., TOBIN, J.D., COHEN, B.H., SCHOCK, N.W., ANDRES, R. Antipyrine metabolism in man: Influence of age, alcohol, caffeine, and smoking. Clinical Pharmacology and Therapeutics 18(4): 425-432, 1975.

(81) WEITMAN, M., SCHEBLE, R., JOHNSON, K.G., ABBEY, H. Correlations among use of drugs. American Journal of Public Health 62: 166-170, February 1972.

(82) WELCH, R.M., CAVALLITO, J., GILLESPIE, D.D. Effect of analgesics and exposure to cigarette smoke on the metabolism of acetophenetidin by rat tissues. Drug Metabolism and Disposition 1(1): 211-215, 1973.

(83) WELCH, R.M., CAVALLITO, J., LOH, A. Effect of exposure to cigarette smoke on the metabolism of benzo(a)pyrene and acetophenetidin by lung and intestine of rats. Toxicology and Applied Pharmacology 23: 749-758, 1972.

(84) WELCH, R.M., DeANGELIS, R.L., WINGFIELD, M., FARMER, T.W. Elimination of antipyrine from saliva as a measure of metabolism in man. Clinical Pharmacology and Therapeutics 18(3): 249-258, 1975.

(85) WELCH, R.M., HSU, S.Y., DeANGELIS, R.L. Effect of Aroclor 1254, phenobarbital, and polycyclic aromatic hydrocarbons on the plasma clearance of caffeine in the rat. Clinical Pharmacology and Therapeutics 22(5): 791-798, 1977.

(86) WELCH, R.M., HUGHES, C.R., DeANGELIS, R.L. Effect of 3-methylcholanthrene pretreatment on the bioavailability of phenacetin in the rat. Drug Metabolism and Disposition 4(4): 402-406, 1976.

(87) WELCH, R.M., LOH, A., CONNEY, A.H. Cigarette smoke: Stimulatory effect on metabolism of 3,4-benzpyrene by enzymes in rat lung. Life Sciences 10(4): 215-221, 1971.

(88) WENZEL, D.G., BROADIE, L.L. Stimulatory effect of nicotine on the metabolism of meprobamate. Toxicology and Applied Pharmacology 8: 455-459, 1966.

(89) WILSON, J.T., VAN BOXTEL, C.J., ALVAN, G., SJOQVIST, F. Failure of vitamin C to affect the pharmacokinetic profile of antipyrine in man. Journal of Clinical Pharmacology 16: 265-270, May/June 1976.

(90) WOOD, A.J.J., VESTAL, R.E., BRANCH, R.A., WILKERSON, G.R., SHAND, D.G. Age-related effects of smoking on elimination of propranolol (P), antipyrine (Ap), and indocyanine green (ICG). Clinical Research 26: 297A, 1978. (Abstract)

(91) YACOBI, A., UDALL, J.A., LEVY, G. Serum protein binding as a determinant of warfarin body clearance and anticoagulant effect. Clinical Pharmacology and Therapeutics 19(5): 552-558, 1976.

(92) YAMAMOTO, I., NAGAI, K., KIMURA, H., IWATSUBO, K. Nicotine and some carcinogens in special reference to the hepatic drug-metabolizing enzymes. Japanese Journal of Pharmacology 16: 183-190, 1966.

(93) ZUSKIN, E., MITCHELL, C.A., BOUHUYS, A. Interaction between effects of beta blockade and cigarette smoke on airways. Journal of Applied Physiology 36(4): 449-452, April 1974.

Specific Drug Interactions

Oral Contraceptives

In early 1970, Frederiksen and Ravenholt (*8*) presented data showing an association between thromboembolism and smoking. Sartwell (*16*), however, reported that he could find no evidence that smoking enhanced the effect of oral contraceptives to produce increased blood clotting. In 1973, the Collaborative Group for the Study of Stroke in Young Women (*5*) stated that cigarette smoking may potentiate the effect of oral contraceptives on thromboembolism or cardiovascular disease. A subsequent report by this Group (*6*) showed that women who took the pill and smoked one pack of cigarettes had a 200 percent increased risk of a stroke. Perhaps the most important articles published on smoking and oral contraceptives were published by Mann, et al. (*12, 13*). In these articles, the authors quantitated the association between cigarette smoking and oral contraceptives. They showed that the relative risk of myocardial infarction increased from 1.2 in women smoking fewer than 15 cigarettes a day, to 4.1 in women smoking 15 to 24 cigarettes a day, and to 11.3 in women smoking 25 or more cigarettes a day. Jain (*9*) reanalyzed the data from the United States and Great Britain and reported that: (1) the use of oral contraceptives in the absence of smoking is considerably safer than no fertility control for all ages, including the group aged 40-44; (2) the use of oral contraceptives among smokers aged 40 and over is substantially more hazardous than no fertility control, although there is little difference for light smokers; (3) the use of oral contraceptives among heavy smokers in the group aged 30-39 may be more hazardous than no fertility control; and (4) the use of oral contraceptives among heavy smokers in the group aged 15-29 may be more hazardous than any other method of fertility regulation. Ory (*15*) has stated that his analyses show "that cigarette smoking is the most important factor in increasing the likelihood of myocardial infarction." The effect is independent of oral contraceptive use, but oral contraceptive use also appears to be a risk factor. The use of oral contraceptives in the absence of other predisposing factors appears, however, to have only a small effect in increasing the risk of dying from myocardial infarction.

Beral (*2*) has shown that the death rate from diseases of the circulatory system in women who used oral contraceptives was 5 times that of controls who had never used them; the death rate in those who had taken the pill continuously for 5 years or more was 10 times that of controls. The author concluded that the excess annual deaths were 1 per 10,000 for oral contraceptive users who had quit smoking and 1 per 3,000 users who smoke.

In a recent article, Jick, et al. (*11*), comparing oral contraceptive users with nonusers, stated that, in otherwise healthy young women, the relative risk of a myocardial infarction is 14. While myocardial

infarction is rare in most healthy women, the risk in women older than 37 years who smoke and take oral contraceptives appears to be high.

Tietze (*18*) has updated his findings on mortality related to pregnancy. His article shows that up to the age of 30 the risk to life from pregnancy and childbirth among noncontraceptors is far in excess of that experienced by users of any method. After age 30, the mortality risk experienced by pill users who smoke rises dramatically, but among nonsmokers the risk remains relatively low—and is lower than the risk of death among noncontraceptors even after age 40.

In another recent study Slone, et al. (*17*) investigated the smoking habits of women under the age of 50 who had survived a recent myocardial infarction. The subjects had not been using oral contraceptives, and other identifiable risk factors were excluded. A dose-response relationship was evident; among women smoking 35 or more cigarettes per day the rate of myocardial infarction was estimated to be some 20-fold higher than among those who had never smoked. This study demonstrates quite strongly that cigarette smoking is a risk factor for myocardial infarction in young women who are otherwise apparently healthy.

Estrogens

A recent report (*10*) of apparently healthy women aged 39 to 45 who were taking noncontraceptive estrogens estimated a relative risk of 7.5 for nonfatal myocardial infarction, when comparing estrogen users with nonusers. All but one of the nonfatal myocardial infarction patients were cigarettes smokers. Although this is only one report, it appears that women aged 39 to 45 may have a substantial risk when they both smoke and take estrogens. Further study on this subject is needed.

Cardiovascular Drugs

There is comparatively little clinical evidence of interactions between smoking and cardiovascular drugs. The ability of smoking to stimulate various hepatic microsomal enzymes is a potentially important effect and affects numerous drugs, but, thus far, few such interactions have been recognized. A second, potentially important set of interactions could arise from interactions with the pharmacologic effects of nicotine.

As summarized in detail in *The Health Consequences of Smoking*(*19*) nicotine causes increased heart rate, blood pressure, cardiac output, stroke volume, myocardial contractility, myocardial oxygen consumption, and arrhythmia formation, most of which is explained by release of catecholamines from both neuronal and extraneuronal sites. Apart from potential toxicity of elevated catecholamines, some interesting potential interactions with drugs can be postulated; these have been

studied to some extent, although not definitively. Aronow, et al. (*1*) have shown increased angina in patients who smoke.

Frankl and Soloff (*7*) studied the interaction of smoking and propranolol. They reported that, in four of five normal subjects, smoking two cigarettes led to a small increase in blood pressure associated with increased cardiac output, increased heart rate, and decreased peripheral resistance (cigarettes are usually found to increase peripheral resistance). When cigarettes were smoked after treatment with propranolol, blood pressure increased further, heart rate and cardiac output fell, and peripheral resistance increased. These results are compatible with the predicted effects of propranolol, viz. beta-blockade blocks the chronotropic, inotropic, and vasodilator effects of the catecholamines (all beta effects), but does not affect their peripheral vasoconstrictor effects (an alpha effect), thus unmasking or exaggerating this effect. Propranolol is known to increase peripheral resistance even in the absence of nicotine, however, and it would have been helpful to examine the contribution of propranolol alone to increased peripheral resistance by studying a group treated with propranolol alone, in addition to the nicotine and nicotine—propranolol groups. The results suggest, however, that the increase in resistance was greater than that caused by propranolol alone; propranolol normally decreases blood pressure, despite the increase in resistance it causes in the absence of smoking, but in this study blood pressure rose after propranolol administration. The reported hemodynamic changes are in a direction generally considered harmful, especially for persons with underlying cardiac disease.

Subsequently, Coffman (*4*) examined a closely related question, measuring blood pressure and vascular resistance in the foot in 13 smoking volunteers before and after propranolol. He found that while nicotine or smoking increased blood pressure and foot resistance over baseline, the addition of propranolol did not seem to exaggerate these effects, as the author felt would have been expected if propranolol unmasked an alpha-adrenergic effect of smoking. This analysis may be incorrect. An unusual finding of this study, similar to that of Frankl and Soloff, is that propranolol increased both foot resistance (expected) and blood pressure (not expected). Propranolol, despite increasing peripheral resistance, is normally a hypotensive agent, presumably because the vasoconstriction it causes is offset by decreased cardiac output. The rise in pressure seen here suggests that the increased catecholamines provoked by smoking were still present when propranolol was given (it was always given after the first smoking period) and that alpha-effects were in fact unmasked by propranolol-inhibition of beta-mediated vasodilation. This explanation is strengthened by the observation that the pre-smoking baseline blood pressure and foot resistance were higher for the second (propranolol) phase of the study, suggesting persistent cigarette effect.

The Frankl and Soloff and the Coffman studies are thus not necessarily incompatible, but their small size and lack of concurrent controls render them inconclusive.

In a more recent study, Carruthers (*3*) examined the effects of smoking low and high nicotine cigarettes on 12 normal volunteer smokers given oxprenolol (a beta-blocker) and placebo on a crossover basis before smoking. Oxprenolol prevented the smoking-induced rise in heart rate and systolic and diastolic pressure seen in placebo-treated subjects. There was no suggestion that it exaggerated this effect. While this study certainly does not demonstrate unmasking of alpha-stimulation, the blood pressure after high-nicotine smoking in oxprenolol-treated patients was equal to the blood pressure before oxprenolol or smoking in these patients. The nicotine thus obliterated the hypotensive effect of oxprenolol.

The possibility that smoking reverses or blocks, even in part, the antihypertensive effect of beta-blockers, a major antihypertensive class, is obviously a suitable subject for study and a matter for concern. We are not aware of any hypertension clinical trial that has analyzed smoking as a covariant. It should also be noted that a "cardioselective" beta-blocker, which would not block the beta-mediated peripheral vasodilating effects of catecholamines, might behave differently from propranolol.

Zuskin, et al. (*21*) studied the interaction on airways of beta-blockade and smoking. They found that, in nonsmokers and light smokers, cigarettes cause decreases in flow rates on maximum or partial expiratory flow-volume curves, evidence of slight obstruction of small airways, and that propranolol alone has no effect on these rates. Propranolol did not add to these effects in light smokers or nonsmokers, but potentiated the constricting effect of smoking in regular smokers, who had little response to smoking alone. This was interpreted as suggesting that beta-adrenergic stimuli protect smokers against vasoconstriction, and that this protection can be removed by beta-blockade. The interaction at this point appears to be of marginal importance, but deserves further study, especially in persons with impaired pulmonary function. Here too, it is likely that cardioselective beta-blockers would behave differently from nonselective ones.

Furosemide

Vapaatalo, et al. (*20*) have reported a reduced diuretic effect of furosemide in smokers, probably related to nicotine-stimulated increased secretion of ADH. This interaction is of negligible clinical significance.

Negative Findings

The ability of cigarette smoke to alter drug metabolism has led to concern that it might alter anticoagulant metabolism and, therefore,

anticoagulant dosage requirements. While many drugs affect warfarin metabolism, Mitchell (*14*) reported that maintenance doses of warfarin were not different in nonsmokers, light smokers, or heavy smokers.

Specific Drug Interactions: References

(1) ARONOW, W.S., KAPLAN, M.A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3): 529-536, September 1968.

(2) BERAL, V. Mortality among oral contraceptive users. Lancet 2: 727-731, October 8, 1977.

(3) CARRUTHERS, M. Modification of the noradrenaline related effects of smoking by beta-blockade. Psychological Medicine, 6: 251-256, 1976.

(4) COFFMAN, J.D. Effect of propranolol on blood pressure and skin blood flow during cigarette smoking. Journal of Clinical Pharmacology 9: 39-44, January/February 1969.

(5) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraception and increased risk of cerebral ischemia or thrombosis. New England Journal of Medicine 288(17): 871-878, April 26, 1973.

(6) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraceptives and stroke in young women: Associated risk factors. Journal of the American Medical Association 231(7): 718-722, February 17, 1975.

(7) FRANKL, W.S., SOLOFF, L.A. The hemodynamic effects of propranolol hydrochloride after smoking. American Journal of the Medical Sciences 254: 623-628, November 1967.

(8) FREDERIKSEN, H., RAVENHOLT, R.T. Thromboembolism, oral contraceptives, and cigarettes. Public Health Reports 85(3): 197-205, March 1970.

(9) JAIN, A.K. Mortality risk associated with the use of oral contraceptives. Studies in Family Planning 8(3): 50-54, March 1977.

(10) JICK, H., DINAN, B., ROTHMAN, K.J. Noncontraceptive estrogens and nonfatal myocardial infarction. Journal of the American Medical Association 239(14): 1407-1408, April 3, 1978.

(11) JICK, H., DINAN, B., ROTHMAN, K.J. Oral contraceptives and nonfatal myocardial infarction. Journal of the American Medical Association 239(14): 1403-1406, April 3, 1978.

(12) MANN, J.I., INMAN, W.H.W. Oral contraceptives and death from myocardial infarction. British Medical Journal 2: 245-248, May 3, 1975.

(13) MANN, J.I., VESSEY, M.P., THOROGOOD, M., DOLL R. Myocardial infarction in young women with special reference to oral contraceptive practice. British Medical Journal 2: 241-245, May 3, 1975.

(14) MITCHELL, A.A. Smoking and warfarin dosage. New England Journal of Medicine 287(22): 1153-1154, November 30, 1972.

(15) ORY, H.W. Association between oral contraceptives and myocardial infarction - A review. Journal of the American Medical Association 237(24): 2619-2622, June 13, 1977.

(16) SARTWELL, P.E. Oral contraceptives and thromboembolism: A further report. American Journal of Epidemiology 94(3): 192-201, September 1971.

(17) SLONE, D., SHAPIRO, S., ROSENBERG, L., KAUFMAN, D.W., HARTZ, S.C., ROSSI, A.C., STOLLEY, P.D., MIETTINEN, O.S. Relation of cigarette smoking to myocardial infarction in young women. New England Journal of Medicine 298(23): 1273-1276, June 8, 1978.

(18) TIETZE, C. New estimates of mortality associated with fertility control. Family Planning Perspectives 9(2): 74-76, March/April 1977.

(19) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition: 1976. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.

(20) VAPAATALO, H.I., NEUVONEN, P.J., TISSARI, A., MANSNER, R., PAASONEN, M.K. Effect of cigarette smoking on diuresis induced by furosemide. Annals of Clinical Research 3: 159-162, 1971.

(*21*) ZUSKIN, E., MITCHELL, C.A., BOUHUYS, A. Interaction between effects of beta blockade and cigarette smoke on airways. Journal of Applied Physiology 36(4): 449-452, April 1974.

Viral Vaccines

Most viral vaccines, such as poliovirus, measles virus, mumps virus, and rubella virus, are primarily administered to children. Some viral vaccines, such as influenza, are administered to persons of all ages in the general population during pandemic periods. During other periods, those persons at high risk, such as the elderly or persons with chronic upper respiratory and other debilitating diseases, are vaccinated. Other vaccines are given to groups of people at high risk; for example, adenovirus vaccine to military recruits or yellow fever vaccine to those individuals travelling in areas of endemic infection.

Very little attention has been paid to whether or not smoking influences the response of individuals to vaccination. Several studies have found increased incidences of respiratory illness in smokers (*21*). On the other hand, Monto and Ross (*15*), in a study of the relationship between the frequency of acute respiratory infections, smoking, and chronic pulmonary disease, found an increase in infections in subjects with chronic lung disease which was independent of the smoking factor.

Studies in Humans

Finklea, et al. (*2*), in a study involving 289 volunteers, reported a significant decrease in the persistence of hemagglutination inhibition antibody among cigarette smokers after natural infection or vaccination with influenza A_2 antigens. Although this investigation suggests a rapid decrease in antibodies to influenza vaccination in the group that smoked when compared to the nonsmoking group, the results obtained in this study have to be criticized for two reasons: the 289 volunteers were subdivided into very small groups making the assessment of statistical significance difficult and the data were not presented in a manner which allowed a judgment regarding the validity of the presumption that the response of the two populations, nonsmokers and smokers, was functioning under the same multinomial distribution upon which the investigators based their statistical analyses.

The only other report in the literature on smoking, vaccines, and the immune response is a study by MacKenzie, et al. (*12*). These investigators studied the effects of cigarette smoking on the response to vaccination against influenza. Their results indicate that a higher number of cigarette smokers than nonsmokers sero-converted after vaccination with live attenuated influenza vaccine as measured by the hemagglutination inhibition test. There was no difference in response between smokers and nonsmokers to killed subunit vaccine. However, when the investigators studied the longevity of the immune response over a period of 50 weeks, they found that the smokers vaccinated with killed subunit vaccine had a significant depression ($t = 2.35$, 111 D.F.,

$P \leq 0.05$) in antibody titer. No significant difference was found between titers of smokers and nonsmokers who received the live attenuated vaccine. Again, although there are indications that smoking influences the immune response, this study has limitations: because of the small number of subjects in each group, significance of differences is difficult to assess; inconsistencies were found in the immune response of subjects to live vaccine versus killed vaccine; and, in the strictest sense, there was a control group for the live influenza vaccines that received injections of saline, but there was no placebo or control group for the subjects administered the killed subunit vaccine by intranasal spray. The one control group was used as the control for both experimentally vaccinated groups.

Animal Model Systems

Thomas, et al. (*19*) reported testing the effects of fresh cigarette smoke on the immune response of mice. They found that the antibody response to sheep red blood cells was inhibited, depending on the concentration of the cigarette smoke solution.

MacKenzie (*11*) developed a model system in mice to study the influence of smoking on influenza virus. He reported that short exposures to cigarette smoke enhanced the response of mice to vaccination while prolonged exposure depressed the humoral response as measured by the hemagglutination inhibition test.

Bacterial Products

There are no reports of studies on the influence of and response to bacterial vaccines or bacterial products in humans who smoke. Campbell and Hilsenroth (*1*) investigated the response of mice immunized with tetanus toxoid after the mice had been exposed to nitrogen dioxide (a byproduct of cigarette smoke) or ozone. The mice were then challenged with tetanus toxin. The results indicated that there was more mortality and morbidity in the animals exposed to the two gases when compared to the controls.

Carcinoembryonic Antigen Test

Gold and Freedman (*4*) reported finding tumor-specific antigens in adenocarcinomata of the human colon. These antigens are not found in normal adult colonic tissues. When rabbits are immunized with these antigens, tumor-specific antibodies can be demonstrated by different immunologic methods, such as agar gel diffusion, immunoelectrophoresis, passive cutaneous anaphylaxis, and the hemagglutination inhibition test. Gold and Freedman (*5*) characterized the antigens and found that, for the most part, they could be detected in cancerous tissues of the human digestive organs. The origin of these organs in fetal life is the endodermally derived epithelium. The antigens were detected in

human fetal gut, liver, and pancreas tissues obtained between 2 and 6 months of gestation. Normal adult colon and the other adult tissues tested, as well as fetal gut, liver, and pancreas in the third trimester, were devoid of these antigens. Gold and Freedman termed these antigenic components of the human digestive system, carcinoembryonic antigen (CEA), and suggested that CEA represented cellular components found in the normal developing (embryonic) digestive system epithelium. These components are repressed after the sixth month of embryonic life but reappear in colon malignancy by derepression of differentiation as the adult colon cells metastasized. Krupey, et al. (*9*) characterized CEA as a protein-polysaccharide complex. It is a glycoprotein of high molecular weight (200,000) normally found as a constituent of the glycocalyx of embryonic endodermal epithelium and is also present in extracts of colon carcinoma cells. Thomson, et al. (*20*) developed a radioimmunoassay to detect CEA circulating in the blood of patients. This test permits the detection of nanogram (ng) amounts of CEA. To obtain more specific antiserum and thereby reduce false positive results in the radioimmunoassay, Krupey, et al. (*10*) developed a procedure to purify CEA used to immunize the rabbits. Originally the CEA test was only sensitive enough to detect concentrations of 2.5 ng/ml but by this improved procedure 1.0-2.0 ng/ml could be detected.

Gold (*3*) reported on a study of 212 sera. Seventy percent (30/43) of the patients with non metastatic cancer had hemagglutination inhibition titers $>$ 1:80 to CEA.

Moore, et al. (*16*) and Rule, et al. (*18*) reported finding elevated CEA levels in patients with inflammatory bowel disease. Holyoke, et al. (*8*) reviewed the literature on CEA and cancers of the gastrointestinal tract and reported that evidence was accumulating that the detection of elevated CEA levels could be used as a tool in prognosis of colon carcinoma after surgical removal of the tumor. However, the use of CEA as a diagnostic tool was doubtful because of the finding of elevated levels of CEA in disease states, such as Crohn's disease and other chronic inflammatory bowel diseases. Meeker, et al. (*14*) reported finding 90 percent (66/73) of patients with gastrointestinal tract cancer with CEA levels above 2.5 ng/ml. In a joint study of the National Cancer Institute of Canada and the American Cancer Society (*17*), the sera of 503 patients were examined for CEA titers to determine whether or not the results of the test were reproducible in different laboratories and whether or not patients with colon tumors could be distinguished from patients with other malignancies. The results indicated that the CEA test was reproducible in different laboratories and that determination of CEA titers was an important aid in the diagnosis of colon cancer.

The results of a large double-blind study by Gold, et al. (*6*), which involved 597 individuals, showed that over 95 percent (83/87) of patients with malignant colon tumors had CEA levels over 2.5 ng/ml.

Hansen, et al. (*7*) have reported on a collaborative study involving some 35,000 plasma samples from more than 10,000 patients. In this study 97 percent (865/892) of the healthy nonsmokers had CEA levels below 2.6 ng/ml and 3 percent (25/892) had CEA levels of 2.6 to 5.0 ng/ml, while 15 percent (93/620) of smokers had levels of 2.6 to 5.0 ng/ml. In the same study, 883 subjects at high risk (uranium miners) were examined: 19 percent (91/484) had CEA levels above 2.5 ng/ml while 3.9 percent (19/484) had CEA levels over 5.0 ng/ml. In an attempt to further correlate elevated CEA levels, these investigators extended their studies to look at the sputum cytology of 581 uranium miners of whom 456 were smokers with a history of smoking (289) or former smokers (167). Uranium miners were considered to be a high risk population for the development of pulmonary cancer. Eighteen percent (52/289) of the subjects had CEA levels above 2.5 ng/ml. The sputum cytological examination revealed nine of these 52 individuals had carcinoma *in situ* and three had carcinoma, while the remaining 28 individuals had mild to marked atypic sputum reports. These results confirmed the previous findings of elevated CEA levels in patients with pulmonary cancers. These investigators were the first to report elevated CEA levels in people who were chronic, heavy smokers.

Meeker, et al. (*14*) reported finding CEA levels greater than 2.5 ng/ml in 11 percent (19/176) of individuals classified as healthy subjects. These investigators examined a number of factors such as sex, age, and so forth, to determine those which might influence CEA levels. The only factor found to influence CEA levels was smoking. When CEA levels of those who did not smoke and those who smoked were compared; a highly significant difference ($P = .005$) was found. The mean level of 1.5 ± 0.96 ng/ml was found in the nonsmokers whereas the smokers had a mean level of 2.1 ± 1.2 ng/ml.

McCartney and Hoffer (*13*) mentioned that chronic cigarette smoking was associated with elevated CEA levels in the absence of other specific diseases, but they did not elaborate further on the subject.

Summary

There is suggestive evidence that antibody titers to natural infection or vaccination with influenza virus in cigarette smokers decrease more rapidly than the titers of nonsmokers. To confirm these findings, studies need to be done with larger groups of individuals.

Carcinoembryonic antigen levels found in many smokers are elevated to the levels observed in patients with proven carcinoma of the colon. The significance of these elevated levels is not clear at this

time. However, when the CEA test is used as an adjunct in diagnosis, this fact needs to be considered when interpreting the results obtained.

Biologicals: References

(1) CAMPBELL, K.I., HILSENROTH, R.H. Impaired resistance to toxin in toxoid-immunized mice exposed to ozone or nitrogen dioxide. Clinical Toxicology 9(6): 943-954, December 1976.

(2) FINKLEA, J.F., HASSELBLAD, V., RIGGAN, W.B., NELSON, W.C., HAMMER, D.I., NEWILL, V.A. Cigarette smoking and hemagglutination inhibition response to influenza after natural disease and immunization. American Review of Respiratory Disease 104(3): 368-376, September 1971.

(3) GOLD, P. Circulating antibodies against carcinoembryonic antigens of the human digestive system. Cancer 20(10): 1663-1667, October 1967.

(4) GOLD, P., FREEDMAN, S.O. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. Journal of Experimental Medicine 121(3): 439-462, March 1, 1965.

(5) GOLD P., FREEDMAN, S.O. Specific carcinoembryonic antigens of the human digestive system. Journal of Experimental Medicine 122(3): 467-481, September 1, 1965.

(6) GOLD, P., WILSON, T., ROMERO, R., SHUSTER, J., FREEDMAN, S.O. Immunology and colonic cancer: Further evaluation of the radioimmunoassay for carcinoembryonic antigen of the human digestive system as an adjunct in cancer diagnosis. Diseases of the Colon and Rectum 16(5): 358-365, September/October 1973.

(7) HANSEN, H.J., SNYDER, J.J., MILLER, E., VANDEVOORDE, J.P., MILLER, O.N., HINES, L.R., BURNS, J.J. Carcinoembryonic antigen (CEA) assay. A laboratory adjunct in the diagnosis and management of cancer. Human Pathology 5(2): 139-147, March 1974.

(8) HOLYOKE, E.D., CHU, T.M., MURPHY, G.P. Carcinoembryonic antigen (CEA) and gastrointestinal malignancy. Review of Surgery 30(5): 305-311, September/October 1973.

(9) KRUPEY, J., GOLD, P., FREEDMAN, S.O. Physicochemical studies of the carcinoembryonic antigens of the human digestive system. Journal of Experimental Medicine 128(3): 387-398, September 1, 1968.

(10) KRUPEY, J., WILSON, T., FREEDMAN, S.O., GOLD, P. The preparation of purified carcinoembryonic antigen of the human digestive system from large quantities of tumor tissue. Immunochemistry 9(4): 617-622, April 1972.

(11) MACKENZIE, J.S. The effect of cigarette smoke on influenza virus infection: A murine model system. Life Sciences 19(3): 409-412, August 1, 1976.

(12) MACKENZIE, J.S., MACKENZIE, I.H., HOLT, P.G. The effect of cigarette smoking on susceptibility to epidemic influenza and on serological responses to live attenuated and killed subunit influenza vaccines. Journal of Hygiene (Cambridge) 77(3): 409-417, December 1977.

(13) MCCARTNEY, W.H., HOFFER, P.B. The value of carcinoembryonic antigen (CEA) as an adjunct to the radiological colon examination in the diagnosis of malignancy. Radiology 110(2): 325-328, February 1974.

(14) MEEKER, W.R., JR., KASHMIRI, R., HUNTER, L., CLAPP, W., GRIFFEN, W.O., JR. Clinical evaluation of carcinoembryonic antigen test. Archives of Surgery 107(2): 266-274, August 1973.

(15) MONTO, A.S., ROSS, H.W. The Tecumseh study of respiratory illness. X. Relation of acute infections to smoking, lung function and chronic symptoms. American Journal of Epidemiology 107(1): 57-64, January 1978.

(16) MOORE, T.L., KANTROWITZ, P.A., ZAMCHECK, N. Carcinoembryonic antigen (CEA) in inflammatory bowel disease. Journal of the American Medical Association 222(8): 944-947, November 20, 1972.

(17) NATIONAL CANCER INSTITUTE OF CANADA/AMERICAN CANCER SOCIETY. A collaborative study of a test for carcinoembryonic antigen (CEA) in the sera of patients with carcinoma of the colon and rectum. A joint National Cancer Institute of Canada/American Cancer Society investigation. Canadian Medical Association Journal 107(1): 25-33, July 8, 1972.

(18) RULE, A.H., STRAUS, E., VANDEVOORDE, J., JANOWITZ, H.D. Tumor-associated (CEA-reacting) antigen in patients with inflammatory bowel disease. New England Journal of Medicine 287(1): 24-26, July 6, 1972.

(19) THOMAS, W.R., HOLT, P.G., KEAST, D. Antibody production in mice chronically exposed to fresh cigarette smoke. Experientia 30(12): 1469-1470, December 15, 1974.

(20) THOMSON, D.M.P., KRUPEY, J., FREEDMAN, S.O., GOLD, P. The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. Proceedings of the National Academy of Sciences, U.S.A. 64(1): 161-167, September 1969.

(21) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition: 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.

Nutrients Interactions

Epidemiology data have long linked smoking with increased risks of cardiovascular disease, increased osteoporosis, amblyopia, and other disorders (*5, 9, 14, 18, 24, 29, 43, 53, 56, 68*). As early as 1939 (*65*), scientists demonstrated that smoking causes changes in levels of nutrients, which may help to explain the impact smoking has on health. Since the complete "cause and effect" relationships of these nutritional changes have not been clearly identified, only those of nutrients for which the effect is more clearly understood will be considered in this section.

Macronutrients

Lipids

Because smoking has been established epidemiologically as a major factor in cardiovascular disease, the interaction between smoking and lipid metabolism has been extensively investigated. Several studies demonstrate that blood cholesterol levels are higher in smokers than in nonsmokers (*52, 55, 72*). In carefully controlled studies, however, Elwood, et al. (*20*) reported that the differences are not statistically significant. An explanation for these observations, proposed by several investigators, is that they are associated with vitamin C metabolism (*35, 38, 62, 63*). These researchers claim that vitamin C has a role in the transport of cholesterol to the liver where catabolism and excretion take place. Smoking has been shown to increase plasma triglyceride levels (*52, 55, 58*) and differences between smokers and nonsmokers are highly significant. Yeung (*72*) has reported that smoking together with oral contraceptives results in even higher plasma triglyceride levels.

Carbohydrates

Several investigators have demonstrated that alterations in carbohydrate metabolism are frequently associated with smoking (*24, 27, 37, 52, 55, 61*). Orsetti, et al. (*44*) supported epidemiological observations in a clinical nutrition study in which both smokers and nonsmokers were required to smoke two cigarettes in a 10 minute period. Of the 18 subjects studied, 10 showed a significant rise in somatotropic hormone for 20 minutes post smoking. Plasma catecholamine levels increased for five of six subjects tested.

Proteins

Albanese, et al. (*3*) in a study involving 7 nonsmokers and 10 smokers, reported a significant difference in protein utilization. Nonsmokers were more efficient in retaining nitrogen than were smokers. The authors concluded that the apparent difference in protein metabolism was associated with impairment of tryptophan utilization. As discussed later, an impairment in protein metabolism may also be partially

responsible for low birthweight found in infants born to smoking mothers. Crosby, et al. (*16*) have shown that smoking mothers had lower leukocyte RNA synthesis and lower plasma levels of 14 amino acids than did non-smoking mothers.

Micronutrients

Vitamin C

Strauss and Scheer (*65*) reported that the urinary excretion of vitamin C was lower in heavy smokers than it was for nonsmokers. Several investigators later showed that smoking causes changes in the vitamin C levels found in plasma and leukocytes (*9, 10, 20, 25, 30, 33, 40, 45, 46, 47, 48, 60, 72, 73*). The reasons for these observed changes have not been completely established. Keith and Pelletier (*34*) have demonstrated a decrease in vitamin C absorption when high levels of nicotine were administered to laboratory animals. Dewhurst and Kitchen (*19*) and Sprince, et al. (*64*) have postulated that there is increased oxidation of vitamin C from compounds, such as acetaldehyde, which are derived from smoking. Other scientists postulate that increased secretion of adrenaline and adrenal steroids stimulated by nicotine causes increased utilization of vitamin C. Vitamin C is known to be essential for the metabolism of tyrosine which, in turn, is a precursor of adrenalin and noradrenalin. The importance of vitamin C in the formation of collagen, the synthesis of neurotransmitters, and in many other biochemical functions has stimulated several hypotheses for the pathogenesis of degenerative diseases for which smoking is known to be a risk factor (*6, 35, 38, 62, 63*).

Vitamin B_{12}

The observation that tobacco amblyopia and nutrition-induced amblyopia respond to hydroxycobalamin, a form of vitamin B_{12}, led to the discovery that smoking lowers both blood and tissue levels of vitamin B_{12} (*2, 11, 15, 22, 32, 36, 49, 50, 51*). The loss of vitamin B_{12} is attributed to the use of this vitamin in the detoxication of cyanide derived from inhaled tobacco smoke (*23, 26, 28, 70, 72*). Predictably, vegetarians have been shown to have lower vitamin B_{12} levels than nonvegetarians, and vegetarians who smoke have the lowest levels of this vitamin (*17, 69*). Schrauzer and Lee (*57*) have postulated that carbon monoxide in tobacco smoke reacts with Co+++ in vitamin B_{12} to form Co++ (*57*). The occurrence of amblyopia is believed to be associated with individuals having a genetic or acquired error of cyanide or vitamin B_{12} metabolism in that cyanide is not converted to thiocyanate, but remains as cyanocobalamin (*13, 27, 54, 71*). Agamanolis, et al. (*1*) have suggested that the occurrence of amblyopia is an early symptom of vitamin B_{12} deficiency and that pernicious anemia and other symptoms occur at a much later stage.

Vitamin B_6

El-Zoghby, et al. (*21*) have reported the possible existence of a smoking-induced vitamin B_6 deficiency, as indicated by the finding that tryptophan metabolites follow different excretion patterns in smokers and nonsmokers. Supplementation with vitamin B_6 restores the excretion of some metabolites for smokers to the levels found in nonsmokers; however, other metabolites remain at abnormal levels despite the additional vitamin B_6. A report by Mitchell and Schandl (*42*) suggests a possible mechanism for vitamin B_6 loss which involves a reaction between vitamin B_6 and carbon monoxide.

Minerals

Some observations have been made that bone mineral losses associated with postmenopause are accelerated with smoking. In two studies involving 72 and 80 women, osteoporosis in nonobese smokers was significantly higher than for nonobese nonsmokers (*8*). Obese women showed no similar effect between smoking and nonsmoking. The increased loss of bone mineral may be a secondary effect induced by other nutritional conditions such as low vitamin C levels.

Other

Obesity

Although many individuals have reported significant weight gains when smoking was terminated, there appears to be no scientific evidence to support the existence of a thermogenesis effect. In a carefully controlled study, Sims (*61*) observed no change in resting metabolic rate, thermic response to exercise or meals, and no change in serum T-3 or T-4. Subjects participating in this study revealed, however, that their appetite ratings were lower during periods of smoking.

Smoking in Pregnancy

Fetal malnutrition associated with smoking mothers has been observed both in the United States and in Great Britain. Results of these studies demonstrate that babies born to smoking mothers are smaller and have a greater risk of perinatal mortality when compared to babies of nonsmoking mothers (*4, 7, 16, 28, 39, 59*). The exact causes of these observations have not been established. It is likely that a combination of nutritional factors, such as lower levels of amino acids, vitamins B_{12} and C, and glucose and fatty acids in maternal blood, contribute to the causes of these observations (*12, 41*). In addition, it has been postulated that higher levels of carbon monoxide, nicotine, and cyanides result in decreased oxygen for the fetus.

Summary

Epidemiologic data have long linked smoking with increased risk of cardiovascular disease, increased osteoporosis, amblyopia, and other disorders. Recent data demonstrate that smoking during pregnancy results in a greater risk of smaller birth weight and perinatal mortality among pregnant women. Smoking causes changes in plasma and leukocyte concentrations of vitamin C and impairs biochemical functions of this vitamin. Vitamin B_{12} is metabolized in the detoxification process of cyanide derived from smoking. Some heavy smokers develop an amblyopia which is reversed by either vitamin B_{12} supplementation or termination of smoking. Evidence is also presented suggesting that smoking may alter the metabolism of lipids, carbohydrates, proteins, and other vitamins such as vitamin B_6.

Nutrient Interactions: References

(1) AGAMANOLIS, D.P., CHESTER, E.M., VICTOR, M., KARK, J.A., HINES, J.D., HARRIS, J.W. Neuropathology of experimental vitamin B-12 deficiency in monkeys. Neurology 26(10): 905-914, October 1976.

(2) AINLEY, R.G. The Farnsworth-Munsell 100 hue test in tobacco amblyopia. Transactions of the Ophthalmological Society of the United Kingdom 90: 765-772, 1970.

(3) ALBANESE, A.A., ORTO, L.A., WEIN, E.H., ZAVATTARO, D.N. Effect of cigarette smoking on protein and amino acid metabolism. I. Tryptophan. Nutrition Reports International 5(4): 245-258, April 1972.

(4) ANDREWS, J., MCGARRY, J.M. A community study of smoking in pregnancy. The Journal of Obstetrics and Gynaecology of the British Commonwealth 79(12): 1057-1073, December 1972.

(5) ARMSTRONG, B., LEA, A.J., ADELSTEIN, A.M., DONOVAN, J.W., WHITE, G.C. RUTTLE, S. Cancer mortality and saccharin consumption in diabetics. British Journal of Preventive and Social Medicine 30(3): 151-157, September 1976.

(6) BAILEY, D.A., CARRON, A.V., TEECE, R.G., WEHNER, H.J. Vitamin C supplementation related to physiological response to exercise in smoking and nonsmoking subjects. American Journal of Clinical Nutrition 23(7): 905-912, July 1970.

(7) BRITISH MEDICAL JOURNAL. Cigarette smoking in pregnancy. British Medical Journal 2(6034): 492, August 28, 1976.

(8) BRITISH MEDICAL JOURNAL. Smokers' bones. British Medical Journal 2(8029): 201, July 24, 1976.

(9) BURR, M.L., ELWOOD, P.C., HOLE, D.J., HURLEY, R.J., HUGHES, R.E. Plasma and leukocyte ascorbic acid levels in the elderly. American Journal of Clinical Nutrition 27(2): 144-151, February 1974.

(10) BURR, R.G., RAJAN, K.T. Leucocyte ascorbic acid and pressure sores in paraplegia. British Journal of Nutrition 28(2): 275-281, 1972.

(11) CANADIAN MEDICAL ASSOCIATION JOURNAL. Tobacco amblyopia. Canadian Medical Association Journal 102(4): 420, February 1970. (Editorial)

(12) CHAMOT, A.P.H. BAZARBACHI, H. Agents toxiques et grossesse (Toxic agents and pregnancy). Gynaecologia 168(5): 318-327, 1969.

(13) CHISHOLM, I.A., PETTIGREW, A.R. Biochemical observations in toxic optic neuropathy. Transactions of the Ophthalmological Society of the United Kingdom 90: 827-838, 1970.

(14) CLEGG, K.M., MACDONALD, J.M. L-ascorbic acid and d-isoascorbic acid in a common cold survey. American Journal of Clinical Nutrition 28(9): 973-976, September 1975.

(15) CREWS, S.J., JAMES, B., MARSTERS, J.B., WEST, R.H. Drug and nutritional factors in optic neuropathy. Transactions of the Ophthalmological Society of the United Kingdom 90: 773-794, 1970.

(16) CROSBY, W.M., METCOFF, J., COSTILOE, J.P., MAMEESH, M., SANDSTEAD, H.H., JACOB, R.A., MCCLAIN, P.E., JACOBSON, G., REID, W., BURNS, G. Fetal malnutrition: An appraisal of correlated factors. American Journal of Obstetrics and Gynecology 128(1): 22-31, May 1, 1977.

(17) DASTUR, D.K., QUADROS, E.V., WADIA, N.H., DESAI, M.M., BHARUCHA, E.P. Effect of vegetarianism and smoking on vitamin B-12, thiocyanate, and folate levels in the blood of normal subjects. British Medical Journal 3: 260-263, July 29, 1972.

(18) DELAHAYE, J.P., BESSET C., TOUBOUL, P. Evolution spontanee et pronostic des arteriopathies atherosclereuses des membres inferieurs (Spontaneous evolution and prognosis of atherosclerotic arterial diseases of the lower limbs). Archives des Maladies du Coeur et des Vaisseaux 63 (Supplement 1): 64-78, 1970.

(19) DEWHURST, F., KITCHEN, D.A. Effect of some 6-substituted benzo(a)pyrene derivatives upon liver enzymes and ascorbic acid excretion in mice. Biochemical Pharmacology 22(7): 789-796, April 1973.

(20) ELWOOD, P.C., HUGHES, R.E., HURLEY, R.J. Ascorbic acid and serum-cholesterol. Lancet 2(7684): 1197, December 5, 1970.

(21) EL-ZOGHBY, S.M., EL-SHAFEI, A.K., ABDEL-TAWAB, G.A., KELADA, F.S. Studies on the effect of reserpine therapy on the functional capacity of the tryptophan-niacin pathway in smoker and non-smoker males. Biochemical Pharmacology 19(5): 1661-1667, May 1970.

(22) FOULDS, W.S. Visual disturbances in systemic disorders, optic neuropathy, and systemic disease. Transactions of the Ophthalmological Society of the United Kingdom, 1969 Session, 89: 125-146, 1970.

(23) FREEMAN, A.G. Thiocyanate metabolism in human vitamin B-12 deficiency. British Medical Journal 1(5847): 231-232, January 27, 1973.

(24) GASTARD, J., JOUBAUD, F., FARBOS, T., LOUSSOUARN, J., MARION, J. PANNIER, M., RENAUDET, F., VALDAZO, R., GOSSELIN, M. Etiology and course of primary chronic pancreatitis in Western France. Digestion 9(5): 416-428, 1973.

(25) GRANT, F.W., COWEN, M.A., OZERENGIN, M.F., BIGELOW, N. Nutritional requirements in mental illness. 1. Ascorbic acid retention in schizophrenia. A reexamination. Biological Psychiatry 5(3): 289-294, December 1972.

(26) HALAWA, B., MAZUREK, W. Wplyw palenia tytoniu na poziom witaminy B-12 w surowicy u ludzi (Effect of Tobacco smoking on vitamin B-12 level in human serum). Wiadomosci Lekarskie 29(6): 469-472, March 15, 1976.

(27) HARRIS, J.O., SWENSON, E.W., JOHNSON, J.E. Human alveolar macrophages: Comparison of phagocytic ability, glucose utilization, and ultrastructure in smokers and nonsmokers. Journal of Clinical Investigation 49(11): 2086-2096, November 1970.

(28) HAUSER, G.A. Genussmittel in der schwangerschaft (Voluptuaries in pregnancy). Therapeutische Umschau 28(7): 430-434, July 1971.

(29) HELMAN, N. Macrocytosis and cigarette smoking (Letter). Annals of Internal Medicine 79(2): 287-288, August 1973.

(30) HUGHES, R.E., JONES, P.R., NICHOLAS, P. Some effects of experimentally-produced cigarette smoke on the growth, vitamin C metabolism, and organ weights of guinea-pigs. Journal of Pharmacy and Pharmacology 22(11): 823-827, November 1970.

(31) ILEBEKK, A., MILLER, N.E., MJOS, O.D. Effects of nicotine and inhalation of cigarette smoke on total body oxygen consumption in dogs. Scandinavian Journal of Clinical and Laboratory Investigation 35(1): 67-72, 1975.

(32) JAYLE, G.E., METGE, P., CHAIX, A., VOLA, J.L., TASSY, A. Exploration fonctionnelle des nevrites optiques alcoolo-tabagiques (Functional exploration of alcohol-tobacco optic neuritis). Archives D'Ophtalmologie 32(1): 79-86, 1972.

(33) KAMPENG, V., VASINARAVONGSE, V., SIDDHIKOL, C. Level of vitamin C in plasma in smokers and nonsmokers among medical students. Sibiraj Hospital Gazette 25(6): 964-971, June 1973.

(34) KEITH, M.O., PELLETIER, O. The effect of nicotine on ascorbic acid retention by guinea pigs. Canadian Journal of Physiology and Pharmacology 51(12): 879-884, December 1973.

(35) KEVANY, J., JESSOP, W., GOLDSMITH, A. The effect of smoking on ascorbic acid and serum cholesterol in adult males. Irish Journal of Medical Science 144(12): 474-477, December 1975.

(36) KNOX, D.L. Neuro-ophthalmology. Annual review. Archives of Ophthalmology 83(1): 103-127, January 1970.

(37) KRISHNASWAMY, K., NADAMUNI NAIDU, A. Microsomal enzymes in malnutrition as determined by plasma half life of antipyrine. British Medical Journal 1(6060): 538-540, February 26, 1977.

(38) LOH, H.S. Cigarette smoking and the pathogenesis of atherosclerosis—a hypothesis. Irish Journal of Medical Science 142(4): 174-178, July 1973.

(39) LUBCHENCO, L.O. The infant who is small for gestational age. Major Problems in Clinical Pediatrics. Volume XIV. The High Risk Infant. Philadelphia, W.B. Saunders, 1976, pp. 181-201.

(40) MCCLEAN, H.E., DODDS, P.M., ABERNETHY, M.H., STEWART, A.W., BEAVEN, D.W. Vitamin C concentration in plasma and leucocytes of men related to age and smoking habit. New Zealand Medical Journal 83(561): 226-229, April 14, 1976.

(41) MCGARRY, J.M., ANDREWS, J. Smoking in pregnancy and vitamin B-12 metabolism. British Medical Journal 2(5805): 74-77, April 8, 1972.

(42) MITCHELL, D.A., SCHANDL, E.K. Carbon monoxide, vitamin B-6, and multiple sclerosis: a theory of interrelationship. American Journal of Clinical Nutrition 26(8): 890-896, August 1973.

(43) MOLLER, E., KLEIN, B. Herzinfarkt und subklinishcer diabetes (Myocardial infarct and subclinical diabetes). Medizinische Welt 21(26): 1191-1194, June 27, 1970.

(44) ORSETTI, A., AMARA, F., COLLARD, F., MIROUZE, J. Influence du tabac sur les hormones essentielles de la glycoregulation (The influence of tobacco on hormones essential to glycoregulation). Nouvelle Press Medicale 4(21): 1571-1572, May 24, 1975.

(45) PELLETIER, O. Cigarette smoking and vitamin C. Nutrition Today 5(3): 12-15, Autumn 1970.

(46) PELLETIER, O., Vitamin C and cigarette smokers. Annals of the New York Academy of Sciences 258: 156-168, 1975.

(47) PELLETIER, O. Vitamin C status of cigarette smokers and nonsmokers. American Journal of Clinical Nutrition 23(5): 520-524, May 1970.

(48) PELLETIER, O., KEITH, M.O. Bioavailability of synthetic and natural ascorbic acid. Journal of the American Dietetic Association 64(3): 271-275, March 1974.

(49) PETTIGREW, A.R., FELL, G.S., CHISHOLM, I.A. Red cell glutathione in tobacco amblyopia. Experimental Eye Research 14(2): 87-90, 1972.

(50) PHILLIPS, C.I., AINLEY, R.G., VAN PEBORGH, P., WATSON-WILLIAMS, E.J., BOTTOMLEY, A.C. Vitamin B-12 content of aqueous humour. Nature 217(5123): 67-68, January 6, 1968.

(51) POTTS, A.M. Tobacco amblyopia. Survey of Ophthalmology 17(5): 313-339, March/April, 1973.

(52) RATZMANN, K.-P., RIEMER, D., SPOERL, L., WEBER, L., WITTKOPF, E. Untersuchungen zur wirkung des zigaretten rauchens auf metaboliten des kodlenhyhrat-und fettstoffwechsels (Investigation of the effect of cigarette smoke on intermediates in carbohydrate and lipid metabolism). Deutsche Gesundheitswesen 34(28): 1618-1620, August 4, 1973.

(53) ROBERTS, D.M. Chronic gastritis, alcohol, and non-ulcer dyspepsia. Gut 13(10): 768-774, October 1972.

(54) ROSSMANN, H. Vitamin B-12 resorption bei der sogenannten tabak-amblyopie (Vitamin B-12 resorption in the so-called tobacco amblyopia). Deutsche Medizinische Wochenschrift 95(8): 419-420, February 20, 1970.

(55) SALAZAR, E., MORAGREGA, J.L., MAGOS, C., ZORRILLA, E., SERRANO, P.A. Alteraciones metabolicas en sobrevivientes de infarto del miocardio (Metabolic changes in survivors of myocardial infarction). Archivos del Instituto de Cardiologia de Mexico 43(1): 4-17, January/February 1973.

(56) SCHETTLER, G., MOERL, H. Risikofaktoren der atherosklerose in beziehung zur lebenserwartung heute und den lebensaussichten morgan (Risk factors of atherosclerosis in relation to life expectancy today and in the future). Medizinische Welt 27(46): 2201-2205, November 12, 1976.

(57) SCHRAUZER, G.N., LEE, L.P. The reduction of vitamin B-12a by carbon monoxide. Archives of Biochemistry and Biophysics 138(1): 16-25, May 1970.

(58) SHANKAR, R. Effect of chronic nicotine administration on the intestinal mucosal alkaline phosphatase in rats. Indian Journal of Experimental Biology 13(4): 360-362, July 1975.

(59) SILVERMAN, H.M. Fetal and newborn adverse drug reactions. A survey of the recent literature. Drug Intelligence and Clinical Pharmacy 8(12): 690-693, December 1974.

(60) SIM, A.K. Ascorbic acid—a survey, past and present. Chemistry and Industry 8(4): 160-165, February 19, 1972.

(61) SIMS, E.A.H. Experimental obesity, dietary-induced thermogenesis, and their clinical implications. Clinics in Endocrinology and Metabolism 5(2): 377-395, July 1976.

(62) SPITTLE, C.R. The action of vitamin C on blood vessels. American Heart Journal 88(3): 387-388, September 1974.

(63) SPITTLE, C.R. Atherosclerosis and vitamin C. Lancet 2(7737): 1280-1281, December 11, 1971.

(64) SPRINCE, H., PARKER, C.M., SMITH, G.G., GONZALES, L.J. Protective action of ascorbic acid and sulfur compounds against acetaldehyde toxicity: Implications in alcoholism and smoking. Agents and Actions 5(2): 164-173, 1975.

(65) STRAUSS, L.H., SCHEER, P. Ueber die Einwirkungen des Nikotins auf den Vitamin C-Haushalt (On the influence of nicotine on the composition of vitamin C). Zeitschrift fur Vitaminforschung 9: 39-48, 1939.

(66) TAMURA, T., INOUE, H. IIDA, T., ONO, H. Studies on the antidotal action of drugs. Part 1. Vitamin C and its antidotal effect against alcoholic and nicotine poisoning. Journal of Nihon University School of Dentistry 11: 149-151, 1969.

(67) TOPORKOVA, I.B. Vitamin C balance in connection with chronic exposure of tobacco industrial workers to tobacco dust. Leningradskii Sanitarno-Gigienicheskii Meditsinskii Institut, Trudy 47: 243-253, 1959.

(68) TSARFIS, T.P., SVERDLOVA, P.S., ILYUSHINA, I.P., GLAZUNOV, I.S., METELITSA, V.I. Disturbance in tolerance to carbohydrates in males 50-59 years old. Terapevticheskii Arkhiv 41(12): 77-80, December 1969.

(69) WADIA, N.H., DESAI, M.M., QUADROS, E.V., DASTUR, D.K. Role of vegetarianism, smoking and hydroxocobalamin in optic neuritis. British Medical Journal 3: 264-267, July 29, 1972.

(70) WELLS, D.G., LANGMAN, M.J.S., WILSON, J. Thiocyanate metabolism in human vitamin B-12 deficiency. British Medical Journal 4(5840): 588-590, December 9, 1972.

(71) WILSON, J., LINNELL, J.C., MATTHEWS, D.M. Plasma-cobalamins in neuro-ophthalmological diseases. Lancet 1(7693): 259-261, February 6, 1971.

(72) YEUNG, D.L. Relationships between cigarette smoking, oral contraceptives, and plasma vitamins A, E, C, and plasma triglycerides and cholesterol. American Journal of Clinical Nutrition 29(11): 1216-1221, November 1976.

(73) YEW, M.-L.S., LO, Y. Levels of optimal vitamin C intake in individuals as estimated by the lingual tests. Proceedings of the Society for Experimental Biology and Medicine 144(2): 626-627, 1973.

Trace Constituents in Smoke

Trace elements in tobacco that are sublimated at the temperature of smoking may interact with dietary components. These elements include organic compounds that are not pyrolyzed at these temperatures and compounds that may be formed during pyrolysis. The interaction may result because cigarette smoke contains: (1) significant amounts of trace components normally present in the food, e.g., heavy metals, pesticides, and naturally occurring carcinogens, which may represent an important additional source of exposure to these compounds; and (2) components that alter the metabolism of food additives or constituents. Because of the large number of components that may occur in cigarette smoke, only those considered significant are discussed here.

Trace Metals

Nadkarni (*12*) has reported that toxic elements in tobacco smoke include cadmium, lead, arsenic, and selenium. Cadmium from cigarettes represents a very substantial additional burden for smokers when compared with that normally present in the diet and other non-industrial sources. For a person smoking two to three packs of cigarettes a day, the estimated respiratory cadmium intake ranges from 4 to 6 μg. The retention of cadmium via this route is high; it has been estimated that of the 4-6 μg of the cadmium in the inhaled smoke, up to 2.82 μg would be absorbed. This represents a very significant exposure when compared with the proportion of cadmium retained from other sources, e.g., of the 50 μg/day cadmium ingested in food, retention may be of the order of only 3.0 μg. The significantly greater retention of cadmium by smokers is clearly reflected in greater levels of tissue cadmium in smokers compared to nonsmokers. Smokers accumulate more cadmium in the kidney cortex, liver, pancreas and other tissues than nonsmokers (*13*). For a person smoking one pack of cigarettes a day for 50 years, Elinder, et al. (*5*) estimated an increase in body burden of cadmium of about 8 mg. In another study, Johnson, et al. (*9*) estimated the body burden of cadmium in nonsmokers to be 10.3 mg compared to 14.9 mg for smokers.

Studies on the contribution of smoking to the body burden of other metals are limited. Cigarette smokers have been shown to have higher lead concentrations in the liver, pancreas, and kidney tissues, and slightly higher levels of lead in muscle and fat than nonsmokers (*6*). Johnson, et al. (*9*) have reported that zinc and mercury concentrations were significantly higher in the pancreas and fat tissues of smokers, but lower in the kidney tissue than in the case of nonsmokers.

^{210}Polonium, which is present in the leaves of tobacco and volatizes at the temperature at which cigarettes burn, is deposited in smoke particles and enters the lung with the particles. The ^{210}Po concentration

in cigarettes varies from 0.15 to 0.63 p Ci/g. Approximately 20 percent of the ^{210}Po content of a cigarette enters the lungs with the smoke stream, with one cigarette yielding about 0.08 p Ci of ^{210}Po to the body. This is almost as much ^{210}Po as a person inhales from the atmosphere in 24 hours (*14*).

There is no information to indicate that the increased body burden of these toxic elements results in toxic effects related to increased exposure to the elements. It is possible that subclinical effects may occur, although these effects cannot be demonstrated by the presently available methodology.

Nitrosamines

Tobacco smoke not only represents a source of exposure to nitrosable amines which can undergo nitrosation, but it is also a major source of exposure to preformed N-nitrosonornicotine (NNN), which is present in processed tobacco. Its concentration ranges from 0.3-90 ppm in smoking tobacco, chewing tobacco, and snuff. Hilfrich, et al. (*8*) have estimated exposure to NNN from tobacco smoke at 140-250 ng/cigarette. Fine (*6*) has estimated the exposure to nitrosamines from tobacco smoke, primarily NNN, to be 4.1 μg/day (from 20 cigarettes) compared to 6 μg/day (nitropyrollidine and other nitrosamines) from food. NNN induces tumors of the esophagus, pharynx, and the nasal cavity in rats, and it is possible that the increased incidence of cancer in tobacco smokers and chewers may be related to the carcinogenicity of this compound (*5*). In addition, it is not known if the possible carcinogenic action of this compound may be additive or may potentiate the effect of nitrosamines occasionally found in the diet.

Schmeltz, et al. (*15*) have detected N-nitrosodiethanolamine in cured tobacco at concentrations ranging from 0.1 to 173 ng/g. They postulate that it is derived from the use of diethanolamine, a solubilizing agent for the plant growth regulator, maleic hydrazide. Schmeltz and Hoffmann (*16*) have reviewed the occurrence of nitrogen-containing compounds in tobacco and tobacco smoke. Included in the list of compounds reported are numerous aliphatic amines, notably secondary and tertiary amines, as well as aromatic amines, which have the potential of being converted to nitrosamines in the presence of nitrite or nitrogen oxide. Because saliva normally contains low levels of nitrite (*18*), there is a potential for nitrosation of the amines to occur *in vivo*. In addition, nitrite in certain processed foods may represent a source of nitrite for nitrosation of these amines. The synthesis of nitrosamines may be further catalyzed by the presence of thiocyanate in saliva. Because thiocyanate levels are greatly increased in the saliva, as well as in the stomach content, of smokers compared to that of nonsmokers, the potential for *in vivo* nitrosation is greatly increased in smokers (*5*). However, other dietary components, e.g. ascorbic acid (*1*) or α-

tocopherol (*10*), may reduce the potential for nitrosation, primarily by reacting with the free nitrite.

Nicotine is a major constituent of tobacco smoke, but Lijinsky and Singer (*11*) report that it is only very slowly nitrosated in aqueous solutions and thus does not provide a significant source for amines that may be nitrosated in the stomach.

Pesticide Residues

Atallah and Dorough (*2*) have reported on studies with cigarettes impregnated with ^{14}C-labelled pesticides (carbaryl, carbofuran, leptophos, DDT, and mirex) and have provided information on both the stability of these pesticides under smoking conditions as well as the amount transferred to mainstream smoke. Mirex was reported to be the most stable compound (70 percent of ^{14}C in mainstream was unchanged mirex). Carbofuran was almost as stable as mirex. From 40 to 45 percent of the ^{14}C in mainstream smoke from carbaryl and DDT was in the form of the parent compound. Leptophos was the least stable, with only 21 percent of the ^{14}C in the mainstream smoke present as the parent compound. Rats which inhaled the ^{14}C-labelled smoke derived from the treated cigarettes did not show patterns or tissue distribution of inhaled ^{14}C-labelled pesticides which could be considered characteristic for a particular type of pesticide. In contrast, Atallah and Dorough (*2*) cited a report by Guthrie (*7*) which states that carbamates and organophosphate pesticides were almost completely degraded during the smoking process.

More information is needed on the nature and ultimate fate of insecticide residues inhaled in tobacco smoke. Based on the information reviewed, it is not possible to assess the health significance of pesticide residues in tobacco.

In addition to the active principals contained in pesticides, other subtances such as surfactants or solubilizing agents of inert carriers may, if transferred to tobacco smoke, interact with compounds in the diet or undergo conversion to potentially hazardous substances in the tobacco leaf itself, e.g., nitrosation of diethanolamine which is used as a solubilizing agent for maleic hydrazide. Very little is known regarding these potential interactions and the effects, if any, in humans.

There is also little information on the fate of N-containing agricultural chemicals after their application to tobacco. Maleic hydrazide is present in cured tobacco (20-30 ppm) and a small portion (4–10 percent) is transferred unchanged to mainstream smoke.

Metabolic Effects

Constituents of tobacco smoke may inhibit or induce enzyme activity in human tissues and alter the rate of metabolism of food additives or food constituents.

Nicotine has been shown to cause significant reduction in rats' intestinal alkaline phosphatase activity. The significance of the reduced activity of this marker enzyme of intestinal mucosa is not known, but it may be indicative of a reduced metabolic activity of the mucosal cells. Shankar (*17*) has postulated that this may be one of the factors causing sensitivities of mucosal cells to acid destruction.

A large number of polynuclear aromatic hydrocarbon (PNAs) have been identified in tobacco smoke. Wynder and Hoffmann (*19*) have reported that the concentration of PNA in the smoke of one cigarette ranges from 0.6-70.0 ng. In addition to their well-known effects as initiating carcinogens, PNAs are well-known inducers of mixed function oxidases. The effect of PNAs on the proliferation of microsomal enzymes and on subsequent increases in cytochrome P-450 has already been discussed in detail. However, it is of interest to note that cigarettes contain substances that may depress the activity of microsomal enzymes at one site and increase them at another site, e.g., cigarette smoke depresses pulmonary aryl hydrocarbon hydroxylase (AHH) activity in guinea pigs but increases liver AHH activity (*3*). The depression of pulmonary AHH activity may be due to the presence of carbon monoxide or cyanide in tobacco smoke combining directly with the cytochromes and rendering them unavailable for their role in the enzymatic action.

It is not known if these metabolic changes can affect the metabolism of food chemicals or food constituents, or if the level of changes that can occur are significant in relation to the inhibition or increase of microsomal activity by normal dietary constituents or contaminants in the diet. Another area of concern relates to the possible effect of enzyme inducers of the developing fetus. Enzyme inducers that cross the placental barrier may effect changes in the enzyme patterns of the developing fetus. Such changes or biochemical imprints may persist throughout life and could possibly result in altered patterns of metabolism of food additives and contaminants. It is not known to what extent, if any, constituents of tobacco smoke may cause these changes. However, a major problem in evaluating any possible effect due to the constituents of tobacco smoke is the lack of knowledge of the quantitative aspect of the relative amounts and activities of the components in tobacco smoke compared with those active substances normally present in the diet or present as contaminants (e.g., environmental contaminants, PCBs, DDT) of the diet, and the possible interactions between such compounds.

Summary

Although cigarette smoking will result in an additional body burden of Cd and Pb, there is little evidence that this will result in known adverse effects. The effects of nitrosamines and inhibitors and activators of enzymes in tobacco smoke have not been established.

Trace Constituents in Smoke: References

(1) ARCHER, M.C., TANNENBAUM, S.R., FAN, T.-Y., WEISMAN, M. Reaction of nitrite with ascorbate and its relation to nitrosamine formation. Journal of the National Cancer Institute, 54(5): 1203-1205, May 1975.

(2) ATALLAH, Y.H., DOROUGH, H.W. Insecticide residues in cigarette smoke. Transfer and fate in rats. Journal of Agriculture and Food Chemistry, 23(1): 64-71, 1975.

(3) BILIMORIA, M.H., JOHNSON, J., HOGG, J.C., WITSCHI, H.P. Pulmonary aryl hydrocarbon hydroxylase: Tobacco smoke-exposed guinea pigs. Toxicology and Applied Pharmacology 41: 433-440, 1977.

(4) BOYLAND, E., WALKER, S.A. Effect of thiocyanate on the nitrosation of amines. Nature, 248: 601-602, April 12, 1974.

(5) ELINDER, C.G., KJELLSTROM, T., FRIBERG, L., LIND, B., LINNMAN, L. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Archives of Environmental Health 31(6): 292-302, November/December 1976.

(6) FINE, D.H. An assessment of human exposure to N-nitroso compounds. Presented at the Fifth meeting on Analysis and Formation of N-nitroso Compounds, International Agency for Research on Cancer, Durham, N.H., August 22-24, 1977, 15 pp.

(7) GUTHRIE, F.E. The nature and significance of pesticide residues on tobacco and in tobacco smoke. Beitrage zur Tabakforschung 4(6): 229-246, November 1968.

(8) HILFRICH, J., HECHT, S.S., HOFFMANN, D. A study of tobacco carcinogenesis. XV. Effects of N'-nitrosonornicotine and N'-nitrosoanabasine in Syrian golden hamsters. Cancer Letters 2: 169-175, 1977.

(9) JOHNSON, D.E., PREVOST, R.J., TILLERY, J.B., THOMAS, R.E. The Distribution of Cadmium and Other Metals in Human Tissue. San Antonio, Southwest Research Institute, September 1977, 231 pp.

(10) KAMM, J.J., DASHMAN, T., NEWMARK, H., MERGENS, W.J. Inhibition of amine-nitrite hepatotoxicity by α-tocopherol. Toxicology and Applied Pharmacology 41: 575-583, September 1977.

(11) LIJINSKY, W., SINGER, G.M. Formation of nitrosamines from tertiary amines and nitrous acid. In: Bogovski, P. and Walker, E.A. (Editors). N-Nitroso Compounds in the Environment. Proceedings of a Working Conference held at the International Agency for Research on Cancer, Lyon, France, October 17-20, 1973. Lyon, International Agency for Research on Cancer, 1975, pp. 111-114.

(12) NADKARNI, R.A. Some considerations of metal content of tobacco products. Chemistry and Industry 17: 693-696, September 7, 1974.

(13) OFFICE OF TOXIC SUBSTANCES. Multimedia Levels—Cadmium. Environmental Protection Agency, Office of Toxic Substances, September 1977, pp. 5-1-5-21, 6-1-6-14.

(14) PARFENOV, Y.D. Polonium-210 in the environment and in the human organism. Atomic Energy Review 12(1): 75-143, 1974.

(15) SCHMELTZ, I., ABIDI, S., HOFFMANN, D. Tumorigenic agents in unburned processed tobacco; N-Nitrosodiethanolamine and 1,1-Dimethylhydrazine. Cancer Letters 2: 125-131, 1977.

(16) SCHMELTZ, I., HOFFMANN, D., Nitrogen-containing compounds in tobacco and tobacco smoke. Chemical Reviews 77(3): 295-311, June 1977.

(17) SHANKAR, R. Effect of chronic nicotine administration on the intestinal mucosal alkaline phosphatase in rats. Indian Journal of Experimental Biology 13: 360-362, July 1975.

(18) TANNENBAUM, S.R., WEISMAN, M., FETT, D. The effect of nitrate intake on nitrite formation in human saliva. Food and Cosmetics Toxicology (Oxford) 14: 549-552, 1976.

(*19*) WYNDER, E.L., HOFFMANN, D. Tobacco and tobacco smoke. Seminars in Oncology 3(1): 5-15, March 1976.

Smoker and Nonsmoker Responses to Diagnostic Tests

Numerous epidemiological studies have indicated that cigarette smokers have increased mortality ratios for lung cancer, coronary heart disease, and nonmalignant respiratory disease. That the relationship is causal, and not purely statistical, was determined through examination of evidence on the biochemical, cytological, pathological, and pathophysiological effects of cigarette smoking (*22*). As more prospective screening studies involving clinical laboratory analyses have been done on apparently healthy subjects (*5, 6, 8, 12*), more differences at the biochemical level have become apparent between smokers and nonsmokers. As discussed in the 1976 *The Health Consequences of Smoking* (*22*), some of the differences in analytical values of clinical/diagnostic tests may be due to the fact that the nicotine in cigarette smoke causes increased levels of serum catecholamines, which in turn lead to increased levels of serum free fatty acids. Other effects, particularly those involving the erythrocyte, are probably the results of the relatively high levels of carbon monoxide in cigarette smoke.

The major portion of the experimental results and data to be presented here was obtained by testing individuals who were apparently normal and healthy and not suffering from any of the smoking-related diseases listed above or from other diseases. The evidence indicates that smoking causes significant changes in the "normal" values in various biochemical and clinical tests that may be done routinely in the clinical laboratory. In addition, values obtained in certain less routine analyses, such as platelet aggregation and carcinoembryonic antigen tests, may depend upon the smoking status of the individual subject. Although conflicting results have been obtained in some of the experimental reports, it is apparent that the smoking status of an individual should be reported along with parameters such as age and sex.

Leukocytes

Results from a large number of studies have shown that smokers have higher numbers of white blood cells than nonsmokers (*3, 4, 5, 12, 13, 16, 17, 20*).

In a study on 108 males aged 20 to 39, Okuno (*17*) found that the leukocyte count was significantly higher in smokers than in nonsmokers. Okuno (*17*) stated that, since his subjects were healthy and completely free of symptoms, smoking alone appeared to be the cause of the increased leukocyte counts. Similar results in leukocyte counts were found by Sagone, et al. (*20*) in a study of 27 healthy white men between the ages of 20 and 32. The 9 men in this study who smoked one or more packs of cigarettes per day had higher white cell counts than the 18 nonsmokers (*20*).

Friedman, et al. (*8*), in a study involving 86,488 ambulatory patients undergoing multiphasic examinations, related the leukocyte count to (1) quantity smoked, (2) inhalation, and (3) smoking duration. Cigarette smokers showed the highest leukocyte counts and nonsmokers showed the lowest. Differences in the mean leukocyte count were shown by Friedman, et al. (*8*) to be present in all ages from 15 to 79, in both sexes, and in all three races tested (yellow, black and white). Data from Friedman, et al. (*8*) showing the leukocyte patterns discussed above are presented in Table 9. These authors suggest that the increased leukocyte counts in smokers might be due to nicotine-induced release of catecholamines or to an irritant effect of smoke on the respiratory tree with resultant inflammation. They state that the age, sex, racial composition, and smoking habits of the reference population should be taken into account in arriving at "normal" values for the leukocyte count.

Corre, et al. (*5*), in a study of 4,264 men, showed that the number of leukocytes is increased in smokers as compared to nonsmokers. Investigation of a subgroup revealed that the increase was in granulocytes, lymphocytes, and monocytes. The authors found no real change in the differential leukocyte count, thus excluding the hypothesis of involvement of an infectious process. As shown in Table 10, their data indicated that the average number of leukocytes is greater in smokers who inhale than in those who do not, regardless of the amount smoked. They also stated that the leukocyte count is higher in light smokers who inhale than in heavy smokers who do not inhale.

Parulkar, et al. (*18*), in an examination of 130 healthy Indian males aged 16 to 60 of different social and economic status, found a direct relationship between smoking and an increase in the lymphocyte count. They suggested the presence of a chronic inflammatory process, such as bronchitis, based on data in which the lymphocyte count was higher in smokers than in nonsmokers, with little change in other types of cells. The data also showed an increase in lymphocyte count with increasing numbers of cigarettes smoked per day. Parulkar, et al. (*18*) noted the difference between results of their work and that of Corre, et al. (*5*).

Helman and Rubenstein (*12*) examined 1,000 patients randomly selected from the clinic population. By chart review, the authors excluded the following: overt or chronic debilitating illness, known chronic respiratory disease, hepatic disease, hematologic disorders, hematinic therapy, history of splenectomy, gastric surgery, and small intestinal surgery. Following complete blood counts, the authors eliminated women with hemoglobin outside the limits of 11.0 to 17.0 gm per 100 ml and men with hemoglobin outside the limits of 13.0 to 19.0 gm per 100 ml. They also eliminated those with gross erythrocytic abnormalities. They stated that, when both sexes and all ages were grouped, it was clear that the heavier the smoking, the higher the

TABLE 9.—Mean leukocyte count in 1,000s (WBC) according to race, sex, and smoking category

Smoking category	Study group: White		Black		Yellow	
	Men	Women	Men	Women	Men	Women
Nonsmokers						
No.	8,246	18,438	1,108	3,199	709	1,308
Mean WBC/cu mm	7.2	7.4	6.3	6.8	7.0	7.3
SD	1.6	1.7	1.5	1.8	1.6	1.7
% ≥ 11,000	1.9	.0	0.5	2.3	2.1	2.3
Cigar or pipe (noncigarette)						
No.	1,573	. . .	214	. . .	42	. . .
Mean WBC/cu mm	7.2	. . .	6.2	. . .	6.7	. . .
SD	1.6	. . .	1.5	. . .	1.3	. . .
% ≥ 11,000	2.2	. . .	0.9	. . .	0.0	. . .
Ex-cigarette→none						
No.	6,065	5,379	503	487	143	136
Mean WBC/cu mm	7.3	7.7	6.7	7.2	7.0	7.5
SD	1.7	2.1	1.7	1.8	1.5	1.8
% ≥ 11,000	3.0	4.9	2.2	3.9	2.1	2.2
Ex-cigarette→cigar or pipe						
No.	1,776	. . .	184	. . .	59	. . .
Mean WBC/cu mm	7.6	. . .	6.7	. . .	7.4	. . .
SD	1.7	. . .	1.9	. . .	2.0	. . .
% ≥ 11,000	4.2	. . .	1.6	. . .	3.4	. . .
Current established cigarette smokers						
No.	14,416	15,972	2,590	2,847	651	441
Mean WBC/cu mm	8.4	8.4	7.2	7.6	7.8	7.9
SD	2.0	2.0	1.9	2.1	1.8	1.8
% ≥ 11,000	10.0	10.0	3.9	6.4	5.8	5.0

SOURCE: Friedman, G.D. (*8*).

white cell count. The authors (*12*) concluded that the cause of smoking-associated leukocytosis is unknown.

Billimoria, et al. (*4*) examined 187 volunteers aged 30 to 60 years divided into heavy and light smokers and nonsmokers. In the male heavy smokers, they found, a significant increase in the leukocyte count, with the differential count indicating rises in neutrophils and lymphocytes. The changes were not significant in the female heavy smoking group.

In an extensive study of erythrocytosis, Sagone and Balcerzak (*19*) noted an increased leukocyte count among the parameters they examined.

TABLE 10.—Number of leukocytes per cu mm in smokers as a function of quantity smoked and of inhalation (number of subjects in parentheses)

Quantity smoked (g./day)	Inhalation status		Significance (p)
	No inhalation	Inhalation	
1–9	5801 (539)	6321 (208)	0.001
10–19	6130 (546)	6930 (563)	0.001
20–29	6263 (397)	7287 (610)	0.001
30 +	6276 (121)	7397 (199)	0.001
Significance (p)	0.05	0.001	

SOURCE: Corre, F. (*5*).

Noble and Penny (*16*) examined leukocyte function and other hematological measurements in a group of 27 healthy white males 20 to 30 years of age. Total leukocyte counts were significantly higher in smokers and temporarily abstaining smokers as compared to the nonsmoking group. Although leukocyte chemotaxis was depressed in the smoking subjects, smoking was not observed to affect the whole blood bactericidal and phagocytic tests with either Staphylococcus aureus or Klebsiella pneumoniae. Anderson, et al. (*2*) observed higher readings in the nitroblue-tetrazolium test among smokers than in nonsmokers and concluded that smoking may give rise to false positive results in this test.

Erythrocytes and Intraerythrocytic Parameters

Okuno (*17*) observed that smokers showed increases in hemoglobin, hematocrit, and mean corpuscular volume when compared to nonsmokers. Similar differences were obtained (*17*) between heavy smokers and light smokers.

In a study of the effects of smoking on tissue oxygen, Sagone, et al. (*20*) demonstrated that smokers had higher values for carboxyhemoglobin, hematocrit, hemoglobin, red cell count, and red cell mass. Red cell 2,3-diphosphoglycerate was not changed in smokers while ATP and P_{50} were significantly lower. The authors suggested that, in cases where a decreased oxygen-hemoglobin affinity has been observed, the hypoxia due to exposure to low levels of carbon monoxide is different from hypoxia due to other causes. It was concluded that adaptation to carbon monoxide in cigarettes is reflected by an increased red cell mass and hemoglobin. In a study by Isager and Hagerup (*14*), a positive correlation between cigarette smoking and hematocrit was found in a group composed of 394 men and 339 women.. Hematocrit values above normal were shown to be more common in cigarette smokers than in nonsmokers, with the differences statistically significant in the male

group. Cigarette consumption and lung function were negatively correlated in both sexes, but there was no evidence of any correlation between lung function and hematological variables (*14*). As Sagone, et al. (*20*) have done, these authors (*14*) suggest that the increase in packed cell volume and hemoglobin in cigarette smokers may be caused by elevated blood levels of carbon monoxide.

Helman and Rubenstein (*12*) related blood parameters to sex, age, and smoking habits. Although Helman and Rubenstein felt that the difference was not clinically significant, they showed that, under age 50, men who smoke have slightly higher hemoglobin levels than nonsmokers. After age 50, the hemoglobin of nonsmokers increases while that of smokers decreases. After age 60, the nonsmoker has a higher hemoglobin level than the smoker. Women smokers were shown (*12*) to have clearly higher levels of hemoglobin than nonsmoking women. These authors (*12*) found higher erythrocyte counts in nonsmoking men than in smoking men, but in women the RBC was independent of smoking. Smokers, both men and women, had higher hematocrit values than nonsmokers. It was found (*12*) that mean corpuscular volume and mean corpuscular hemoglobin are higher in smokers than in nonsmokers in both sexes and increase with age. Further, nonsmoking men were shown to have a slightly higher mean corpuscular hemoglobin concentration than men smokers and women. The authors (*12*) suggest that carbon monoxide and cyanide in cigarette smoke may be responsible for the increased hemoglobin and hematocrit in smokers with no increase in red cell count.

Heavy smoking was suggested as a reversible cause of polycythemia by Sagone and Balcerzak (*19*). They evaluated five smokers who were found to have very high values for hemoglobin, hematocrit, and erythrocyte mass as compared to nonsmokers. They reported that the patients did not have lung disease, shunt physiology, hemoglobin with increased oxygen affinity, erythropoietin-producing tumor, renal disease, or polycythemia rubra vera. In the period of 3 to 3 1/2 months after two of the subjects stopped smoking, it was observed that they both showed large decreases in erythrocyte mass and hematocrit values. The erythrocytosis found by these authors (*19*) appeared to be an adaptation to carboxyhemoglobin and a decreased oxygen-carrying capacity.

Cholesterol, Triglycerides, Lipoproteins

The effects of smoking on serum lipid levels are discussed in *The Health Consequences of Smoking* (*22*) with respect to coronary heart disease and immediate or acute effects of cigarette smoking. Inconsistencies in results described there are still prevalent. Howell (*13*) found no significant variation in either serum cholesterol or beta lipoprotein levels between heavy smokers, nonsmokers, and ex-smokers. On the other hand, Billimoria, et al. (*4*) found that male heavy smokers showed

increases in most indices associated with lipids. Compared with male nonsmokers, the male heavy smokers had a higher fasting serum turbidity and higher levels of cholesterol, serum phopholipids and triglycerides. The esterified fatty acid index of beta and pre-beta lipoprotein was also higher in male heavy smokers. Changes in cholesterol levels, the beta-esterified fatty acid index, phospholipids, and serum fasting turbidity were not observed in female heavy smokers in this study.

Other Chemistry Tests

Dales, et al. (*6*) studied levels of eight serum components in more than 65,000 cigarette smokers and nonsmokers. Creatinine and albumin levels were lower in smokers in both sexes, while the opposite was true for 1-hour post-challenge serum glucose. Globulin levels were consistently lower in women smokers, while uric acid levels were lower in male smokers. Cholesterol levels were higher in white men who smoked, but not in black male smokers. Calcium and serum glutamic oxalacetic transaminase (SGOT) levels of smokers were similar to those of nonsmokers. While alcohol consumption played a role in smoker-nonsmoker differences in serum glucose concentration, no additional factors were identified that could explain relationships to smoking for the other chemistries studied.

Glauser, et al. (*9*) examined seven subjects during a period in which they were smoking and 1 month after cessation of smoking. Statistically significant decreases were observed in protein-bound iodine level, 30-minute postprandial blood glucose level, and serum calcium level.

Clotting Factors

In a controlled, double-blind study, Levine (*15*) showed that the smoking of a single cigarette increased the platelet's response to a standard aggregating stimulus (Figure 7). The platelet effect appeared to be independent of the rise in plasma-free fatty acid which followed cigarette smoking. It was suggested that potentiation of platelet aggregation might help explain the increased incidence of arterial thrombi in cigarette smokers.

Hawkins (*11*) examined the relationship between smoking, platelet function, and thrombosis in a group of healthy young men divided into nonsmokers, light smokers, and heavy smokers. It was observed that platelets from smoking subjects seemed to be more active when aggregated with ADP than those from nonsmokers. When samples from each group were compared, a lower concentration of ADP was required in the two smoking groups to induce permanent platelet aggregates. The coagulation time of whole blood of smokers during a nonsmoking period was significantly shorter than that of nonsmokers. In the heavy smoking group there was an increase in maximum tensile

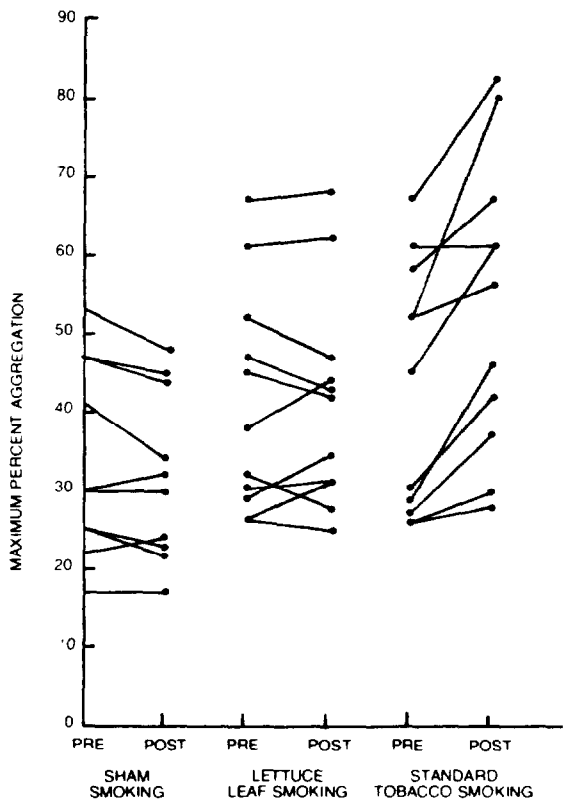

FIGURE 7.—Maximum platelet aggregation in response to a fixed dose of ADP. Paired experiments before and after sham smoking, non-nicotine cigarette smoking, and standard cigarette smoking
SOURCE: Levine, P.H. (*15*).

strength of the clot, when compared with the clot strength of nonsmokers.

Billimoria, et al. (*4*) observed no changes in fibrinogen levels or platelet adhesiveness. However this group of workers did find euglobulin lysis times significantly longer for both male and female heavy smokers. It was also determined that Stypven clotting times of heavy smokers were significantly shortened in both males and females.

Dintenfass (*7*) examined a group of blood viscosity factors in 125 healthy male Caucasian smokers and nonsmokers of 45 to 55 years of age. Hematocrit values, fibrinogen levels, plasma viscosity, blood viscosity, and red cell aggregation were elevated in the smokers.

Table 11.—CEA titers in selected groups of 2107 healthy subjects*

	Number	0.0–2.5 mg/ml	2.6–5.0 mg/ml	5.1–10.0 mg/ml	> 10.0 mg/ml
Nonsmokers	892	865	25	2	0
Presently smoking	620	502	93	19	6
Former smokers	235	219	12	2	2
Pregnant females	369	316	11	3	0

*Individuals with no known disease.
SOURCE: Hansen, H.J. (*10*).

Carcinoembryonic Antigen

In a study by Stevens and MacKay (*21*), sera from 955 unselected persons aged 60 years and older, obtained as part of a population survey, were tested for carcinoembryonic antigen (CEA). Among the 903 current smokers, ex-smokers, and nonsmokers who had no detectable cancer, a positive test (5 ng/ml or greater) was found in 13.6 percent of the 110 smokers but in only 1.8 percent of the 433 nonsmokers. Similar results were obtained by Alexander, et al. (*1*) who determined CEA levels in 276 healthy volunteers, of whom 154 were smokers and 122 were nonsmokers. They found mean CEA levels to be significantly higher in smokers than in nonsmokers, and a significantly higher percentage of smokers had elevated CEA levels. The results (*21*) also indicated that CEA levels of smokers declined to those of nonsmokers in about three months after cessation of smoking.

Hansen, et al. (*10*) in a collaborative study evaluating the clinical usefulness of the CEA assay in more than 10,000 patients and healthy subjects, suggested that the patient's smoking history must be taken into consideration when interpreting the CEA titer. As shown in Table 11, these investigators (*10*) found that 25 of 620 healthy subjects who were smokers had CEA titers above the value used to separate normals from abnormals.

Summary and Conclusions

1. Cigarette smoking is associated with an increase in leukocytes which appears to be dependent on the amount of smoke inhaled.
2. Cigarette smoking may cause increases in red cell mass, hemoglobin, carboxyhemoglobin, hematocrit, and mean corpuscular volume.
3. Cigarette smoking appears to have an effect on serum levels of creatinine, albumin, globulin, and uric acid.
4. Cigarette smoking appears to increase platelet aggregation, plasma viscosity, blood viscosity, and tensile strength of the clot along with a decrease in coagulation time.

5. Cigarette smoking appears to increase the serum carcinoembryonic antigen level in otherwise healthy individuals.

6. The majority of the blood components elevated due to cigarette smoking appear to revert to approximately normal levels after cessation of smoking.

7. The smoking status of an individual should be included in reports of clinical/diagnostic tests performed on that individual.

Smoker and Nonsmoker Responses to Diagnostic Tests: References

(1) ALEXANDER, J.C., JR., SILVERMAN, N.A., CHRETIEN, P.B. Effect of age and cigarette smoking on carcinoembryonic antigen levels. Journal of the American Medical Association 235(18): 1975-1979, May 3, 1976.

(2) ANDERSON, R., RABSON, A.R., SHER, R., KOORNHOF, H.J. The N.B.T. test in cigarette smokers. American Journal of Clinical Pathology 61(6): 879, June 1974.

(3) BANKS, D.C. Smoking and leucocyte-counts. Lancet 2(7728): 815, October 9, 1971.

(4) BILLIMORIA, J.D., POZNER, H., METSELAAR, B., BEST, F.W., JAMES, D.C.O. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis 21(1): 61-76, January/February 1975.

(5) CORRE, F., LELLOUCH, J., SCHWARTZ, D. Smoking and leucocyte-counts. Lancet 2(7725): 632-634, September 18, 1971.

(6) DALES, L.G., FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C. Cigarette smoking and serum chemistry tests. Journal of Chronic Diseases 27(6): 293-307, August 1974.

(7) DINTENFASS, L. Elevation of blood viscosity, aggregation of red cells, haematocrit values and fibrinogen levels in cigarette smokers. Medical Journal of Australia 1(20): 617-620 May 17, 1975.

(8) FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C., FELDMAN, R., COLLEN, M.F. Smoking habits and the leukocyte count. Archives of Environmental Health 26(3): 137-143, March 1973.

(9) GLAUSER, S.C., GLAUSER, E.M., REIDENBERG, M.M., RUSY, B.F., TALLARIDA, R.J. Metabolic changes associated with the cessation of cigarette smoking. Archives of Environmental Health 20(3): 377-381, March 1970.

(10) HANSEN, H.J., SNYDER, J.J., MILLER, E., VANDEVOORDE, J.P., MILLER, O.N., HINES, L.R., BURNS, J.J. Carcinoembryonic antigen (CEA) assay: A laboratory adjunct in the diagnosis and management of cancer. Human Pathology 5(2): 139-147, March 1974.

(11) HAWKINS, R.I. Smoking, platelets and thrombosis. Nature 236(5348): 450-452, April 28, 1972.

(12) HELMAN, N., RUBENSTEIN, L.S. The effects of age, sex, and smoking on erythrocytes and leukocytes. American Journal of Clinical Pathology 63(1): 35-44, January 1975.

(13) HOWELL, R.W. Smoking habits and laboratory tests. Lancet 2(7664): 152, July 18, 1970.

(14) ISAGER, H., HAGERUP, L. Relationship between cigarette smoking and high packed cell volume and haemoglobin levels. Scandinavian Journal of Haematology 8(4): 241-244, 1971.

(15) LEVINE, P.H. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. Circulation 48(3): 619-623, September 1973.

(16) NOBLE, R.C., PENNY, B.B. Comparison of leukocyte count and function in smoking and nonsmoking young men. Infection and Immunity 12(3): 550-555, September 1975.

(17) OKUNO, T. Smoking and blood changes. Journal of the American Medical Association 225(11): 1387-1388, September 10, 1973.

(18) PARULKAR, V.G., BALSUBRAMANIAM, P., BARUA, M.J., BHATT, J.V. Smoking and differential leucocyte (W.B.C.) count. Journal of Postgraduate Medicine 21(2): 75-77, April 1975.

(*19*) SAGONE, A.L., JR., BALCERZAK, S.P. Smoking as a cause of erythrocytosis. Annals of Internal Medicine 82(4): 512-515, April 1975.

(*20*) SAGONE, A.L., JR., LAWRENCE, T., BALCERZAK, S.P. Effect of smoking on tissue oxygen supply. Blood 41(6): 845-851, June 1973.

(*21*) STEVENS, D.P., MACKAY, I.R. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 2(7840): 1238-1239, December 1, 1973.

(*22*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition: 1976. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. (CDC) 78-8357, 1976, 657 pp.

Interactions with Radiation

In studies of humans, radiation exposures to the lungs of uranium miners who smoked cigarettes produced much more lung cancer than did similar exposures to nonsmoking miners (*3*). It is not known whether lung cancer induction by other forms of ionizing and nonionizing radiation is similarly conditioned by smoking nor whether other cancer sites are involved (*5*). Archer, et al. (*2*) also noted some evidence of decreased pulmonary function and excess mortality from chronic respiratory disease among uranium miners who smoked cigarettes compared with nonsmoking miners. However, the authors indicated that other substances in the mining environment, such as silica dust and diesel exhaust, may play a role in the onset of these conditions (*1*).

Experimental studies have shown some synergistic effects between ionizing radiation exposure and chemical carcinogens such as those contained in cigarette smoke (*6*). Results from a study of dogs at Battelle Northwest, sponsored by the Department of Energy, indicate that the effects of exposures to smoking and radiation are similar to those in uranium miners (*4*). It is suggested that when epidemiological studies of bladder and laryngeal cancer are undertaken, the possible synergistic effects of smoking and exposure to radiation be considered by appropriate study design and analysis of data.

Interactions with Radiation: References

(1) ARCHER, V.E., BRINTON, H.P., WAGONER, J.K. Pulmonary function of uranium miners. Health Physics 10(12): 1183-1194, 1964.

(2) ARCHER, V.E., GILLAM, J.D., WAGONER, J.K. Respiratory disease mortality among uranium miners. Annals of the New York Academy of Sciences 271: 280-293, May 28, 1976.

(3) ARCHER, V.E., WAGONER, J.K., LUNDIN, F.E., JR. Uranium mining and cigarette smoking effects on man. Journal of Occupational Medicine 15(3): 204-211, March 1973.

(4) FILIPY, R.E., STUART, B.O., PALMER, R.F., RAGAN, H.A., HACKETT, P.L. The effects of inhaled uranium mine air contaminants in beagle dogs. In: Karbe, E., Park, J. F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. Berlin, Springer-Verlag, 1974, pp. 403-410.

(5) LUNDIN, F.E., JR. An exposure-time-response model for lung cancer mortality in uranium miners—effects of radiation exposure, age, and cigarette smoking. Presented at the Second Conference on Quantitative Aspects of Environmental Epidemiology, sponsored by the SIAM Institute for Mathematics and Society, June 26-30, 1978, 22 pp.

(6) MCGANDY, R.B., KENNEDY, A.R., TERZAGHI, M., LITTLE, J.B. Experimental respiratory carcinogenesis: Interaction between alpha radiation and benzo(a)pyrene in the hamster. In: Karbe, E., Park, J.F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. Berlin, Springer-Verlag, 1974, pp. 485-491.

13. OTHER FORMS OF TOBACCO USE.

CONTENTS

LIST OF TABLES

Introduction

This review of the health effects of tobacco use other than cigarette smoking includes a revision of the chapter on pipes and cigars from the 1973 *Health Consequences of Smoking* and information on tobacco chewing and snuff dipping. Because these forms of tobacco are used mainly by men in the United States, most studies report data based only on male populations. This information can be applied to the small numbers of women who use other forms of tobacco only with caution because there is some difference in the impact of cigarette smoking on men and on women.

Pipes and Cigars

Prospective epidemiologic studies show that individuals who smoke only pipes and cigars have overall mortality rates slightly higher than nonsmokers, but lower than cigarette smokers. Pipe and cigar smokers have only slightly elevated cause-specific mortality rates for coronary heart disease, lung cancer, and chronic obstructive pulmonary disease when compared to nonsmokers, but their mortality rates for oral cavity cancers often equal or exceed those of cigarette smokers. Examination of the combined use of cigarettes and pipes or cigars is complex and may lead to confusion in two areas.

First, overall mortality rates of those who smoke pipes, cigars, or both in combination with cigarettes appear to be intermediate between the high mortality rates of cigarette smokers and the lower rates of those who smoke only pipes or cigars. This should not be taken to suggest that smoking pipes or cigars in combination with cigarettes diminishes the harmful effects of cigarette smoking. Analysis of mortality associated with smoking combinations of cigarettes, pipes, and cigars should be standardized for the level of consumption of each of the products smoked in terms of the amount and duration of smoking and the depth and degree of inhalation. For example, cigar smokers who also smoke a pack of cigarettes a day might be expected to have mortality rates somewhat higher than those who smoke only a pack of cigarettes a day, assuming that both groups smoke cigarettes in the same way. Mixed smokers who inhale pipe or cigar smoke in a manner similar to the way they smoke cigarettes might be expected to have higher mortality rates than mixed smokers who do not inhale cigars and pipes and resist inhaling cigarettes. Unfortunately, little published material on mixed cigarette, pipe, and cigar smoking contains these types of analyses or controls.

Second, a paradox seems to exist between reduced mortality rates for ex-smokers of cigarettes, compared to continued smokers, and increased mortality rates for ex-smokers of pipes and cigars. Ex-cigarette smokers experience a relative decline in overall and certain specific causes of mortality following cessation. This decline is

important but indirect evidence that cigarette smoking is a major cause of elevated mortality rates experienced by current cigarette smokers.

In contrast to this finding, several prospective epidemiological investigations, Hammond and Horn (*52*), Best (*11*), Kahn (*69*), and Hammond (*50*), have reported higher death rates for ex-pipe and ex-cigar smokers than for current pipe and cigar smokers. This phenomenon was analyzed by Hammond and Garfinkel (*51*). They found that the development of ill health often results in a cigarette smoker giving up the habit, reducing his daily tobacco consumption, switching to pipes or cigars, or choosing a cigarette low in tar and nicotine. In many instances, a smoking-related disease is the cause of ill health. Thus, the group of ex-smokers includes people who are already ill from smoking-related diseases and who therefore have higher overall and specific mortality rates. With the passage of time after cessation of cigarette smoking, a relative decrease in mortality is observed due to decreased mortality rates in those who quit smoking for reasons other than ill health and in the dwindling number of ill ex-smokers.

The beneficial effects of cessation tend to be obscured by the high mortality rates of those who quit smoking for reasons of illness. A similar principle operates for ex-pipe and ex-cigar smokers; because of the lower initial risk of smoking these forms and the smaller margin of benefit following cessation, the effect produced by the ill ex-smokers creates a larger and more persistent impact on the mortality rates than is seen in cigarette smoking. For these reasons, a detailed analysis of mortality among ex-pipe and ex-cigar smokers will not be undertaken in this review.

For specific causes of death, the tables below summarize the mortality and relative risk ratios reported in major prospective and retrospective studies of pipe and cigar smokers. The smoking categories used include: cigar only, pipe only, total pipe and cigar, cigarette only, and mixed. Mortality and relative risk ratios are calculated relative to nonsmokers.

Prevalence of Pipe, Cigar, and Cigarette Usage

Prevalence of pipe, cigar, and cigarette smoking in the United States was estimated by the National Clearinghouse for Smoking and Health from population surveys conducted in 1964, 1966, 1970, and 1975 (*90*, *91*, *92*). In each survey, over 2,500 interviews were conducted on a national probability sample stratified by type of population and geographic area. The use of these products among adults aged 21 and older, summarized in Table 1, reflects the continued decline in the percentage of the population using tobacco products. Table 2 shows the use of different tobacco products by age group.

TABLE 1.—Percent distribution of U.S. male smokers aged 21 and older by type of tobacco used for the years 1964, 1966, 1970, and 1975

Forms used	1964 (percent)	1966 (percent)	1970 (percent)	1975 (percent)
Total pipe	18.7	19.2	17.9	12.4
Total cigar	29.9	26.7	21.2	19.9
Total cigarette	52.9	52.4	42.3	39.3

SOURCE: National Clearinghouse for Smoking and Health (*90,91,92*).

TABLE 2.—Percent distribution of U.S. male smokers by type of tobacco used and age, for 1970

Forms used	Age groups				
	21 to 34	35 to 44	45 to 54	55 to 64	65 to 75+
1. Cigar only	3.7	6.5	4.7	6.7	9.3
2. Pipe only	4.3	3.5	3.0	3.2	3.6
3. Pipe and cigar	3.8	3.3	5.2	4.4	6.9
4. Cigarette only	28.8	29.0	27.1	24.3	13.6
5. Cigarette and cigar	6.8	10.4	5.5	5.2	4.2
6. Cigarette and pipe	6.6	4.4	5.6	4.0	3.8
7. Cigarette, pipe, and cigar	5.8	4.8	5.0	4.0	1.4
8. Nonsmoker	40.2	38.1	43.9	48.2	57.2
Total	100.0	100.0	100.0	100.0	100.0
Number of persons in sample	1,009	528	523	405	388
Total pipe users	20.5	16.0	18.8	15.6	15.7
Total cigar users	20.1	25.0	20.4	20.3	21.8
Total cigarette users	48.1	48.6	43.3	37.5	23.0

SOURCE: National Clearinghouse for Smoking and Health (*91*).

TABLE 2.—continued. Prevalence of snuff use and tobacco chewing in the United States

	1970		1975	
	Male	Female	Male	Female
Snuff	2.9	1.4	2.5	1.3
Chewing	5.6	0.6	4.9	0.6

SOURCE: National Clearinghouse for Smoking and Health (*91,92*)

The Definition and Processing of Cigars, Cigarettes, and Pipe Tobaccos

Cigarettes

The U.S. Government has defined tobacco products for tax purposes. Cigarettes are defined as "(1) Any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (2) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette described in subparagraph (1)." Cigarettes are further classified by size, but virtually all cigarettes sold in the United States are "small cigarettes" which by definition weigh "not more than 3 pounds per thousand," which is not more than 1.361 grams per cigarette (*44, 130, 141*).

Cigars

Cigars have been defined for tax purposes as: "Any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco (other than any roll of tobacco which is a cigarette within the meaning of subparagraph (2) of the definition for cigarette)" (*141*). In order to clarify the meaning of "substance containing tobacco," the Treasury Department has stated that, "The wrapper must (1) contain a significant proportion of natural tobacco; (2) be within the range of colors normally found in natural leaf tobacco; (3) have some of the other characteristics of the tobaccos from which produced; e.g., nicotine content, pH, taste, and aroma; and (4) not be so changed in the reconstitution process that it loses all the tobacco characteristics" (*131*). Further, "To be a cigar, the filler must be substantially of tobaccos unlike those in ordinary cigarettes and must not have any added flavoring which would cause the product to have the taste or aroma generally attributed to cigarettes. The fact that a product does not resemble a cigarette (such as many large cigars do not) and has a distinctive cigar taste and aroma is of considerable significance in making this determination" (*45, 131*).

Pipe Tobaccos

The definition of pipe tobacco used by the U.S. Government was repealed in 1966, and there is no Federal tax on pipe tobaccos. The most popular pipe tobaccos are made of Burley; however, many pipe tobaccos are blends of different types of tobacco. A few contain a significant proportion of midrib parts that are crushed between rollers. "Saucing" material, or casings containing licorice, sweetening agents, sugars, and other flavoring materials are added to improve the flavor, aroma, and smoke taste. These additives modify the characteristics of smoke components (*141*).

Conclusion

Because of the curing and processing methods used in the production of cigar and pipe tobaccos, there are significant physical and chemical differences between pipe and cigar tobaccos and those used in cigarettes. The extent to which these changes may alter the health consequences of smoking pipes and cigars can best be estimated by an analysis of the potentially harmful chemical constituents found in the smoke of these tobaccos, the tumorigenic activity of smoke condensates in experimental animals, and a review of the epidemiological data which have accumulated on the health effects of pipe and cigar smoking.

Chemical Analysis of Cigar Smoke

Only a few studies have been conducted that compare the chemical constituents of cigar smoke with those found in cigarette smoke. Hoffmann, et al. (*60*) compared the yields of several chemical components in the smoke from a plain 85 mm cigarette, two types of cigars, and a pipe. The particulate matter, nicotine, benzo(a)pyrene, and phenols were determined quantitatively in the smoke of these tobacco products. One cigar tested was a 135-mm-long, 7.8-g, U.S.-made cigar. The other was a handmade Havana cigar 147 mm long weighing 8.6 g. The relative content of nicotine in the particulate matter produced by the cigars was similar to that of the cigarette tars. The benzo(a)pyrene and phenol concentrations in the cigar condensate was two to three times greater than in cigarette tar. Kuhn (*78*) compared the alkaloid and phenol content in condensates from an 80-mm bright-blend cigarette sold commercially in Austria with that obtained from 103-mm cigars. These were tested with and without the use of a cellulose acetate filter. The concentrations of total alkaloids and phenol in the cigar smoke condensate were essentially the same as in the cigarette condensate, but pyridine values were about 2 1/2 times higher in the cigar condensate.

Campbell and Lindsey (*21*) measured the polycyclic hydrocarbon levels in the smoke of a small popular-type cigar 8.8 cm long, weighing

TABLE 3.—A comparison of several chemical compounds found in the mainstream smoke of cigars, pipes, and cigarettes

Compound	Micrograms per 100 g. of tobacco consumed		
	Cigars	Pipes[1]	Cigarettes
Acenaphthylene	1.6	29.1	5.0
Anthracene	11.9	110.0	10.9
Pyrene	17.6	75.5	12.5
3,4-benzpyrene	3.4	8.5	.9

[1]With a light pipe tobacco.
SOURCE: Campbell, J.M., (*21*).

1.9 g. Significant quantities of anthracene, pyrene, fluoranthene, and benzo(a)pyrene were detected in the unsmoked cigar tobacco, in concentrations much greater than those found in Virginia cigarettes but of the same order as those found in some pipe tobaccos. The smoking process contributed considerably to the hydrocarbon content of the smoke. Table 3 compares the concentrations in the mainstream smoke of cigarettes, cigars, and pipes of four hydrocarbons frequently found in condensates. The authors reported that the mainstream smoke from a popular brand of small cigar contained the polycyclic aromatic hydrocarbons: acenaphthylene, phenanthrene, anthracene, pyrene, fluoranthene, and benzo(a)pyrene. The concentrations of these hydrocarbons in the mainstream smoke were greater than those found in Virginia cigarette smoke.

Osman, et al. (*94*) analyzed the volatile phenol content of cigar smoke collected from a 7-g American-made cigar with domestic filler. After quantitative analysis of phenol, cresols, xylenols, and meta and para ethyl phenol, the authors concluded that the levels of these compounds were generally similar to those reported for cigarette smoke. Osman and Barson (*93*) also analyzed cigar smoke for benzene, toluene, ethyl benzene, m-, p-, and o-xylene, m- and p-ethyltoluene, 1,2,4-trimethylbenzene, and dipentene and generally found levels within the range of those previously reported for cigarette condensates.

Brunnemann and Hoffmann (*18*) found that the mainstream smoke from regular and small cigars contains more carbon monoxide per puff and per gram of tobacco burned than filtered or unfiltered cigarettes. This greater production of carbon monoxide was confirmed by Harke (*54*).

In summary, available evidence suggests that cigar smoke contains many of the same chemical constituents, including nicotine and other

alkaloids, phenols, and polycyclic aromatic hydrocarbons as are found in cigarette smoke. Most of these compounds are found in concentrations which equal or exceed levels found in cigarette tar.

Mortality

Overall Mortality

Several large prospective studies have examined the health consequences of various forms of smoking and the results of these investigations have been reviewed in previous reports of the Surgeon General in which the major emphasis was on cigarette smoking and its effect on overall and specific mortality and morbidity. The following pages present a current review of the health consequences of smoking pipes and cigars. Data from the prospective investigations of Dunn, et al. (*40*), Buell, et al. (*20*), Hirayama (*58*), and Weir and Dunn (*134*) are not cited because in these studies a separate category for pipe and cigar smokers was not established.

The smoking habits and mortality experience of 187,783 white men between the ages of 50 and 69, followed for 44 months, were reported by Hammond and Horn (*53*). The overall mortality rates of men who smoked pipes or cigars were slightly higher than the rates of men who never smoked. The overall mortality rate of cigar smokers was slightly higher than that of pipe smokers.

Doll and associates (*34, 35, 38*) followed the mortality of 41,000 British physicians for 20 years and reported an overall mortality ratio of 1.09 for men who smoked only pipes and cigars and who had never been cigarette smokers. When compared to nonsmokers, the mortality ratio for mixed smokers of cigarette, pipe, and cigar was 1.20. This represents a slight increase in the ratios since the report of the 10-year follow-up. Best (*11*), in a study of 78,000 Canadian veterans, reported overall mortality rates of pipe and cigar smokers slightly above those of nonsmokers. Rogot (*104*), in an update of Kahn's study of over 293,000 U.S. veterans, found that pipe smokers had only a minimally increased risk of death when compared to nonsmokers, but the risk for cigar smokers was substantially higher. The risk for combined pipe and cigar smoking was between the risks of either one separately. Hammond (*50*) examined the smoking habits of and mortality rates experienced by 440,559 men and found that pipe smokers experienced mortality rates similar to those of men who never smoked regularly, whereas cigar smokers had death rates somewhat higher than men who never smoked regularly. Table 4 summarizes some of the results of those studies.

Thus, data from the major prospective epidemiological studies demonstrate that the use of pipes and cigars results in a small but definite increase in overall mortality. Cigar smokers have somewhat higher death rates than pipe smokers, and mixed smokers who use

TABLE 4.—Mortality ratios for total deaths by type of smoking (males only)

Author, reference	Smoking type							
	Non-smoker	Cigar only	Pipe only	Cigar and pipe	Cigarette and cigar	Cigarette and pipe	Mixed (cigarette and other)	Cigarette only
Hammond and Horn[1] (*52*)	1.00	1.22	1.12	1.10	1.36	1.50	1.43	1.68
Doll and Peto (*58*)	1.00	....	....	1.09	....	....	1.20	1.64
Best (*11*)	1.00	1.06	1.05	.98	1.22	1.26	1.13	1.54
Kahn (*69*)	1.00	1.10	1.07	1.08	....	....	1.51	1.84
Hammond[2] (*50*)	1.00	1.25	1.19	1.01	....	....	1.57	1.86

[1]Only mortality ratios for ages 50 to 69 are presented.
[2]Only mortality ratios for ages 55 to 64 are presented.

cigarettes in addition to pipes and cigars appear to experience an intermediate level of mortality that approaches the mortality experience of cigarette smokers.

Mortality and Dose-Response Relationships

A consistent association exists between overall mortality and the total dose of smoke a cigarette smoker receives. The methods most frequently used to measure dosage of tobacco products are: amount smoked, degree of inhalation, duration of smoking experience, age at initiation, and the amount of tar in a given tobacco product. For cigarette smokers, the higher the dose as measured by any of these parameters, the greater the mortality. The significance of the small increase in overall mortality that occurs for the entire group of pipe and cigar smokers can be analyzed by examining the mortality of subgroups defined by similar measures of dosage as used in the study of cigarette smokers.

Amount Smoked

Hammond and Horn (*52*) reported an increase in the overall mortality of pipe and cigar smokers with an increase in the amount smoked. Individuals who smoked more than four cigars a day or more than six pipefuls a day had death rates significantly higher than men who never smoked ($P < 0.05$ for cigar smokers and $P < 0.05$ for pipe smokers) (Table 5). Cigar and pipe users who smoked less than this amount experienced an overall mortality similar to men who never smoked. The study of Canadian veterans (*11*) also contained evidence of a dose-response in mortality by amount smoked for cigar smokers. No dose-response relationship was observed among pipe smokers (Table 6). Kahn (*69*) reported a consistent increase in overall mortality with an increase in the amount smoked for both pipe and cigar smoke

TABLE 5.—Mortality ratios for total deaths of cigar and pipe smokers by amount smoked

Amount smoked	Number of deaths		
	Observed	Expected	Mortality ratio
Nonsmoker	1,664	1,664	1.00
Cigar only:			
Total	653	598	1.09
1 to 4 cigars	410	400	1.03
> 4 cigars	229	185	1.24
Pipe only:			
Total	609	560	1.09
1 to 10 pipefuls	391	374	1.05
> 10 pipefuls	204	172	1.19

SOURCE: Hammond, E.C., Horn, D. (*52*).

(Table 7). Hammond (*50*) found no consistent relationship between overall mortality and the number of cigars or pipefuls smoked (Table 8).

The above evidence suggests that a dose-response relationship may exist between the number of cigars and pipefuls smoked and overall mortality. However, because of the high-mortality rate of ex-smokers of cigars and pipes, it is difficult to interpret the data presented without including this group with the continuing smokers. Without data which examine patterns of both daily rate of smoking and inhalation at various age levels, no firm conclusions can be drawn as to the nature of this dosage relationship.

Inhalation

Inhalation of tobacco smoke directly exposes the bronchi and the lungs to smoke and results in the absorption of the soluble constituents of the gas and particulate phases. Without inhalation, tobacco smoke reaches mainly the oral cavity and some upper digestive and respiratory tracts but it does not reach the lungs where further direct effects and systemic absorption of various chemical compounds can occur.

The condensate of pipe and cigar smoke is generally found to be alkaline when the pH is measured by suspending a Cambridge filter in CO_2-free water. Cigarette condensate is slightly acidic as measured by this method. Since alkaline smoke is more irritating to the respiratory

TABLE 6.—Mortality ratios for total deaths of cigar and pipe smokers by amount smoked

Amount smoked	Number of deaths		
	Observed	Expected	Mortality ratio
Nonsmoker	—	—	1.00
Cigar only:			
Total	90	82.07	1.10
1 to 2 cigars	64	56.05	1.14
3 to 10 cigars	23	19.40	1.19
> 10 cigars	1	1.59	.63
Pipe only:			
Total	570	566.99	1.00
1 to 10 pipefuls	374	370.09	1.01
10 to 20 pipefuls	141	140.84	1.00
> 20 pipefuls	36	35.90	1.00

SOURCE: Best, E.W.R. (*11*).

tract, it has been assumed that the more alkaline smoke of pipes and cigars was in part responsible for the lower levels of inhalation reported by pipe and cigar smokers. Brunnemann and Hoffmann (*19*) have analyzed the pH of whole, mainstream smoke of cigarettes and cigars on a puff-by-puff basis using a pH electrode suspended in mainstream smoke. Smoke from several U.S. brands of cigarettes was found to be acidic throughout the entire length of the cigarette. Of interest was the finding that cigar smoke also had an acidic pH for the first two-thirds of the cigar and became alkaline only in the last 20 to 40 percent of the puffs from the cigar. Epidemiological evidence indicates that most cigar smokers do not inhale the smoke while most cigarette smokers do. The fact that smoke from the first half or more of a cigar is acidic, near the range of pH values commonly found in cigarette smoke, and becomes alkaline only toward the end of the cigar might suggest that the pH of the smoke of a tobacco product may not be the only factor that influences inhalation patterns. Perhaps tar and nicotine levels as well as the concentration of other irritating chemicals also affect the degree to which a tobacco smoke will be inhaled.

Nicotine is rapidly absorbed into the blood stream from the lungs when tobacco smoke is inhaled. The amount of nicotine absorbed from the lungs is primarily a function of the nicotine concentration in the

TABLE 7.—Mortality ratios for total deaths of cigar and pipe smokers by age and amount smoked

Amount smoked	Mortality ratio, age	
	55 to 64	65 to 74
Nonsmoker	1.00	1.00
Cigar only:		
Total	1.01	1.08
1 to 4 cigars per day	.89	1.00
5 to 8 cigars per day	1.14	1.23
> 8 cigars per day	1.65	1.28
Pipe only:		
Total	1.08	1.06
1 to 4 pipefuls per day	1.16	.91
5 to 19 pipefuls per day	1.04	1.10
> 19 pipefuls per day	1.04	1.18

SOURCE: Kahn, H.A. (*69*).

TABLE 8.—Mortality ratios for total deaths of cigar and pipe smokers by amount smoked

Amount smoked	Mortality ratio	Amount smoked	Mortality ratio
Nonsmoker	1.00	Current pipe smokers:	
Current cigar smokers:		Total	1.04
Total	1.09	1 to 9 pipefuls per day	1.08
1 to 4 cigars per day	1.03	> 9 pipefuls per day	.92
> 4 cigars per day	1.18		

SOURCE: Hammond, E.C. (*50*)

smoke and the depth of inhalation. Some nicotine may also be absorbed through the mucous membranes of the mouth. This is more likely to occur under alkaline conditions when nicotine is unprotonated (*4, 19, 108*). This suggests that cigar smokers may absorb some nicotine through the oral cavity without inhaling, particularly during the time

that the smoke from the cigar is alkaline. With the development of sensitive measures of serum nicotine levels (*65*), the extent to which nicotine is absorbed through the membranes of the mouth in pipe and cigar smokers can be more accurately determined.

Inhalation patterns of smokers were determined in several of the large prospective and some of the retrospective epidemiological studies. Inhalation was usually determined by the administration of a questionnaire that required a subjective evaluation of one's own patterns of inhalation. Although the accuracy of these questionnaires has not been confirmed by an objective measure of inhalation, such as carboxyhemoglobin or serum nicotine levels, their reliability is supported by mortality data which demonstrate higher overall and specific death rates with self-reported increases in the depth of inhalation.

Doll and Hill (*34*) and Hammond (*50*) presented information on inhalation patterns of pipe, cigar, and cigarette smokers. Some 80 to 90 percent of cigarette smokers reported inhaling, the majority inhaling moderately or deeply, whereas more pipe and cigar smokers denied inhaling at all. For each type of smoking, less inhalation was reported by older smokers. This change may represent less awareness of inhalation, differences in smoking habits of successive cohorts of smokers, or it may reflect the operation of selective factors which favor survival of noninhalers.

The Tobacco Research Council of the United Kingdom has, since 1957, periodically reported the use of tobacco products by the British. Recent reports edited by Todd have contained data on the inhalation pattern of cigar, pipe, and cigarette smokers (*126*, *127*, *128*). Table 9 shows that most cigarette smokers inhale a "lot" or "fair amount" whereas most pipe and cigar smokers do not inhale at all or "just a little." Little change is observed in the inhalation patterns of a given product since 1968.

Carbon monoxide is poorly absorbed by the oral mucosa and, therefore, carboxyhemoglobin levels represent a good measure of the degree of inhalation of a given smoker. Several investigators (*22*, *68*, *101*) have found that pipe and cigar smokers have lower levels of carboxyhemoglobin than cigarette smokers and that the levels in pipe and cigar smokers who have never smoked cigarettes approach the levels found in nonsmokers.

The overall mortality rates of current pipe smokers who inhaled at least slightly were reported by Hammond (*50*) as being somewhat higher than for men who never smoked regularly. The overall mortality rates of current cigar smokers who reported inhaling at least slightly were appreciably higher than for men who never smoked regularly.

Evidence indicates that cigarette smokers inhale smoke to a greater degree than smokers of cigars or pipes. Once a smoker has learned to

TABLE 9.—The extent of inhaling pipes, cigars, and cigarettes by British males aged 16 and over in 1968 and 1971

Amount of inhalation	Tobacco product					
	Cigars		Pipes		Cigarettes	
	1968	1971	1968	1971	1968	1971
Inhale a lot	23	19	8	8	47	47
Inhale a fair amount	16	19	10	8	31	30
Inhale just a little	27	27	24	26	13	15
Do not inhale at all	34	35	59	58	9	8
Total	100	100	100	100	100	100

SOURCE: Todd, G.F. (*127,128*)

inhale cigarettes, however, there appears to be a tendency also to inhale the smoke of other tobacco products. For cigars, this is evidently true whether one smokes both cigarettes and cigars or switches from cigarettes to cigars.

Bross and Tidings (*17*) examined the inhalation patterns of smokers of large cigars and cigarettes and those who switched from one tobacco product to another. Nearly 75 percent of those currently smoking only cigarettes reported inhaling "almost every puff" and only 7 percent never inhaled. The opposite was true for persons who had always smoked only cigars, among whom 4 percent reported inhaling almost every puff and 89 percent saying they never inhaled. Cigar smokers who also smoked cigarettes reported intermediate levels of inhalation between the cigar-only and cigarette-only categories. Inhalation patterns were similar whether the individual continued to smoke both products, stopped smoking cigarettes but continued smoking cigars, or stopped smoking cigarettes and switched to cigars. In all three groups, about 20 percent reported inhaling "almost every puff." This suggests that, once an individual's inhalation patterns are established on cigarettes, he may be more likely to inhale cigar smoke if he switches to cigars or uses both cigars and cigarettes than the cigar smoker who has not smoked cigarettes.

Todd (*128*) reported similar data for a sample of smokers in the United Kingdom. The prevalence of inhaling a "lot" or "fair amount" of smoke was highest among cigarette smokers who were currently smoking cigarettes (77 percent) and lowest among current cigar smokers who had previously smoked only cigars or pipes (18 percent). Individuals who switched from cigarettes to cigars maintained somewhat higher levels of cigar smoke inhalation than those cigar smokers who had never smoked cigarettes (30 percent).

TABLE 10.—Mortality ratios for total cancer deaths in cigar and pipe smokers. A summary of prospective epidemiological studies

Author, reference	Type of smoking				
	Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only
Hammond and Horn (*52*)....	1.00	1.34	1.44	....	1.97
Best (*11*).....	1.00	1.13	1.38	....	2.06
Hammond (*50*).....	1.00	....	....	1.21	1.76
Kahn (*69*).....	1.00	1.22	1.25	1.25	2.21

Todd (*127*) examined further the relationship between the inhalation of cigarette and cigar smoke. In general, cigarette smokers who switched to cigars were much less likely to report inhaling cigar smoke than cigarette smoke; however, those who in the past reported inhaling cigarette smoke a "lot" or "fair amount" were much more likely to report inhaling cigar smoke to the same degree than those ex-cigarette smokers who in the past did not inhale the smoke of their cigarettes.

This evidence has been confirmed by measuring carboxyhemoglobin levels in former cigarette smokers who now smoke cigars or pipes. Castleden and Cole (*22*) found that men who had smoked cigars or a pipe, but who had not previously smoked cigarettes, had carboxyhemoglobin levels similar to urban nonsmokers. However, men who had switched from cigarettes to pipes or cigars had levels comparable to cigarette smokers. This was true even in those pipe and cigar smokers who denied inhaling. Cowie, et al. (*25, 26*) found similar results in eight subjects who had recently switched to cigars; seven subjects had similar carboxyhemoglobin levels before and after switching from smoking cigarettes to cigars. Smokers who inhale cigars have been found to have carboxyhemoglobin levels even higher than those found in cigarette smokers who inhale (*46, 68*).

Specific Causes of Mortality

Cancer

Several prospective epidemiological studies have shown a significantly higher overall cancer mortality among pipe and cigar smokers compared to the cancer mortality of nonsmokers (Table 10).

Pipe and cigar smokers have much higher rates of cancer at certain sites than at others. The upper airway and upper digestive tracts appear to be the most likely target organs. The relationship of pipe and

cigar smoking to the development of specific cancers is summarized below.

Cancer of the Lip

Approximately 1,500 new cases of cancer of the lip are reported each year. Because of the possibility of early detection and surgical accessibility of cancers in this area, there are less than 200 deaths from cancer of the lip each year in the United States. Some of the earliest scientific investigations exploring the association between tobacco use and disease examined the smoking patterns of individuals with cancer of the lip.

Broders (*16*) in 1920 examined the smoking habits of patients in a retrospective study of 526 cases of epithelioma of the lip and 500 controls. Of the cancer cases, 59 percent smoked pipes, whereas this was true for only 28 percent of the controls. No association was found between cigar or cigarette smoking and cancer of the lip.

In a retrospective study of 439 clinic patients with cancer of the lip and 300 controls conducted in Sweden, Ebenius (*41*) reported a significant association between pipe smoking and cancer of the lip. A total of 61.8 percent of the lip cancer cases smoked pipes, while only 22.9 percent of the controls smoked pipes. No association was found between the use of cigarettes, cigars, or chewing tobacco and cancer of the lip.

In other retrospective studies, Levin, et al. (*80*) and Sadowsky, et al. (*105*) reviewed cases of cancer of the lip. In both studies, a strong association was found between pipe smoking and cancer of the lip but no significant association was found between the use of tobacco in other forms and cancer at this site. Other studies support their findings (*70, 121, 142*).

In summary, it appears that there are several factors involved in the etiology of cancer of the lip. Among the various forms of tobacco use, pipe smoking, either alone or in combination with other forms of smoking, seems to be a cause of cancer of the lip. Table 11 summarizes the results of these retrospective studies.

Oral Cancer

The lips, oral cavity, and pharynx are the sites most consistently exposed to tobacco smoke. Data from the epidemiological studies suggest that little difference exists between the smoking of cigarettes, pipes, or cigars and the risk of developing oral cancer.

Hammond and Horn (*52*) examined the association between smoking in various forms and cancer of the combined sites of lip, mouth, pharynx, larynx, and esophagus. The mortality ratios were 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers, compared to nonsmokers.

TABLE 11.—Relative risk of lip cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Broders (*16*):		Relative risk	1.0	0.8	4.3	....	0	....
Cases	537	Percent cases	7	19	41	....	1	....
Controls	500	Percent controls	4	16	6	....	26	....
Ebenius (*41*):		Relative risk	1.0	.7	4.1	0.5	....	....
Cases	439	Percent cases	49	6	41	4	....	....
Controls	300	Percent controls	65	12	13	10	....	....
Levin (*80*):		Relative risk	1.0	1.9	2.9	....	1.4	....
Cases	143	Percent cases	15	27	48	....	45	....
Controls	554	Percent controls	22	20	24	....	46	....
Sadowsky (*105*):		Relative risk	1.0	1.1	4.3	2.6	1.4	0.4
Cases	571	Percent cases	8	2	18	6	44	22
Controls	615	Percent controls	13	3	7	4	53	19
Wynder [1] (*142*):		Relative risk	0	.8	1.8	....	1.0	2.2
Cases	14	Percent cases	0	7	29	....	36	29
Controls	115	Percent controls	24	9	16	....	36	13
Staszewski (*121*):		Relative risk	1.0	....	....	2.1	2.4	....
Cases	394	Percent cases	7	....	....	12	73	....
Controls	912	Percent controls	13	....	....	11	61	....
Keller (*70*):		Relative risk	1.0	1.4	4.0		2.6	
Cases	301	Percent cases	7	2	6	1	60	6
Controls	265	Percent controls	17	4	3	0	53	0

[1]Percentage based on less than 20 patients. Ratios: relative to cigarette smokers.

Doll and Peto (*38*) reported the mortality for all respiratory cancers except lung and found mortality ratios of 9 for pipe and cigar smokers who had never smoked cigarettes, 10 for pipe and cigar smokers who had smoked cigarettes, and 14 for cigarette smokers.

A detailed analysis of oral cancer was presented by Kahn (*69*) who differentiated between cancer of the oral cavity and cancer of the pharynx. The mortality ratios for oral cancers were 1.00 for those who never smoked, 3.89 for all pipe and cigar smokers, and 4.09 for cigarette smokers. A further breakdown of the pipe and cigar smokers demonstrated a mortality ratio of 4.11 for cigar smokers, 3.12 for pipe smokers, and 3.89 for smokers of pipes and cigars. For cancer of the pharynx, the mortality ratios were 1.00 for those who never smoked, 3.06 for all pipe and cigar smokers, and 12.5 for cigarette smokers. No deaths occurred among those who smoked only cigars. The mortality ratio was 1.98 for pipe smokers. Hammond (*50*) combined cancers of

TABLE 12.—Mortality ratios for oral cancer in cigar and pipe smokers. A summary of prospective epidemiological studies

Author, reference	Smoking type					
	Non-Smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn[1] (*52*)	1.00	5.00	3.50	....	5.06	....
Doll and Hill[2] (*38*).....	1.00	....	....	[3]9.00	14.00	10.00
Hammond (*50*).....	1.00	....	....	4.94	9.90[3]	....
Kahn (*69*):						
Oral[4].....	1.00	4.11	3.12	3.89	4.09	....
Pharynx.....	1.00	....	1.98	3.06	12.54	....

[1]Combines data for oral, larynx, and esophagus.
[2]Figures for all non-lung respiratory cancers.
[3]Mortality ratios for ages 45 to 64 only are presented.
[4]Excludes pharynx.

the lip, oral cavity, and pharynx. The pipe and cigar smokers had a mortality ratio of 4.94 and the cigarette smokers a mortality ratio of 9.90 compared to nonsmokers.

These studies are summarized in Table 12. They demonstrate that smokers experience a large and significant risk of developing cancer of the oral cavity compared to nonsmokers. This risk seems to be about the same for all smokers whether an individual uses a pipe, cigar, or cigarette.

Several epidemiological investigations have demonstrated an association between the combined use of alcohol and tobacco and the development of oral cancer. A few of these studies (*71, 82, 83, 138*) contain data on pipe and cigar smokers. Heavy smoking and heavy drinking are associated with higher rates of oral cancer than are seen with either habit alone.

Cancer of the Larynx

Because of its proximity to the oral cavity, the larynx probably has an exposure to smoke drawn through the mouth similar to that of the buccal cavity and pharynx. Tobacco smoke that is not inhaled may still reach as far as the larynx and upper trachea. Pipe and cigar smokers develop cancer of the larynx at rates comparable to those of cigarette smokers, i.e., several times those of nonsmokers. The similarity of the mortality ratios of cancer of the larynx for smoking in various forms

suggests that the carcinogenic potentials of the smoke from cigars, pipes, and cigarettes are quite alike at this site.

Several of the prospective epidemiological studies include data on deaths from cancer of the larynx for pipe and cigar smokers as well as for cigarette smokers. Hammond and Horn (*52*) combined data for cancer of the larynx with cancer of the esophagus and oral cavity. The mortality ratios compared to nonsmokers were 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers. There were no deaths from carcinoma of larynx among nonsmokers in the study of British physicians by Doll and Hill (*34*), but the death rate for cancer of the larynx among pipe and cigar smokers was 0.10 per 1,000 while the death rate for cigarette smokers was 0.05 per 1,000. Kahn (*69*) reported mortality ratios for cancer of the larynx of 10.33 for cigar-only smokers, 9.44 for individuals smoking both pipes and cigars but not cigarettes, 7.28 for all pipe and cigar categories combined, and 9.95 for cigarette-only smokers. No deaths from cancer of the larynx occurred in pipe smokers. Hammond (*50*) reported a mortality ratio of 3.37 for all pipe and cigar smokers and a mortality ratio of 6.09 for cigarette smokers in the age category 45 to 64. Wynder, et al. (*137*, *142*) distinguished between intrinsic and extrinsic larynx cancers.

Histologic changes of the larynx in relation to smoking in various forms were described by Auerbach, et al. (*7*). Microscopic sections of the larynx from 942 subjects were examined for the presence of atypical nuclei and proliferation of cell rows. Sections were taken from four separate areas of the larynx in each case. Among those who smoked cigars and pipes but not cigarettes, only 1 percent had no atypical cells and more than 75 percent of the subjects had lesions with 50 to 69 percent atypical cells. Four of the cigar and pipe smokers had carcinoma *in situ*, and in one of these four cases early invasion was seen in three of the sections. Of those who never smoked regularly, 75 percent had no atypical cells. The cigar and pipe smokers had a percentage of cells with atypical nuclei similar to that of cigarette smokers who smoked one to two packs per day.

Cancer of the Esophagus

The esophagus is not directly exposed to tobacco smoke drawn into the mouth but it does have contact with tobacco smoke that is condensed on the mucous membranes of the mouth and pharynx and then swallowed. The esophagus is also exposed to a portion of tobacco smoke deposited in the mucus cleared from the lung by the ciliary mechanism or by coughing. Variations in inhalation of a tobacco product may not appreciably alter the exposure the esophagus receives from smoke dissolved in mucus and saliva. This possibility receives support from the prospective and retrospective epidemiological studies which demonstrate similar mortality rates for cancer of the esophagus in smokers of cigars, pipes, and cigarettes.

TABLE 13.—Mortality ratios for cancer of the esophagus in cigar and pipe smokers. A summary of prospective epidemiological studies

Author, reference	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn[1] (*52*)	1.00	5.00	3.50	....	5.06	....
Doll and Peto (*38*)	1.00	....	....	3.70	4.70	9.0
Hammond (*50*)	1.00	....	....	3.97	4.17[2]	....
Kahn (*69*)	1.00	5.33	1.99	4.05	6.17	....

[1]Combines data for oral, larynx, and esophagus.
[2]Mortality ratio for ages 45 to 64.

In the prospective epidemiological studies, cigar, pipe, and cigarette smokers had similar mortality ratios for cancer of the esophagus. Hammond and Horn (*52*) combined the categories of carcinoma of the esophagus, larynx, pharynx, oral cavity, and lip and described mortality ratios of 5.00 for cigar smokers, 3.50 for pipe smokers, and 5.06 for cigarette smokers. The 20-year followup of British physicians (*38*) showed mortality ratios for cancer of the esophagus of 3.7 for pipe and cigar smokers, 4.7 for cigarette smokers, and 9.0 for mixed smokers.

Kahn (*69*) reported the following mortality ratios for smoking in various forms compared to nonsmokers: cigar only, 5.33; pipe only, 1.99; pipe and cigar but not cigarettes, 4.17; all pipes and cigars combined, 4.05; and cigarettes only, 6.17. The results of these prospective studies are summarized in Table 13.

Several retrospective investigations have also examined the association between smoking in various forms and cancer of the esophagus. These studies suggest that cigar, pipe, and cigarette smokers develop cancer of the esophagus at rates substantially higher than those seen in nonsmokers and that little difference exists between these rates observed in smokers of pipes and cigars and cigarettes.

Histologic changes in the esophagus in relation to smoking in various forms were investigated by Auerbach, et al. (*9*).

Several retrospective studies conducted in the United States and other countries have examined the synergistic roles of tobacco use and heavy alcohol intake on the development of cancer of the esophagus. Four of these investigations contain data on pipe and cigar smoking (*15*, *82*, *83*, *136*). It appears that smoking in any form in combination

TABLE 14.—Relative risk of cancer of the esophagus for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Sadowsky (*105*):		Relative risk	1.0	4.8	3.8	5.1	3.8	3.3
Cases	104	Percent cases	4	5	8	6	60	18
Controls	615	Percent controls	13	3	7	4	53	19
Wynder (*142*):		Relative risk	1.0	3.1	2.1	....	2.6	.4
Cases	39	Percent cases	13	15	18	....	51	3
Controls	115	Percent controls	24	9	16	....	36	13
Pernu (*99*):		Relative risk	1.0	....	3.0	....	2.7	5.9
Cases	202	Percent cases	17	....	7	....	59	18
Controls	713	Percent controls	39	....	5	....	50	7
Schwartz (*113*):		Relative risk	1.0	....	2.6	....	11.7	8.6
Cases	249	Percent cases	2	....	2	....	88	7
Controls	249	Percent controls	18	....	7	....	67	7
Wynder and Bross (*136*):		Relative risk	1.0	3.6	9.0	6.0	2.8	3.7
Cases	150	Percent cases	5	19	9	4	51	11
Controls	150	Percent controls	15	16	3	2	55	9
Bradshaw and Schonland (*15*):		Relative risk	1.0	....	4.8	....	2.3	....
Cases	117	Percent cases	15	....	41	....	63	....
Controls	366	Percent controls	32	....	18	....	58	....
Martinez (*82*):		Relative risk	1.0	2.0	....	....	1.5	2.2
Cases	120	Percent cases	8	9	....	....	31	43
Controls	360	Percent controls	14	8	....	....	34	34
Martinez[1] (*83*):		Relative risk	1.0	2.0	2.8	....	1.7	2.5
Cases	346	Percent cases	21	10	15	....	34	34
Controls	346	Percent controls	22	9	1	....	36	25

[1]This study combines data for oral cancer and cancer of the esophagus.

with heavy drinking results in especially high rates of cancer of the esophagus.

Lung Cancer

Several prospective epidemiological studies have demonstrated higher lung cancer mortality ratios for pipe and cigar smokers than for nonsmokers, but the risk of developing lung cancer for pipe and cigar smokers is less than for cigarette smokers. Table 15 presents a summary of these prospective studies.

TABLE 15.—Mortality ratios for lung cancer deaths in male cigar and pipe smokers. A summary of prospective studies

Author, reference	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*52*).	1.00	1.02	3.00	....	10.73	7.63
Doll and Peto (*38*).....	1.00	....	....	5.80	14.00	8.20
Best (*11*).....	1.00	2.94	4.35	....	14.91	....
Kahn (*69*).....	1.00	1.59	1.84	1.67	12.14	....

TABLE 16.—Lung cancer death rates for cigar and pipe smokers by amount smoked

Smoking type	Death rate per 100	Number of deaths
Nonsmoker.....	0.07	3
Cigar and pipe:		
1 to 14 g per day.....	.42	12
15 to 24 g per day.....	.45	6
24 g per day.....	.96	3
Cigarette only.....	.96	143

SOURCE: Doll, R., (*34*)

Dose-response relationships such as those that helped demonstrate the nature of the association between cigarette use and lung cancer could not be as thoroughly studied for pipe and cigar smokers because of the relatively few smokers in these categories. Although the number of deaths were few, Doll and Hill (*34*) reported increased death rates from lung cancer for pipe and cigar smokers with increasing tobacco consumption (Table 16). Kahn (*69*) also demonstrated a dose-response relationship for lung cancer by the amount smoked (Table 17).

A few of the retrospective studies contained enough smokers to allow an examination of dose-response relationships for pipe and cigar smoking and lung cancer (*1, 81, 100, 105*). These are summarized in Table 18. An increased risk of developing lung cancer was demonstrated with the increased use of pipes and cigars as measured by amount smoked and inhalation. The retrospective investigation of

TABLE 17.—Lung cancer mortality ratios for cigar and pipe smokers by amount smoked

Smoking type	Mortality ratio	Number of deaths
Nonsmoker	1.00	78
Cigar smokers:		
< 5 cigars per day	1.14	12
5 to 8 cigars per day	2.64	11
> 8 cigars per day	2.07	2
Pipe smokers:		
< 5 pipefuls per day	.77	2
5 to 19 pipefuls per day	2.20	12
> 19 pipefuls per day	2.47	3
Cigar and pipe:		
8 or less cigars, 19 or less pipefuls	1.62	18
> 8 cigars, > 19 pipefuls	2.19	2

SOURCE: Kahn, H.A. (*69*)

Abelin and Gsell (*1*) is of particular interest. The smoking habits of 118 male patients with cancer of the lung from a rural area of Switzerland were compared with those reported in a survey of all male inhabitants of a town in the same region. About 20 percent of the population of this area were regular cigar smokers, the most popular cigar being the Stuempen, a small Swiss-made machine-manufactured cigar cut at both ends with an average weight of 4.5 g. In this investigation, cigar smokers experienced a risk of developing lung cancer that was similar to the risk of cigarette smokers. A dose-response relationship was demonstrated for inhalation and amount smoked. These data suggest that the heavy smoking of certain cigars may result in a risk of lung cancer that is similar to that experienced by cigarette smokers.

Sanderud (*106*) examined histologic sections from the bronchial tree of 100 male autopsy cases for the presence of squamous epithelial metaplasia. In this study, 39 percent of the population were nonsmokers, 20 percent were pipe smokers, and 38 percent smoked cigarettes. A total of 80 percent of the pipe smokers and cigarette smokers demonstrated squamous metaplasia of the bronchial tree, whereas only

TABLE 18.—Relative risk of lung cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

Author, reference	Number	Relative risk ratio and percentage of cases and controls by type of smoking						
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Levin (*80*):		Relative risk	1.0	0.7	0.8	....	2.1	....
Cases	236	Percent cases	15	11	14	....	66	....
Controls	481	Percent controls	22	23	25	....	44	....
Schrek (*110*):		Relative risk	1.0	.6	.7	....	1.7	....
Cases	82	Percent cases	15	4	5	....	61	....
Controls	522	Percent controls	22	23	11	....	59	....
Wynder and Graham (*140*):		Relative risk	1.0	5.1	3.6	....	15.7	....
Cases	605	Percent cases	1	4	4	....	91	....
Controls	780	Percent controls	15	8	12	....	65	....
Doll and Hill (*86*):		Relative risk	1.0	....	5.1	....	9.6	....
Cases	1,357	Percent cases	.5	....	4	....	74	....
Controls	1,357	Percent controls	5	....	7	....	69	....
Koulumies (*77*):		Relative risk	1.0	....	9.6	....	29.3	....
Cases	812	Percent cases	.6	....	2	....	77	....
Controls	300	Percent controls	18	....	6	....	76	....
Sadowsky (*105*):		Relative risk	1.0	2.4	1.4	....	3.7	5.6
Cases	477	Percent cases	4	2	3	....	57	31
Controls	615	Percent controls	13	3	7	....	53	19
Wynder and Cornfield (*139*):		Relative risk	1.0	2.5	4.0	....	8.5	....
Cases	63	Percent cases	4	13	6	....	77	....
Controls	133	Percent controls	21	27	8	....	45	....
Randig (*100*):		Relative risk	1.0	5.3	5.0	....	5.0	....
Cases	415	Percent cases	1	21	11	....	67	....
Controls	381	Percent controls	6	19	11	....	64	....
Mills and Porter (*86*):		Relative risk	1.0	....	....	6.0	5.4	....
Cases	444	Percent cases	7	....	....	37	55	....
Controls	430	Percent controls	31	....	....	26	43	....
Mills and Porter (*87*):		Relative risk	1.0	....	....	2.8	4.5	....
Cases	484	Percent cases	8	....	....	13	78	....
Controls	1,588	Percent controls	28	....	....	16	57	....

54 percent of the nonsmokers had this abnormality. Knudtson (*76*) also studied histologic changes.

Auerbach, et al. (*8*) examined 36,340 histologic sections obtained from 1,522 white adults for various epithelial lesions including:

TABLE 18.—Relative risk of lung cancer for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies–continued

Author, reference	Number		Relative risk ratio and percentage of cases and controls by type of smoking					
			Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Schwartz and Denoix (*111*):		Relative risk	1.0	....	4.7	....	13.5	....
Cases	430	Percent cases	1	....	6	....	96	....
Controls	430	Percent controls	11	....	14	....	78	....
Stocks (*123*):		Relative risk	1.0	....	3.1	....	5.0	....
Cases	2,101	Percent cases	2	....	9	....	89	....
Controls	5,960	Percent controls	9	....	13	....	78	....
Lombard and Snegireff (*81*):		Relative risk	1.0	....	....	1.7	8.1	....
Cases	500	Percent cases	2	....	....	4	95	....
Controls	1,839	Percent controls	10	....	....	15	75	....
Pernu (*99*):		Relative risk	1.0	....	4.2	....	9.2	11.1
Cases	1,477	Percent cases	7	....	4	....	77	13
Controls	713	Percent controls	39	....	5	....	50	7
Wicken (*135*):		Relative risk	1.0	....	....	2.2	4.3	4.2
Cases	803	Percent cases	4	....	....	10	78	7
Controls	803	Percent controls	14	....	....	16	64	6
Abelin and Gsell (1):		Relative risk	1.0	3.4	4.5	....	5.7	
Cases	118	Percent cases	2	28	7	....	....	24
Controls	524	Percent controls	35	19	6	....	....	10
Wynder (*144*):		Relative risk	1.0	....	....	2.0	12.4	....
Cases	210	Percent cases	3	....	....	5	92	....
Controls	420	Percent controls	21	....	....	15	47	....

presence or absence of ciliated cells, thickness or number of cell rows, atypical nuclei, and the proportion of cells of various types. The pathologic findings in the bronchial epithelium of pipe and cigar smokers were compared to those found in nonsmokers and cigarette smokers. Pipe and cigar smokers had abnormalities that were intermediate between those of nonsmokers and cigarette smokers, although cigar smokers had pathologic changes that in some categories approached the changes seen in cigarette smokers.

Tumorigenic Activity

Several experimental investigations have been conducted to examine the relative tumorigenic activity of tobacco smoke condensates obtained from cigarettes, cigars, and pipes. Most of these studies were standardized in an attempt to make the results of the cigar and pipe

experiments more directly comparable with the cigarette data, and most used the shaved skin of mice for the application of tar. Tars from cigars, pipes, and cigarettes were usually applied on an equal weight basis so that qualitative differences in the tars could be determined. In several experiments, the nicotine was extracted from the pipe and cigar condensates in an attempt to reduce the acute toxic effects that resulted in animals from the high concentrations of nicotine frequently found in these products.

Wynder and Wright (*146*) examined the differences in tumorigenic activity of pipe and cigarette condensates. Tars were obtained by the smoking of a popular brand of king-size cigarettes and from the same cigarette tobacco smoked in 12 standard-grade briar bowl pipes. Both the cigarettes and pipes were puffed three times a minute with a 2-second puff and a 35-ml volume. Both the cigarettes and pipes attained similar maximum combustion zone temperatures; however, the use of cigarette tobacco in the pipe resulted in a combustion chamber temperature that averaged about 150° centrigrade higher than temperatures achieved when pipe tobacco was used. Chemical fractionation was accomplished and equal concentrations of the neutral fraction were applied in three weekly applications to the shaved skin of CAF_1 and Swiss mice. The results indicate that neutral tar obtained from cigarette tobacco smoked in pipes is more active than that obtained in the usual manner from cigarettes. About twice as many cancers were obtained in both the CAF_1 and the Swiss mice, and the latent period was about 2 months shorter.

Extending these data, Croninger, et al. (*27*) examined the biologic activity of tars obtained from cigars, pipes, and cigarettes. Each form of tobacco was smoked as it was manufactured in a manner to simulate human smoking or to maintain tobacco combustion. The whole tar was applied in dilutions of one-to-one and one-to-two with acetone to the shaved backs of female CAF_1 and female Swiss mice using three applications each week for the life span of the animal. The nicotine was extracted from the pipe and cigar condensates to reduce the acute toxicity of the solutions. In the Swiss mice, pipe, cigar, and cigarette tars produced both benign and malignant tumors. The incidence rates of malignant tumors given as percents were: 44, 41, and 37, respectively. These results suggested a somewhat higher degree of carcinogenic activity for cigar and pipe tars than for cigarette tar.

Similar results were reported by Kensler (*72*), who applied condensates obtained from cigars and cigarettes to the shaved skin of mice. The incidence of papillomas produced by cigar smoke concentrate was no different from that produced by the cigarette smoke condensate. Similarly, there was no difference between cigar and cigarette smoke condensates when carcinoma incidences were compared.

Homburger, et al. (*62*) prepared tars from cigar, pipe, and cigarette tobaccos that were smoked in the form of cigarettes. In this way, all

tobaccos were smoked in an identical manner and uniform combustion temperatures were achieved. Because of this standardization, differences in tumor yield could be attributed to tobacco blend and not to the manner in which the tars were prepared. The whole tars were diluted one-to-one with acetone and applied to the shaved skin of CAF_1 mice three times a week for the life span of the test animal. Skin cancers were produced more quickly with pipe and cigar smoke condensates than with cigarette smoke condensates. This suggests that the smoking of pipe and cigar tobaccos in the form of cigarettes does not alter the condensates to any significant degree. Davies and Day (*29*) and Roe, et al. (*103*) conducted other tumorigenic studies.

These experimental data suggest that cigar and pipe tobacco condensates have a carcinogenic potential that is comparable to cigarette condensates. This is supported by human epidemiological data for those sites exposed equally to the smoke of cigars, pipes, and cigarettes. The partially alkaline smoke derived from pipes and cigars is generally not inhaled, and as a result there appears to be a lower level of exposure of the lungs and other systems to the harmful properties of pipe and cigar smoke than occurs with cigarette smoking. It is anticipated that modifications in pipe tobacco or cigars which would result in a product that was more readily inhalable would eventually result in elevated mortality from cancer of the lung, bronchitis and emphysema, arteriosclerotic cardiovascular diseases, and the other conditions which have been clearly associated with cigarette smoking.

Cardiovascular Diseases

Pipe and cigar smokers experience only a small increase in mortality from coronary heart disease above the rates of nonsmokers. Cigarette smokers have higher death rates from cerebrovascular disease than nonsmokers, whereas pipe and cigar smokers have cerebrovascular death rates that are only slightly above the rates of nonsmokers. Table 19 summarizes the major prospective epidemiological investigations that examined the association of smoking in various forms with total cardiovascular diseases, coronary heart disease, with cerebrovascular disease. Doll and Hill (*33*), Best (*11*), and Kahn (*69*) examined dose-response relationships for pipe and cigar smokers and reported a slight increase in mortality from coronary heart disease with an increase in the number of cigars or pipefuls smoked.

Other prospective epidemiological studies have also examined the relationship of smoking in various forms to coronary heart disease and related risk factors. Jenkins, et al. (*66*), in the Western Collaborative Group Study of coronary heart disease (CHD), reported an incidence of coronary heart disease in men aged 50 to 59 who were pipe and cigar smokers that was intermediate between the rates seen in cigarette smokers and nonsmokers. No increase in incidence of coronary heart

TABLE 19.—Mortality ratios for cardiovascular deaths in male cigar and pipe smokers. A summary of prospective epidemiological studies

Author, reference	Category	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*52*).	Cardiovascular total.	1.00	1.26	1.07	....	1.57	....
	Coronary.....	1.00	1.28	1.03	....	1.70	....
	Cerebrovascular....	1.00	1.31	1.23	....	1.30	....
Doll and Hill (*38*).	Cardiovascular total.	1.00	....	....	.81	1.38	.81
	Coronary.....	1.00	....	....	1.03	1.62	1.28
	Cerebrovascular....	1.00	....	....	1.15	1.34	1.21
Best (*11*).	Cardiovascular total.	1.00	1.14	.95	....	1.52	....
	Coronary.....	1.00	.99	1.00	....	1.60	....
	Cerebrovascular....	1.00	1.28	.85	....	.88	....
Hammond[1] (*50*).	Cardiovascular total.	1.00	....	....	1.06	1.90	....
	Coronary.....	1.00	1.35	1.19	....	1.09	1.41
	Cerebrovascular....	1.00	....	....	1.09	1.41	1.40
Kahn (*69*).	Cardiovascular total.	1.00	1.05	1.06	1.05	1.75	....
	Coronary.....	1.00	1.04	1.08	1.05	1.74	....
	Cerebrovascular....	1.00	1.08	1.09	1.06	1.52	....

[1]Mortality ratios for ages 55 to 64 only are presented.

disease was seen among the pipe and cigar smokers in the younger age groups. Shapiro, et al. (*115*), in a study of the health insurance plan (HIP) population, reported incidence rates for myocardial infarction (MI), angina pectoris, and possible MI, in pipe and cigar smokers that were similar to the incidence rates seen in cigarette smokers. These rates were considerably higher than those of nonsmokers. Data from the Pooling Project (*64*) suggested that the incidence of CHD deaths, sudden death, and the first major coronary event in pipe and cigar smokers was intermediate between the incidence experienced by cigarette smokers and nonsmokers. In contrast to these studies, Doyle, et al. (*39*) reported no increase in CHD deaths, myocardial infarction, or angina pectoris in pipe and cigar smokers over the rates of nonsmokers in the Framingham study.

The retrospective studies of Mills and Porter (*85*), Villiger and Heyden-Stucky (*133*), Schimmler, et al. (*109*), and Hood, et al. (*63*) contained data suggesting that pipe and cigar smokers experience mortality rates from coronary heart disease that are essentially similar

to those experienced by cigarette smokers. The retrospective study of Spain and Nathan (*120*) reported lower rates of coronary heart disease for pipe and cigar smokers than were found in nonsmokers.

Van Buchem (*132*) and Dawber, et al. (*30, 31*) examined serum cholesterol levels in groups of individuals classified according to smoking habits. In these two studies, pipe and cigar smokers had serum cholesterol levels that were nearly identical with the levels found in nonsmokers.

Tibblin (*125*) and Dawber, et al. (*30, 31*) investigated the effect of smoking on blood pressure. The proportion of smokers decreased in groups with higher blood pressures, although this was not as dramatic for pipe and cigar smokers as it was for cigarette smokers. Kesteloot and Van Houte (*75*) found that pipe and cigar smokers had slightly lower blood pressures than nonsmokers, in contrast to cigarette smokers who had minimally elevated blood pressures in comparison to nonsmokers.

Chronic Obstructive Pulmonary Disease

Chronic bronchitis and pulmonary emphysema account for most of the morbidity and mortality from chronic respiratory disease in the United States. The relationship between smoking pipes and cigars and these diseases is summarized in this section and in Table 20.

In a retrospective study of 1,189 males and matched controls in Northern Ireland, Wicken (*135*) investigated smoking in various forms and mortality from bronchitis. The relative risk ratios compared to nonsmokers for mortality from chronic bronchitis were 1.98 for all smokers, 1.55 for pipe and cigar smokers, 2.25 for cigarette smokers, and 1.49 for mixed smokers.

From a review of these prospective and retrospective studies, it appears that pipe and cigar smokers experience mortality rates from bronchitis and emphysema that are higher than the rates of nonsmokers. Although these mortality rates approach those of cigarette smokers, in most instances they are intermediate between the rates of cigarette smokers and nonsmokers.

Pipe and cigar smokers have significantly more respiratory symptoms and illnesses than nonsmokers. Those studies which contain data on pipe and cigar smoking as related to respiratory symptoms are summarized in Table 21.

Haenszel and Hougen (*48*) showed an increased prevalence of persistent cough and phlegm in pipe and cigar smokers compared to nonsmokers and were able to show that the prevalence increased with increasing amount smoked.

Only a few studies have examined pulmonary function in pipe and cigar smokers. There appears to be little difference in pulmonary

TABLE 20.—Mortality ratios for chronic obstructive pulmonary deaths (COPD) in male cigar and pipe smokers. A summary of prospective epidemiological studies

Author, reference	Category	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (*52*).	COPD total	1.00	1.29	1.77	....	2.85	....
	Exmphsema	....	....	....	....	....	....
	Bronchitis	....	....	....	....	....	....
Doll and Hill (*34,35,38*).	COPD total	1.00	....	....	9.33	24.67	11.33
	Emphysema	....	....	....	....	....	....
	Bronchitis	1.00	....	....	4.00	7.00	6.67
Best (*11*).	COPD total	....	....	....	....	....	....
	Emphysema	1.00	3.33	.75	....	5.85	....
	Bronchitis	1.00	3.57	2.11	....	11.42	....
Hammond (*50*).	COPD total	....	....	....	....	....	....
	Emphysema	1.00	....	....	1.37	6.55[1]	....
	Bronchitis	....	....	....	....	....	....
Kahn (*69*).	COPD 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	....

[1]Only mortality ratios for ages 55 to 64 are presented.

function values for pipe and cigar smokers as compared to nonsmokers (Table 22).

Naeye (*88*) conducted an autopsy study on 322 Appalachian coal workers who were classified according to the type of coal mined and tobacco usage. Emphysema was slightly greater in cigarette smokers, as were anatomic evidences of chronic bronchitis and bronchiolitis. Those changes found in pipe and cigar smokers were intermediate between those of cigarette-smoking miners and nonsmoking miners.

Changes in pulmonary histology in relation to smoking habits and age were examined by Auerbach, et al. (*6, 10*). Fibrosis, alveolar rupture, thickening of the walls of small arteries, and thickening of the walls of the pulmonary arterioles were found to be highly related to the smoking habits of the 1,340 male subjects examined. The 91 pipe and cigar smokers over the age of 60 were found to have somewhat more alveolar rupture than the men of the same age distribution who never smoked regularly. However, pipe and cigar smokers as a group had far less rupture than cigarette smokers. The same relations as described above were found for fibrosis, thickening of the walls of the arterioles and small arteries, and padlike attachments to the alveolar septums.

TABLE 21.—Prevalence of respiratory symptoms and illness by type of smoking

Author, reference	Number and type of population	Illness	Percent prevalence			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Boake (*12*).	Parents of 59 families.	Cough.	32	32	48	....
		Sputum production.	24	15	20	....
		Chest illness.	5	4	5	....
Edwards (*42*).	1,737 male outpatients.	Chronic bronchitis.	17	19[1]	31	14
Ashford (*5*).	4,014 male workers in 3 Scottish collieries.	Bronchitis.	10	35[1]	21	37
		Pneumoconiosis.	11	34[1]	14	2
Bower (*14*).	95 male bank employees.	Cough.	0	0	29	....
		Sputum production.	8	15	33	....
		Wheeze.	8	31	33	....
		Chest illness.	15	54	40	....
Wynder (*143*).	315 male patients in New York and 315 male patients in California.	Cough (New York).	14	33	56	51
		Cough (California).	22	30	67	66
		Influenza (New York).	11	21	24	....
		Influenza (California).	28	24	31	....
		Chest illness (New York).	9	10	12	....
		Chest illness (California).	7	6	11	....
Densen (*32*).	5,287 male postal and 7,213 male transit workers in New York City.	Persistent cough.	7	11	25	....
		Persistent sputum production.	11	16	26	....
		Dyspnea.	16	19	26	....
		Wheeze.	14	21	32	....
		Chest illness.	13	16	18	....
Cederlof (*23*).	4,379 twin pairs, all U.S. veterans.	Cough.	4	7	17	....
		Prolonged cough.	2	4	11	....
		Bronchitis.	2	3	10	....
Rimington (*102*).	41,729 male volunteers.	Chronic bronchitis.	5	9[1]	17	....

Tobacco smoke has been shown experimentally to have a ciliostatic

TABLE 21.—Prevalence of respiratory symptoms and illness by type of smoking–continued

Author, reference	Number and type of population	Illness	Percent prevalence			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Comstock (*24*).	670 male telephone employees.	Persistent cough.	10	16	41	....
		Persistent sputum	13	20	42	....
		Dyspnea.	33	39	44	....
		Chest illness in past 3 yrs.	14	18	20	....
Lefcoe and Wonnacott (*79*).	310 male physicians in London, Ontario.	Chronic respiratory disease.	9	18	44	....
		Chronic bronchitis.	1	12	34	....
		Obstructive lung disease.	1	3	4	....
		Asthma.	7	3	6	....
		Rhonchi.	0	3	9	....
Haenszel and Hougen (*48*).	6,712 Norwegian males and 3,887 siblings who emigrated.	Persistent cough and phlegm, age 35-54.	3.0	8.7	14.8	14.5
		Persistent cough and phlegm, age 55–74.	3.7	7.2	15.0	14.3
		Chronic bronchitis, age 35–54.	0.4	1.1	1.9	1.3
		Chronic bronchitis, age 55–74.	1.3	1.6	3.7	3.5

[1]Figures for pipe only.

effect on the respiratory epithelium. The interval between puffs, the amount of volatile and particulate compounds in the smoke, and the exposure volume have been shown to influence the toxic effect of tobacco smoke. Dalhamn and Rylander (*28*) exposed the upper trachea of anesthetized cats to the smoke of cigarettes and cigars, observing the effect on ciliary activity through an incident-light microscope. A chemical analysis of the gas and particulate phases revealed that the cigar smoke was more alkaline and, in general, contained higher concentrations of isoprene, acetone, acetonitrile, toluene, and total particulate matter compared to cigarette smoke. The average number of puffs required to arrest ciliary activity was found to be 73 for the cigarette smoke and 114 for the cigar smoke. The difference is statistically significant ($P < 0.01$). Of the two smokes, the smoke with the highest concentration of volatile compounds was found to be the least ciliostatic. This suggests that the degree of ciliotoxicity of a

TABLE 22.—Pulmonary function values for cigar and pipe smokers as compared to nonsmokers

Author, reference	Number and type of population	Function	Type of smoking			
			Non-smoker	Total pipe and cigar	Cigarette only	Mixed
Ashford (5).	4,014 male workers in 3 Scottish collieries.	$FEV_{1.0}$	3.39	2.59[1]	3.14	2.62
Goldsmith, et al. (47).	3,311 active or retired longshoremen.	Puffmeter	313.63	299.26	303.44	....
		$FEV_{1.0}$	2.99	2.80	2.91	....
		TVC	3.87	3.68	3.88	....
Comstock (24).	670 male telephone employees.	$FEV_{1.0}$	3.12	3.26	2.82	....
Lefcoe and Wonnacott (79).	310 male physicians in London, Ontario.	$FEV_{1.0}$	3.39	3.17	3.11	....
		MMFR liters per second	4.09	4.17	3.64	....

[1]Figures for pipe only.

smoke is not necessarily correlated to the level of one or several of the substances found in the smoke. Passey, et al. (*95*, *96*, *97*) studied smoke effects in rats.

Gastrointestinal Disorders

Cigar and pipe smokers experience higher death rates from peptic ulcer disease than nonsmokers. These rates are higher for gastric ulcers than for duodenal ulcers but are somewhat less than those rates experienced by cigarette smokers. Retrospective or cross-sectional studies by Trowell (*129*), Allibone and Flint (*3*), Doll, et al. (*37*), and Edwards, et al. (*42*) contain data on ulcer disease in pipe smokers as well as cigarette smokers, but no association was found between pipe smoking and ulcer disease in these investigations.

Snuff and Chewing Tobacco

In the United States most of the tobacco consumed is used in pipes, cigars, or cigarettes, forms that involve combustion. Nicotine and other substances can be absorbed through the oral mucosa, however, and so tobacco can also be chewed, inhaled into the nose, or retained between the cheek and gum.

A variety of forms of tobacco are designed for noncombustive use (*141*). Plug tobacco contains Burley, cigar, and Virginia tobaccos sweetened with honey, sugars, molasses, syrups, and licorice, pressed into flattened blocks and then wrapped with natural leaf. Scrap chewing tobacco is made from fermented cigar leaf tobacco. Some brands are only lightly sweetened, whereas others carry large amounts of sugars, syrups, licorice, and other flavoring materials. The treated tobacco is not compressed, but is packaged as loose pieces of cut strips. In some countries, chewing tobacco is made from tar-like material extracted by boiling the green leaves in water. This extract is mixed with slaked lime or wood ashes. When dipped into this mixture, cured leaf absorbs it. These materials are then twisted into strands and allowed to dry. In India, betel nut may be mixed with tobacco leaf to make a chewing tobacco.

Dark air-cured and fire-cured tobaccos are powdered, flavored, and variously packaged to make snuff. The consumer places the snuff between the lower lip and gum, inhales a pinch into the nostril, or dips a moistened brush into the snuff and places the brush between the cheek and gum.

Prevalence of Snuff Use and Tobacco Chewing

Only a small percentage of the United States population chews tobacco (Table 2), and an even smaller percentage uses snuff (*91*, *92*). Use of these products is more frequent in males than in females, and usage is relatively stable.

The combination of the low prevalence of snuff use and tobacco chewing and the low incidence of oral cancer in the U.S. makes it difficult to accumulate the large numbers of subjects necessary for an adequate epidemiologic study. Many of those who now use snuff or chew tobacco are either current or former smokers and, therefore, are likely to obscure an independent effect of snuff or chewing tobacco. Finally, such use involves a very small percentage of the population ethnically, geographically, and culturally different from the general population, which makes it difficult to compare incidence rates with the general population.

Because of these problems, many of the studies on tobacco chewing have been done in Asia, where the prevalence of both oral cancer and tobacco chewing is higher. The validity of applying those results to the United States is questionable, however, because of differences in the type of tobacco chewed, nutritional status, and social habits.

Benign Oral Lesions and Oral Cancer

A population of 15,000 snuff users, 75 percent female, from a large clinic in the southern U.S., was examined by Smith, et al. (*117*) for oral lesions. In most patients no mucosal abnormalities were found, even in the areas of the mouth where the tobacco quid was usually held. Only

1,751 (11.7 percent) demonstrated any mucosal change, and only 157 had lesions suspicious enough to biopsy. The biopsies showed early epithelial changes, such as atrophy, but none of the biopsies showed changes consistent with dyskeratosis or malignancy. Of the 1,751 patients who showed some tissue change by visual examination and had cytologic examinations performed, 1,502 had normal findings, 12 had unsatisfactory smears, and 237 had benign hyperkeratosis. Seventy-five percent of the subjects were followed with repeated cytologic smears at 6-month intervals for 5 1/2 years, and none showed any mucosal changes different from the original testing. The conclusion was that snuff is not a risk factor for oral cancer and is not associated with an excess incidence of other oral lesions.

Roed-Petersen and Pindborg (*103a*), who studied 450 Danish patients with oral leukoplakias, of whom 32 used snuff, were unable to show any difference between snuff-associated leukoplakias and other leukoplakias in degree of dysplasia observed histologically or in malignant development.

In contrast to these negative studies, a number of studies from Asia have found an association between tobacco chewing and oral lesions, but, again, questions of application to an American population arise. Mehta, et al. (*84*), conducted a house-to-house survey of 101,761 villagers in the Poona district of India and found a prevalence of leukoplakia of 1.18 percent in male chewers of tobacco, and 1.84 percent in female chewers. Nonchewers had rates of 0.05 percent for males and 0.04 percent for females. Smokers and those with mixed habits had rates higher than persons who just chewed tobacco. Smith, et al. (*118*) found an increased prevalence of leukoplakia in tobacco chewers compared to nonchewers among 57,518 industrial workers of Gujarat, but none of the tobacco-chewing subjects had developed oral cancer during a 2-year follow-up (*116*). Mehta, et al. (*84*) also found an increased prevalence of leukoplakia in Bombay policemen, but found that the lesions in tobacco chewers tended to regress, whereas lesions in smokers did not.

Jussawalla and Deshpande (*67*) conducted a retrospective study of 2,005 oral cancer patients and matched controls. They found chewing to be associated with an increased risk of cancer of the anterior two-thirds of the tongue, alveolus, buccal mucosa, hard palate, base of the tongue, tonsil, oropharynx, hypopharynx, and esophagus. The risk was greatest for sites where the bolus was retained for a significant length of time, and the locations of greatest risk were considerably different from the sites affected in smokers. They felt that this was due to the different exposures experienced by smokers and chewers. Soda (*119*) also found an excess risk of oral cancer in chewers with a different distribution of lesion sites between chewers and smokers. Shanta and Krishnamurthi (*114*), Sanghvi, et al. (*107*), and Paymaster (*98*) have also found an association between oral cancer and tobacco habits,

especially the use of "pan" consisting of green leaf in which sliced betel nut, tobacco dust, slaked lime, liquified catechu, and other spices are rolled.

In summary, there does seem to be an association between tobacco chewing and leukoplakia and oral cancer in Asia, but it is not clear that the same risk holds true in the United States due to a difference in the tobacco being chewed and to differences in the nutritional status and other characteristics of the population.

Conclusions

Pipe and cigar smokers in the United States as a group experience overall mortality rates that are slightly higher than those of nonsmokers, but at rates substantially lower than those of cigarette smokers. This appears to be due to the fact that the total exposure to smoke that a pipe or cigar smoker receives from these products is relatively low. The typical cigar smoker smokes fewer than 5 cigars a day and the typical pipe smoker consumes less than 20 pipefuls a day. Most pipe and cigar smokers report that they do not inhale the smoke. Those who do, say they inhale infrequently and only slightly.

As a result, the harmful effects of cigar and pipe smoking appear to be largely limited to those sites which are exposed to the smoke of these products. Mortality rates from cancer of the oral cavity, intrinsic and extrinsic larynx, pharynx, and esophagus are approximately equal in users of cigars, pipes, and cigarettes. Inhalation is evidently not necessary to expose these sites to tobacco smoke, and these sites account for only about 5 percent of the cancer mortality among men.

Coronary heart disease, lung cancer, emphysema, and chronic bronchitis clearly are associated with cigarette smoking; but for cigar and pipe smokers, death rates from these diseases are not greatly elevated above the rates of nonsmokers. These diseases seem to depend on moderate to deep inhalation to bring the smoke into direct contact with the tissue at risk or to allow certain constituents, such as carbon monoxide, to be systematically absorbed through the lungs or to affect the temporal patterns of absorption of other constituents, such as nicotine, that can be absorbed either through the oral mucosa or through the lungs. Evidence from countries where smokers tend to consume more cigars and inhale them to a greater degree than in the United States indicates that rates of lung cancer become elevated to levels approaching those of cigarette smokers.

Data on the chemical constituents of cigar, pipe, and cigarette smoke suggest that the composition of these products is similar. Pipe and cigar smoke, however, tends to be more alkaline than cigarette smoke, and fermented tobaccos commonly used in pipes and cigars contain less reducing sugars than the rapidly dried varieties commonly used in cigarettes.

Experimental evidence suggests little difference between the tumorigenic activities of tars obtained from cigar or cigarette tobaccos. Malignant skin tumors appear somewhat more rapidly and in larger numbers in animals whose skin has been painted with cigar tars than in those animals painted with cigarette tars.

It must be concluded that some risk exists from smoking cigars and pipes, as currently used in the United States, but for most diseases the risk is small relative to the enormous risk of smoking cigarettes. Nevertheless, changes in patterns of usage that would bring about increased exposure either through increased use of cigars and pipes or increased inhalation of pipe and cigar smoke have the potential of producing risks similar to those now incurred by cigarette smokers.

Tobacco chewing is associated with an increased risk of leukoplakia and oral cancer in Asian populations, but the risk for populations in the United States is not clear. An increased risk of oral leukoplakia associated with snuff use in the U.S. has not been demonstrated.

Other Forms of Tobacco Use: References

(1) ABELIN, T., GSELL, O.R. Relative risk of pulmonary cancer in cigar and pipe smokers. Cancer 20(8): 1288-1296, August 1967.

(2) ALLIBONE, A., FLINT, F.J. Bronchitis, aspirin, smoking, and other factors in the aetiology of peptic ulcer. Lancet 2(7039): 179-182, July 26, 1958.

(4) ARMITAGE, A.K., TURNER, D.M. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. Nature 226(5252): 1231-1232, June 27, 1970.

(5) ASHFORD, J.R., BROWN, S. DUFFIELD, D.P., SMITH, C.S., FAY, J.W.J. The relation between smoking habits and physique, respiratory symptoms, ventilatory function, and radiological pneumoconiosis amongst coal workers at three Scottish collieries. British Journal of Preventive and Social Medicine 15: 106-117, 1961.

(6) AUERBACH, O., GARFINKEL, L., HAMMOND, E.C. Relation of smoking and age to findings in lung parenchyma: A microscopic study. Chest 65(1): 29-35, January 1974.

(7) AUERBACH, O., HAMMOND, E.C., GARFINKEL, L. Histologic changes in the larynx in relation to smoking habits. Cancer 25(1): 92-104, January 1970.

(8) AUERBACH, O., STOUT, A.P., HAMMOND, E.C., GARFINKEL, L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. New England Journal of Medicine 267(3): 111-125, July 19, 1962.

(9) AUERBACH, O., STOUT, A.P., HAMMOND, E.C., GARFINKEL, L. Histologic changes in esophagus in relation to smoking habits. Archives of Environmental Health 11: 4-15, July 1965.

(10) AUERBACH, O., STOUT, A.P., HAMMOND, E.C., GARFINKEL, L. Smoking habits and age in relation to pulmonary changes. Rupture of alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. New England Journal of Medicine 269: 1045-1054, November 14, 1963.

(11) BEST, E.W.R., MCGREGOR, J.T. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966, 137 pp.

(12) BOAKE, W.C. A study of illness in a group of Cleveland families. XVIII. Tobacco smoking and respiratory infections. New England Journal of Medicine 259(26): 1245-1249, December 25, 1958.

(14) BOWER, G. Respiratory symptoms and ventilatory function in 172 adults employed in a bank. American Review of Respiratory Disease 83: 684-689, 1961.

(15) BRADSHAW, E., SCHONLAND, M. Oesophageal and lung cancers in Natal African males in relation to certain socio-economic factors. An analysis of 484 interviews. British Journal of Cancer 23(2): 275-284, June 1969.

(16) BRODERS, A.C. Squamous-cell epithelioma of the lip. A study of Five hundred and thirty-seven cases. Journal of the American Medical Association 74(10): 656-664, March 6, 1920.

(17) BROSS, I., TIDINGS, J. Switching from cigarettes to small cigars–is it likely to reduce the health hazards of smoking? Paper presented at the Sixty-Fourth Annual Meeting of the American Association for Cancer Research, Atlantic City, N.J., April 11-13, 1973. Proceedings of the American Association for Cancer Research 14: 21, March 1973. (Abstract)

(18) BRUNNEMANN, K.D., HOFFMANN, D. Chemical studies on tobacco smoke. XXIV. A quantitative method for carbon monoxide and carbon dioxide in cigarette and cigar smoke. Journal of Chromatographic Science 12(2): 70-75, February 1974.

(19) BRUNNEMANN, K.D., HOFFMANN, D. The pH of tobacco smoke. Food and Cosmetics Toxicology 12: 115-124, 1974

(20) BUELL, P., DUNN, J.E., JR., BRESLOW, L. Cancer of the lung and Los Angeles-type air pollution. Prospective study. Cancer 20(12): 2139-2147, December 1967.

(21) CAMPBELL, J.M., LINDSEY, A.J. Polycyclic hydrocarbons in cigar smoke. British Journal of Cancer 11: 192-195, 1957.

(22) CASTLEDEN, C.M., COLE, P.V. Inhalation of tobacco smoke by pipe and cigar smokers. Lancet 2(7819): 21-22, July 7, 1973.

(23) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. Archives of Environmental Health 18(6): 934-940, June 1969.

(24) COMSTOCK, G.W., BROWNLOW, W.J., STONE, R.W., SARTWELL, P.E. Cigarette smoking and changes in respiratory findings. Archives of Environmental Health 21(1): 50-57, July 1970.

(25) COWIE, J., BALL, K.P., SILLETT, R.W. Changing to cigar smoking. Postgraduate Medical Journal 49(576): 707-710, October 1973.

(26) COWIE, J., SILLETT, R.W., BALL, K.P. Carbon-monoxide absorption by cigarette smokers who change to smoking cigars. Lancet 1(7811): 1033-1035, May 12, 1973.

(27) CRONINGER, A.B., GRAHAM, E.A., WYNDER, E.L. Experimental production of carcinoma with tobacco products. V. Carcinoma induction in mice with cigar, pipe, and all-tobacco cigarette tar. Cancer Research 18(11): 1263-1271, December 1958.

(28) DALHAMN, T., RYLANDER, R. Ciliotoxicity of cigar and cigarette smoke. Archives of Environmental Health 20(2): 252-253, February 1970.

(29) DAVIES, R.F., DAY, T.D. A study of the comparative carcinogenicity of cigarette and cigar smoke condensate on mouse skin. British Journal of Cancer 23(2): 363-368, June 1969.

(30) DAWBER, T.R. The interrelationship of tobacco smoke components to hyperlipidemia and other risk factors. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, pp. 285-292.

(31) DAWBER, T.R., KANNEL, W.B., REVOTSKIE, N., STOKES, J., III, KAGAN, A., GORDON, T. Some factors associated with the development of coronary heart disease. Six years' follow-up experience in the Framingham study. American Journal of Public Health and the Nation's Health 49(10): 1349-1356, October 1959.

(32) DENSEN, P.M., JONES, E.W., BASS, H.E., BREUER, J. A survey of respiratory disease among New York City postal and transit workers. I. Prevalence of symptoms. Environmental Research 1(3): 262-286, November 1967.

(33) DOLL, R., HILL, A.B. Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 205-215.

(34) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors (Part 1). British Medical Journal 1(5395): 1399-1410, May 30, 1964.

(35) DOLL, R. HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors (Concluded). British Medical Journal 1(5396): 1460-1467, June 6, 1964.

(36) DOLL, R., HILL, A.B. A study of the aetiology of carcinoma of the lung. British Medical Journal 2: 1271-1286, December 13, 1952.

(37) DOLL, R., JONES, F.A., PYGOTT, F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet 1(7022): 657-662, March 29, 1958.

(38) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2(6051): 1525-1536, December 25, 1976.

(39) DOYLE, J.T., DAWBER, T.R., KANNEL, W.B., KINCH, S.H., KAHN, H.A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, NY,..., and Framingham, Mass, Studies. Journal of the American Medical Association 190(10): 886-890, December 7, 1964.

(40) DUNN, J.E., JR., LINDEN, G., BRESLOW, L. Lung cancer mortality experience of men in certain occupations in California. American Journal of Public Health and the Nation's Health 50(10): 1475-1487, October 1960.

(41) EBENIUS, B. Cancer of the lip. A clinical study of 778 cases with particular regard to predisposing factors and radium therapy. Acta Radiologica 24 (Supplement 48): 1-232, 1943.

(42) EDWARDS, F., MCKEOWN, T., WHITFIELD, A.G.W. Association between smoking and disease in men over sixty. Lancet 1(7065): 196-200, January 24, 1959.

(44) FRANKENBURG, W.G. Chemical changes in the harvested tobacco leaf. Part I. Chemical and enzymic conversions during the curing process. Advances in Enzymology 6: 309-387, 1946.

(45) FRANKENBURG, W.G. Chemical changes in the harvested tobacco leaf. Part II. Chemical and enzymic conversions during fermentation and aging. Advances in Enzymology 10: 325-441, 1950.

(46) GOLDMAN, A.L. Cigar inhaling. American Review of Respiratory Disease 113(1): 87-89, January 1976.

(47) GOLDSMITH, J.R., HECHTER, H.H., PERKINS, N.M., BORHANI, N.O. Pulmonary function and respiratory findings among longshoremen. American Review of Respiratory Diseases 86(6): 867-874, December 1962.

(48) HAENSZEL, W., HOUGEN, A. Prevalence of respiratory symptoms in Norway. Journal of Chronic Diseases 25(9): 519-544, September 1972.

(50) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 127-204.

(51) HAMMOND, E.C., GARFINKEL, L. The influence of health on smoking habits. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 269-285.

(52) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. I. Total mortality. Journal of the American Medical Association 166(10): 1159-1172, March 8, 1958.

(53) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. Journal of the American Medical Association 166(11): 1294-1308, March 15, 1958.

(54) HARKE, H.-P. The problem of "passive smoking". Muenchener Medizinische Wochenschrift 112(51): 2328-2334, December 18, 1970.

(58) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. A report on five years of follow-up. Presented at the American Cancer Society's Fourteenth Science Writers' Seminar, Clearwater Beach, Florida, March 27, 1972, 15 pp.

(60) HOFFMANN, D., RATHKAMP, G., WYNDER, E.L. Comparison of the yields of several selected components in the smoke from different tobacco products. Journal of the National Cancer Institute 31(3): 627-637, September 1963.

(62) HOMBURGER, F., TREGER, A., BAKER, J.R. Mouse-skin painting with smoke condensates from cigarettes made of pipe, cigar, and cigarette tobaccos. Journal of the National Cancer Institute 31(6): 1445-1459, December 1963.

(63) HOOD, B., TIBBLIN, G., WELIN, G., ORNDAHL, G., KORSAN-BENGTSEN, K. Myocardial infarction in early age. III. Coronary risk factors and their deficient control. Acta Medica Scandinavica 185(4): 241-251, April 1969.

(64) INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES. Primary prevention of the Atherosclerotic diseases. Atherosclerosis Study Group and Epidemiology Study Group. Circulation 42(6): A-55-A-95, December 1970.

(65) ISAAC, P.F., RAND, M.J. Cigarette smoking and plasma levels of nicotine. Nature 236(5345): 308-310, April 7, 1972.

(66) JENKINS, C.D., ROSENMAN, R.H., ZYZANSKI, S.J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1140-1155, December 1968.

(67) JUSSAWALLA, D.J., DESHPANDE, V.A. Evaluation of cancer risk in tobacco chewers and smokers: An epidemiologic assessment. Cancer 28(1): 244-252, July 1971.

(68) KAHN, A., RUTLEDGE, R.B., DAVIS, G.L., ALTES, J.A., GANTNER, G.E., THORNTON, C.A., WALLACE, N.D., FERGUSON, S.S. A Study of Carbon Monoxide Sources in the St. Louis Metropolitan Population and Some Policy Implications. CUERS Report No. 4. Edwardsville, Illinois, Southern Illinois University at Edwardsville, Center for Urban and Environmental Research and Services, September 1975, 105 pp.

(69) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph No. 19. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, January 1966, pp. 1-125.

(70) KELLER, A.Z. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. American Journal of Epidemiology 91(5): 486-499, May 1970.

(71) KELLER, A.Z. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. Cancer 20(6): 1015-1022, June 1967.

(72) KENSLER, C.J. The pharmacology of tobacco smoke effects of chronic exposure. In: James, G., Rosenthal, T. (Editors). Tobacco and Health. Springfield, Illinois, Charles C. Thomas, 1962, pp. 5-20.

(75) KESTELOOT, H., VAN HOUTE, O. An epidemiologic survey of arterial blood pressure in a large male population group. American Journal of Epidemiology 99(1): 14-29, January 1974.

(76) KNUDTSON, K.P. The pathologic effects of smoking tobacco on the trachea and bronchial mucosa. American Journal of Clinical Pathology 33(4): 310-317, April 1960.

(77) KOULUMIES, M. Smoking and pulmonary carcinoma. Acta Radiologica 39(3): 255-260, March 1953.

(78) KUHN, H. A comparative study of cigarette and cigar smoke. In: Proceedings of the Fourth International Tobacco Scientific Congress, The National Tobacco Board of Greece, Athens, September 19-26, 1966, pp. 967-971.

(80) LEVIN, M.L., GOLDSTEIN, H., GERHARDT, P.R. Cancer and tobacco smoking. A preliminary report. Journal of the American Medical Association 143(4): 336-338, May 27, 1950.

(81) LOMBARD, H.L., SNEGIREFF, L.S. An epidemiological study of lung cancer. Cancer 12(2): 406-413, March/April 1959.

(82) MARTINEZ, I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. Journal of the National Cancer Institute 42(6): 1069-1094, June 1969.

(83) MARTINEZ, I. Retrospective and prospective study of carcinoma of the esophagus, mouth, and pharynx in Puerto Rico. Boletin de la Asociacion Medica de Puerto Rico 62(6): 170-178, June 1970.

(84) MEHTA, F.S., SHROFF, B.C., GUPTA, P.C., DAFTARY, D.K. Oral leukoplakia in relation to tobacco habits. A ten-year follow-up study of Bombay policemen. Oral Surgery, Oral Medicine, Oral Pathology 34(3): 426-433, September 1972.

(85) MILLS, C.A., PORTER, M.M. Tobacco smoking and automobile-driving stress in relation to deaths from cardiac and vascular causes. American Journal of the Medical Sciences 234(1): 35-43, July 1957.

(86) MILLS, C.A., PORTER, M.M. Tobacco smoking habits and cancer of the mouth and respiratory system. Cancer Research 10: 539-542, 1950.

(87) MILLS, C.A., PORTER, M.M. Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. Cancer Research 17(6): 981-990, July 1957.

(88) NAEYE, R.L. Structural features in Appalachian coal workers. In: Key, M.M., Kerr, L.E., Bundy, M. (Editors). Pulmonary Reactions to Coal Dust. A Review of U.S. Experience. New York, Academic Press, 1971, pp. 93-110.

(90) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Use of Tobacco. Practices, Attitudes, Knowledge, and Beliefs, United States—Fall 1964 and Spring 1966. U.S. Department of Health, Education, and Welfare, Public Health Service, National Clearinghouse for Smoking and Health, July 1969, 807 pp.

(91) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, DHEW Publication No. (HSM) 73-8227, June 1973, 129 pp.

(92) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1976.

(93) OSMAN, S., BARSON, J. Hydrocarbons of cigar smoke. Tobacco 159(24): 30-32, December 11, 1964.

(94) OSMAN, S., SCHMELTZ, I., HIGMAN, H.C., STEDMAN, R.L. Volatile phenols of cigar smoke. Tobacco 157(9): 30-32, August 30, 1963.

(95) PASSEY, R.D., BLACKMORE, M. Biological effects of cigar and cigarette smoke. British Empire Cancer Campaign for Research, Annual Report 44(Part 2): 6, 1966.

(96) PASSEY, R.D., BLACKMORE, M. The causation of lung cancer. Some experimental biological effects of cigar and cigarette smoke. Thorax 22(3): 290, May 1967. (Abstract)

(97) PASSEY, R.D., BLACKMORE, M., WARBRICK-SMITH, D., JONES, R. Smoking risks of different tobaccos. British Medical Journal 4(5781): 198-201, October 23, 1971.

(98) PAYMASTER, J.C. Some observations on oral and pharyngeal carcinomas in the State of Bombay. Cancer 15(3): 578-583, May/June 1962.

(99) PERNU, J. An epidemiological study on cancer of the digestive organs and respiratory system. A study based on 7,078 cases. Annales Medicinae Internae Fenniae 49(Supplement 33): 1-117, 1960.

(100) RANDIG, K. Untersuchungen zur Aetiologie des Bronchialkarzinoms (Investigations on the aetiology of bronchial carcinoma). Oeffentliche Gesundheitsdienst 16(9): 305-313, December 1954.

(*101*) REA, J.N., TYRER, P.J., KASAP, H.S., BERESFORD, S.A.A. Expired air carbon monoxide, smoking, and other variables. A community study. British Journal of Preventive and Social Medicine 27(2): 114-120, May 1973.

(*102*) RIMINGTON, J. Chronic bronchitis, smoking and social class. A study among working people in the towns of Mid and East Cheshire. British Journal of Diseases of the Chest 63(4): 193-205, October 1969.

(*103*) ROE, F.J.C., CLACK, J.C., BISHOP, D., PETO, R. Comparative carcinogenicity for mouse-skin of smoke condensates prepared from cigarettes made from the same tobacco cured by two processes. British Journal of Cancer 24(1): 107-121, March 1970.

(*103a*) ROED-PETERSEN, B., PINDBORG, J.J. A study of Danish snuff-induced oral leukoplakias. Journal of Oral pathology 2: 301-313, 1973

(*104*) ROGOT, E. Smoking and mortality among U.S. veterans. Journal of Chronic Diseases 27: 189-203, 1974.

(*105*) SADOWSKY, D.A., GILLIAM, A.G., CORNFIELD, J. The statistical association between smoking and carcinoma of the lung. Journal of the National Cancer Institute 13(5): 1237-1258, April 1953.

(*106*) SANDERUD, K. Squamous metaplasia of the respiratory tract epithelium: An autopsy study of 214 cases. II. Relation to tobacco smoking, occupation and residence. Acta Pathologica et Microbiologica Scandinavica 43: 47-61, 1958.

(*107*) SANGHVI, L.D., RAO, K.C.M., KHANOLKAR, V.R. Smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. British Medical Journal 1(4922): 1111-1114, May 7, 1955.

(*108*) SCHIEVELBEIN, H., EBERHARDT, R. Cardiovascular actions of nicotine and smoking. Journal of the National Cancer Institute 48(6): 1785-1794, June 1972.

(*109*) SCHIMMLER, W., NEFF, C., SCHIMERT, G. Risikofaktoren und Herzinfarkt. Eine retrospektive Studie (Risk factors and myocardial infarct. A retrospective study). Muenchener Medizinische Wochenschrift 110(27): 1585-1594, July 5, 1968.

(*110*) SCHREK, R., BAKER, L.A., BALLARD, G.P., DOLGOFF, S. Tobacco smoking as an etiologic factor in disease. I. Cancer. Cancer Research 10(1): 49-58, January 1950.

(*111*) SCHWARTZ, D., DENOIX, P.-F. L'enquete Francaise sur l'etiologie du cancer broncho-pulmonaire. Role du tabac (French investigation on the etiology of bronchopulmonary cancer. Role of tobacco). Semaine des Hopitaux de Paris 33(62/7): 3630-3643, October 30, 1957.

(*113*) SCHWARTZ, D., FLAMANT, R., LELLOUCH, J., DENOIX, P.-F. Results of a French survey on the role of tobacco, particularly inhalation, in different cancer sites. Journal of the National Cancer Institute 26(5): 1085-1108, May 1961.

(*114*) SHANTA, V., KRISHNAMURTHI, S. A study of aetiological factors in oral squamous cell carcinoma. British Journal of Cancer 13(3): 381-388, September 1959.

(*115*) SHAPIRO, S., WEINBLATT, E., FRANK, C.W., SAGER, R.V. Incidence of coronary heart disease in a population insured for medical care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. American Journal of Public Health and the Nation's Health 59 (6, Supplement, Part 2): 1-101, June 1969.

(*116*) SILVERMAN, S., JR., BHARGAVA, K., MANI, N.J., SMITH, L.W., MALAOWALLA, A.M. Malignant transformation and natural history of oral leukoplakia in 57,518 industrial workers of Gujarat, India. Cancer 38(4): 1790-1795, October 1976.

(*117*) SMITH, J.F., MINCER, H.A., HOPKINS, K.P., BELL, J. Snuff-dipper's lesion. A cytological and pathological study in a large population. Archives of otolaryngology 92(5): 450-456, November 1970.

(*118*) SMITH, L.W., MALAOWALLA, A.M., BHARGAVA, K., MANI, N.J. A report on the study of oral cancer and precancerous lesions among 57,518 industrial workers of Gujarat, Phase I. Oral Cancer Research Project, Government Dental College and Hospital, Ahmedabad, Gujarat, India, September 1, 1973.

(*119*) SODA, T. Cancer of oral cavity. Asian Medical Journal 12(10): 228-234, October 1969.

(*120*) SPAIN, D.M., NATHAN, D.J. Smoking habits and coronary atherosclerotic heart disease. Journal of the American Medical Association 177(10): 683-688, September 9, 1961.

(*121*) STASZEWSKI, J. Palenie a rak wargi, jamy ustnej, migdalkow i krtani (Tobacco smoking and its relation to cancer of the mouth, tonsils and larynx). Nowotwory 10(2): 121-132, 1960.

(*123*) STOCKS, P. Cancer incidence in North Wales and Liverpool region in relation to habits and environment. British Empire Cancer Campaign Thirty-fifth Annual Report Covering the Year 1957, Supplement to Part II, 1957, 156 pp.

(*125*) TIBBLIN, G. High blood pressure in men aged 50—A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1-84, 1967.

(*126*) TODD, G.F. (Editor). Statistics of Smoking in the United Kingdom. Research Paper I, 4th Edition. London, Tobacco Research Council, 1966, 103 pp.

(*127*) TODD, G.F. (Editor) Statistics of Smoking in the United Kingdom. Research Paper 1, 5th Edition. London, Tobacco Research Council, 1969, 124 pp.

(*128*) TODD, G.F. (Editor). Statistics of Smoking in the United Kingdom. Research Paper I, 6th Edition. London, Tobacco Research Council, 1972, 132 pp.

(*129*) TROWELL, O.A. The relation of tobacco smoking to the incidence of chronic duodenal ulcer. Lancet 1: 808-809, April 14, 1934.

(*130*) UNITED STATES CODE OF FEDERAL REGULATIONS. Title 26 (Internal Revenue Service) Part 270—Manufacture of Cigars and Cigarettes. (As adopted at 26 F.R. 8173, effective October 1, 1961). B(270)3-B(270)5, October 31, 1970.

(*131*) U.S. DEPARTMENT OF THE TREASURY. Revenue Ruling 69-198. Internal Revenue Cumulative Bulletin: 359, 1969-1.

(*132*) VAN BUCHEM, F.S.P. Serum lipids, nutrition and atherosclerotic complications in man. Acta Medica Scandinavica 181(4): 403-416, 1967.

(*133*) VILLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen Infarktpatienten und Kontrollpersonen in der Ostschweiz (The infarct profile. Differences between infarct patients and control persons in East Switzerland). Schweizerische Medizinische Wochenschrift 96(23): 748-758, 1966.

(*134*) WEIR, J.M., DUNN, J.E., JR. Smoking and mortality: A prospective study. Cancer 25(1): 105-112, January 1970.

(*135*) WICKEN, A.J. Environmental and Personal Factors in Lung Cancer and Bronchitis Mortality in Northern Ireland, 1960-62. Research Paper 9. London, Tobacco Research Council, 1966, 84 pp.

(*136*) WYNDER, E.L., BROSS, I.J. A study of etiological factors in cancer of the esophagus. Cancer 14(2): 389-413, March/April 1961.

(*137*) WYNDER, E.L., BROSS, I.J., DAY, E. A study of environmental factors in cancer of the larynx. Cancer 9(1): 86-110, January/February 1956.

(*138*) WYNDER, E.L., BROSS, I.J., FELDMAN, R.M. A study of the etiological factors in cancer of the mouth. Cancer 10(6): 1300-1323, November/December 1957.

(*139*) WYNDER, E.L., CORNFIELD, J. Cancer of the lung in physicians. New England Journal of Medicine 248(11): 441-444, March 12, 1953.

(*140*) WYNDER, E.L., GRAHAM, E.A. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: A study of six hundred and eighty-four proved cases. Journal of the American Medical Association 143(4): 329-336, May 27, 1950.

(*141*) WYNDER, E.L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, 730 pp.

(*142*) WYNDER, E.L., HULTBERG, S., JACOBSSON, F., BROSS, I.J. Environmental factors in cancer of the upper alimentary tract. A Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. Cancer 10(3): 470-487, May/June 1957.

(*143*) WYNDER, E.L., LEMON, F.R., MANTEL, N. Epidemiology of persistent cough. American Review of Respiratory Diseases 91(5): 679-700, May 1965.

(*144*) WYNDER, E.L., MABUCHI, K., BEATTIE, E.J., JR. The epidemiology of lung cancer. Recent trends. Journal of the American Medical Association 213(13): 2221-2228, September 28, 1970.

(*145*) WYNDER, E.L., NAVARRETE, A., AROSTEGUI, G.E., LLAMBES, J.L. Study of environmental factors in cancer of the respiratory tract in Cuba. Journal of the National Cancer Institute 20(4): 665-673, April 1958.

(*146*) WYNDER, E.L., WRIGHT, G. A study of tobacco carcinogenesis. I. The primary fractions. Cancer 10(2): 255-271, March/April 1957.

14. CONSTITUENTS OF TOBACCO SMOKE.

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Introduction

Our understanding of cigarette smoke—its generation, physical composition, toxicity, pharmacology, behavioral effects, and techniques to modify its composition—has advanced considerably since the last review on cigarette smoke in the 1972 report on *The Health Consequences of Smoking.*

Technology has played an important role in advancing our understanding of cigarettes and their resulting smoke. One aspect in particular that has improved our understanding is the development of new instrumentation and miniaturization of analytical tools. For example, Baker (*1*) reported on the use of a fiber-optic probe system for determining and differentiating solid and gas temperatures within the coal of a burning cigarette. The advance made it possible for Osdene (*5*) to define more clearly the reaction mechanisms that occur in the burning cigarette. Such information should make intelligible modification of cigarettes and cigarette smoke more of a science and less of an art. Another example has been the development and refinement of the Thermal Energy Analyzer, which allows scientists to quantify the level of N-nitrosamines in cigarette smoke (*2, 3*). The development of reconstituted tobacco sheet technology, designed, at least in part, for better utilization of the tobacco plant in cigarette manufacture, has given manufacturers additional control over the delivery of certain constituents of cigarette smoke, permitting alteration of the combustion process and consequently the levels of smoke condensate produced (*4*).

In this chapter we will consider the tobacco as a raw material, how it is made into cigarettes, the cigarette smoke generation process, the composition of cigarette smoke, physiological responses to cigarette smoke, the pharmacology of nicotine as a component of cigarette smoke, and efforts to define less hazardous cigarettes through cigarette smoke modification. Also, consideration will be given to the effects of smoke characteristics on smoking behavior and, therefore, on the dose inhaled by man and experimental animals.

Introduction: References

(*1*) BAKER, R.R. Temperature distribution inside a burning cigarette. Nature 247: 405-406, February 8, 1974.

(*2*) BRUNNEMANN, K.D., YU, L., HOFFMANN, D. Assessment of carcinogenic volatile N-nitrosamines in tobacco and in mainstream and sidestream smoke from cigarettes. Cancer Research 37(9): 3218-3222, September 1977.

(*3*) FINE, D.H., RUFEH, F., LIEB, D., ROUNBEHLER, D.P. Description of the thermal energy analyzer (TEA) for trace determination of volatile and nonvolatile N-nitroso compounds. Analytical Chemistry 47(7): 1188-1191, June 1975.

(*4*) MATTINA, C.F., SELKE, W.A. Reconstituted tobacco sheets. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume 1. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76-1221, 1976, pp. 67-72.

(*5*) OSDENE, T.S. Reaction mechanisms in the burning cigarette. In: Fina, N. J. (Editor). The Recent Chemistry of Natural Products, Including Tobacco: Proceedings of the Second Philip Morris Science Symposium. New York, Philip Morris, Inc., 1976, pp. 42-59.

The Cigarette: Composition and Construction

Tobacco, a member of the nightshade family (*28*), is an important agricultural and economic crop that is produced in almost all parts of the world and used in nearly every country. The tobacco plant *Nicotiana tabacum L.* is a native plant of the Americas and is used primarily for the manufacture of cigarettes, cigars, pipe tobaccos, and to a lesser extent for oral consumption. Its dominance for smoking use is generally attributed to a few of its combustion products which induce physiological effects to be discussed later in this chapter. The tobacco plant is an excellent material for research in plant and biological science (*24*).

The characteristics of tobacco smoke are primarily functions of the physical and chemical properties of the leaf; hence, one can approximate the levels of nicotine, tar, and other smoke components based on certain physical and chemical properties of the leaf (*32*). Wide variations in botanical, chemical, and physical characteristics of leaf tobacco are found among the various species, types, varieties, strains, and grades; the quality of the tobacco leaves is predetermined by genetic makeup and subsequently influenced by weather conditions, cultural practices, soil properties, curing, and other post-harvest handling practices (*27*).

The relatively sweet Orinoco-type tobacco, *Nicotiana tabacum L.* was successfully introduced for cultivation in Jamestown, Virginia in 1611 and into Europe, Asia, and South Africa by the early part of the 17th century. Worldwide production has increased in recent years (*26*). During the years 1973 through 1975, worldwide total acreages of tobacco harvested were 10.1, 10.5, and 10.7 million acres; yields per acre were 1,054, 1,080, and 1,088 pounds; and total production was 10.7, 11.4, and 11.7 billion pounds, respectively (*26*).

Asian countries lead the world in tobacco production followed by North America, Europe, and South America (*26*). The highest yield per acre appears to be in the People's Republic of China, followed by the United States. The U.S. production for all types of tobacco in 1975 was 2.19 billion pounds. Table 1 summarizes U.S. tobacco production.

Since 1964, when the first Surgeon General's Report on Smoking and Health was published, there has been a gradual and continued increase in the number of cigarettes manufactured in the United States (*35*). It should be noted, however, that per capita consumption has decreased from 11.53 pounds in 1964 to 9.14 pounds in 1975, and total tobacco consumption has declined from 1.41 billion pounds in 1964 to 1.35 billion pounds in 1975. This reduction is due largely to the reduced waste of the tobacco biomass. These results are described in Figure 1.

Figure 2 describes the tobacco use for men and women 21 and older for the years 1970 and 1975. It should be noted that there was an

TABLE 1.—U.S. tobacco production in 1964, 1968, and 1975 by types

Type and crop year	Acreage	Yield per acre	Production
	1,000 acres	pounds	million lbs.
Flue-cured (Types 11-14)			
1964	628	2,211	1,388
1968	533	1,841	981
1975	717	1,973	1,415
Fire-cured (Types 21-23)			
1964	32	1,716	55
1968	23	1,689	39
1975	23	1,601	37
Burley (Type 31)			
1964	307	2,022	620
1968	238	2,372	563
1975	282	2,265	639
Maryland (Type 32)			
1964	39	1,085	42
1968	29	1,100	32
1975	24	1,050	25
Dark air-cured (Type 35-37)			
1964	14	1,735	24
1968	11	1,757	19
1975	9	1,690	15
Cigar filler (Type 41-44)			
1964	31	1,683	52
1968	23	1,766	41
1975	14	1,663	23
Cigar binder (Type 51-55)			
1964	14	1,862	26
1968	9	1,821	17
1975	13	1,851	23
Cigar wrapper (Type 61-62)			
1964	14	1,530	21
1968	13	1,343	19
1975	5	1,409	8
Puerto Rican Filler (Type 46)			
1964	31	1,231	38
1968	6	1,271	8
1975	3	1,500	4
Total U. S. tobacco (Types 11-72*)			
1964	1,109	2,044	2,266
1968	885	1,941	1,718
1975	1,090	2,008	2,189

*Includes Perique
SOURCE: U.S. Department of Agriculture (*55*).

increase in the percentage consumption for males and females under 21 years old. Cigarettes are by far the largest single tobacco product.

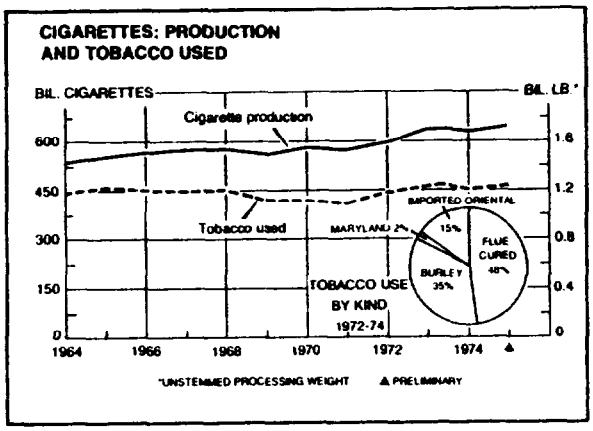


FIGURE 1.—In the United States flue-cured tobacco is the most important domestic type, with burley in second place. Note that cigarette production has increased while the tobacco used has remained about the same since 1964. This is due to use of stems, reconstituted sheets and filters in cigarette manufacture in recent years — formerly discarded as "waste".
SOURCE: Tso, T.C. (*27*).

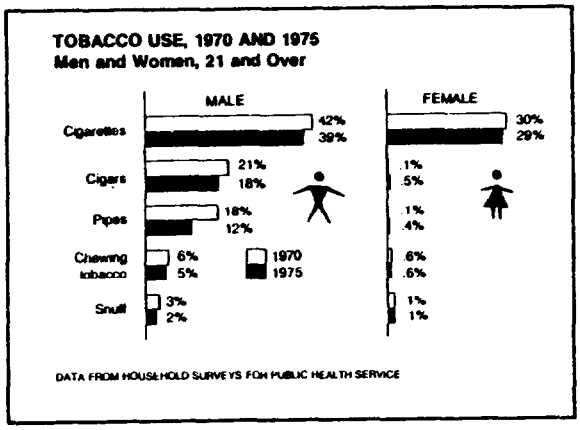


FIGURE 2.—Use of tobacco by men for cigarettes, cigars, pipes, chewing tobacco and snuff all showed a decrease in the 5-year period 1970–75. Use of tobacco by women also showed a slight drop in cigarettes, but a slight increase in use of cigars and pipes.
SOURCE: Tso, T.C. (*27*).

Types and Classes of Tobacco

There are at least 65 species within the genus *Nicotiana*. The species

Nicotiana tabacum L. is the main commercially grown species. This species has been established as a natural hybrid between *N. Sylvestris* and *N. Otophora* (*37*).

The types of tobacco generally used in smoking products are bright (flue-cured), Burley, Maryland, and cigar tobaccos, as well as oriental (aromatic) tobaccos. These types make up the bulk of the tobacco products (Table 1). Other types of tobacco exist, such as Perique, Latakia, and several Indian types, but they are not generally used in U.S. tobacco blends. Over the years, new varieties of bright, Burley, and other tobaccos have been developed that are multiple-disease resistant to specific tobacco diseases (*23*, *28*).

Within the species of *N. tabacum*, many varieties and types show wide differences in their chemical composition (*28*). Numerous germ plasms are available in the USDA collection, including approximately 1,000 tobacco introductions, 400 established varieties, and 100 breeding lines. Tso (*30*) reported that, in a preliminary examination of randomly selected samples from tobacco introductions, there was a threefold variation in sterol content, a tenfold variation in nitrate content, a thirtyfold variation in alkaloid content, and a fivefold variation in phenolic content. He concluded that greater variations probably exist among types not yet studied.

Based on methods of curing and the cultivar (a variety of tobacco within a tobacco type) used, leaf tobaccos produced in the United States are separated into the major classes shown in Table 2. There are five classes of air-cured tobacco including light air-cured, dark air-cured, and three kinds of cigar tobaccos: filler, binder, and wrapper (*26*, *28*). Filler is tobacco that makes up the bulk of a cigar, and wrapper is used for the outside covering. Binder is now used primarily for scrap chewing. Binding material for cigars is now made from reconstituted tobacco sheet (RTS). (RTS is also used in the manufacture of cigarettes, as will be discussed later.) Each of these tobaccos has specific characteristics and is produced for a specific purpose.

Under class, the subdivision is "types" (*26*, *27*), based on location of production, method of culture, and in most cases, plant cultivar. The cured leaf from each type is further subdivided into grade groups named on the basis of either principal use in manufacture or stalk position under the U.S. Government grading system. Each of the subdivisions is composed of several grades, determined by several elements of quality, such as body, texture, and color.

Physical and Chemical Characteristics

In addition to the genetic makeup, environmental factors, including mineral nutrition, soil properties, moisture supply, temperature, and light intensity, affect the chemical composition and physical properties of the leaf (*26*, *28*). The relationships among these factors and the

TABLE 2.—Classes and types of tobacco established by the U.S. Department of Agriculture

Type of curing and class	Type no.	Type name or locality
Flue-cured, Class 1	11A	Old Belt-Virginia and North Carolina
	11B	Middle Belt-Virginia and North Carolina
	12	Eastern North Carolina
	13	Border Belt-Southeastern North Carolina and South Carolina
	14	Georgia and Florida
	21	Virginia
Fire-cured, Class 2	22	Eastern-Kentucky and Tennessee Western-Kentucky and Tennessee
Air-cured		
Class 3A (light air-cured)	31	Burley
	32	Maryland
Class 3B (dark air-cured)	35	One-Sucker
	36	Green River
	37	Virginia Sun-Cured
Class 4 (cigar filler)	41	Pennsylvania Seedleaf, or Broadleaf
	42	Gebhardt
	43	Zimmer Spanish
	44	Little Dutch
	46	Puerto Rico
Class 5 (cigar binder)	51	Connecticut Broadleaf
	52	Connecticut Havana Seed
	53	New York and Pennsylvania Havana Seed
	54	Southern Wisconsin
	55	Northern Wisconsin
Class 6 (cigar wrapper)	61	Connecticut Valley Shade-Grown
	62	Georgia and Florida Shade-Grown
Miscellaneous, Class 7	72	Louisiana Perique
	77	Domestic Aromatic

SOURCE: U.S. Department of Agriculture (*36*).

tricarboxylic acid (TCA) cycle help define the smoking quality of tobacco leaves (*3*).

Smoking quality of tobacco leaf is determined to a great extent by the balance between the carbon and the nitrogen fractions (*28*). Atmospheric CO_2 is assimilated by the tobacco leaf through photosynthesis, while nitrogen is accumulated by the roots from the soil. The net result of nitrogen assimilation is, therefore, the utilization of a portion of newly photosynthesized carbon chains into the nitrogenous pool. Thus, when the nitrogen supply is abundant, more amino acids and nicotine and less sugar and starch will be synthesized. If the nitrogen supply is limited, acetate will accumulate from the TCA cycle and increase the production of carbohydrates, fats, volatile oils, resins, and polyterpines (*26, 28*). These variations will effect the resulting leaf

TABLE 3.—Approximate composition of freshly harvested tobacco leaves

Constituents	Bright cigarette tobacco	Cigar filter tobacco
	%	%
Carbohydrates	23.0	3.0
Protein	12.2	17.3
Soluble N compounds	3.3	6.7
Inorganics	12.0	14.0
Cellulose and lignin	10.0	9.5
Pentosans	2.0	3.0
Pectins	7.0	7.0
Ether-soluble resins	7.5	7.0
Tannins	2.0	2.5
Organic acids	13.0	13.0
Not identified	8.0	17.0

SOURCE: Frankenburg, W.C. (*7*).

texture, color, porosity, and combustibility. Examples include those tobaccos used in cigarette production, Turkish and bright (flue-cured), as well as cigar tobacco types. The Turkish tobacco is produced with limited supplies of nutrients and water, thus giving leaves more hydrocarbons and highly aromatic qualities (*26*). Cigar tobacco is grown with an abundant nitrogen supply yielding leaves high in protein and nicotine levels. Flue-cured tobacco is intermediary but slightly toward the carbon side. Table 3 illustrates typical differences among major constituents of bright and cigar tobacco leaves at harvest, and Table 4 describes the ranges of various constituents of the four main tobaccos used in cigarette production. Other environmental factors, such as the time of topping and the amount of sunshine (*27*), also play a role in the carbon-nitrogen balance.

The lower right portion of Figure 1 indicates that bright (or flue-cured) tobacco is the most widely used domestic type in the United States, while Burley, a light, air-cured type, ranks second in importance. Together, they account for most of the tobacco used. Typical values are flue-cured (45–75 percent), Burley (15–45 percent), Turkish (5–13 percent), and Maryland (1–7 percent) tobaccos (*26*). Some RTS is also used (*15–17*). The Standard Experimental Blend (SEB) used in the National Cancer Institute's experimental cigarettes, based on 1970 sales-weighted averages, are comparable (*15–17*).

The physical and chemical characteristics of tobacco leaf and smoke are unavoidably related to one another. Recent studies, particularly with bright tobaccos, show that characteristics such as leaf thickness, rate of leaf burn, and moisture content are significantly correlated with combustibility. Factors that promote good burning will generally

TABLE 4.—Range of chemical composition of tobacco being used in cigarettes*

Constituents	Flue-cured	Burley	Maryland	Oriental
Total nitrogen	1.00–3.00	1.50–4.50	1.25–3.00	1.40–3.50
Protein nitrogen	0.40–1.30	0.50–2.40	0.70–1.50	0.75–1.30
α-Amino nitrogen	0.08–0.45	0.10–0.50	0.08–0.36	0.10–0.54
Nicotine	0.80–3.50	0.40–4.50	0.65–2.00	0.50–1.30
Petroleum ether extractive	3.00–7.50	2.50–6.00	3.50–6.50	3.50–7.00
Starch	1.75–8.00	0.50–3.00	1.00–3.50	1.90–10.00
Soluble sugars	6.00–32.00	0.10–1.50	0.50–1.50	3.00–19.00
Nonvolatile acids**	9.00–26.00	15.00–38.00	13.00–25.00	16.00–23.00
Water-soluble acids**	2.50–5.00	0.30–3.50	0.40–3.50	-
pH (not %)	4.40–5.70	5.20–7.50	5.30–7.00	4.90–5.25

*Ranges in %.
**Milliliters of 0.1 *N* alkali per gram tobacco.
SOURCE: Darkis, F.R. (*2*).

result in lower levels of TPM in smoke, lower nicotine, cresols, volative phenols, hydrogen cyanide, and benz(*a*)anthracene, but will yield higher levels of acetaldehyde, acrolein, and carbon monoxide. The position of tobacco leaves on the stalk is known to influence greatly the resultant smoke characteristics (*37*). Present evidence shows that for higher leaf positions on the stalk, the combustibility is lower, the filling value of the tobacco is less, and the TPM, nicotine, HCN, volatile phenols, and polynuclear aromatic hydrocarbons in the mainstream smoke are higher. Thus, stalk position is an important indicator of both physical and chemical properties of the leaf and aids in interpreting precursors of the final product between leaf and smoke components. Table 5 shows some typical relationships between leaf characteristics and position on the stalk (*8*, *26*, *37*). Table 6 relates the effect of stalk positions and smoking properties (*27*). Similar data have been described by Wolf (*37*).

Culture and Harvesting Practices

Wolf (*37*) has reviewed the practices employed in tobacco culture and harvesting. A standard field practice with all domestic types of tobacco plants (except shadegrown cigar wrappers) is topping (removal of early blossoms) and suckering (removal of secondary buds) to promote the proper development in leaf size and thickness.

Priming (the removal of mature leaves at successive intervals) results in the maximum yield and quality from tobacco plants since leaves at different stalk positions mature at different stages. Depending on the type of tobacco plant and the weather conditions during harvest, there may be as many as nine primings.

Stalk-cutting is another method of harvesting, involving cutting the plant at the lowest stalk position and harvesting the entire plant at one

TABLE 5.—Stalk positions and leaf characteristics

Properties of Tobacco Types	Lower Leaves	Middle Leaves	Upper Leaves*
Flue-cured tobacco			
Cell membrane substances	Comparatively Higher	Comparatively Lower	Comparatively Lower
Total sugar	Lower	Higher	Lower
Total acid	Higher	Lower	Medium
α-amino N	Higher	Lower	Higher
Nicotine	Lower	Medium	Higher
Water-soluble N, total N	Medium	Lower	Higher
Soluble ash	Higher	Lower	Medium
Tannins, resins	Lower	Higher	Higher
pH	Higher	Lower	Lower
Air-cured Burley			
Color	Lighter	Darker	Darker
Porosity	More	Less	Less
Density	Lighter	Heavier	Heavier
Ammonium N, amino N, amido N	Lower	Medium	Higher
Nicotine N	Lower	Medium	Higher

*Not including uppermost tips.
SOURCE: Harlan, W.R. (*8*), Tso, T.C. (*27*).

TABLE 6.—Stalk positions and smoking properties

Smoking properties	Lower leaves	Upper and middle leaves
Strength (N compounds)	relatively light	relatively strong
Aromaticity (tannins, resins)	aromatic	highly aromatic
Mildness (sugars, starch, oxalic acid) and sharpness (cell membrane substances, ash constituents, citric acid)	somewhat sharp	mild

SOURCE: Harlan, W.R. (*8*), Tso, T.C. (*27*).

time. In general, Burley and Maryland tobaccos are harvested by stalk-cutting.

The application of herbicides to control weeds, fertilizers to enhance plant growth, pesticides to treat soil and control plant diseases, and insecticides may directly or indirectly leave residues on plant material; this factor must be considered when the characteristics of the tobacco leaf and smoke chemistry are examined.

Curing and Aging

The green tobacco leaf primed from the plant goes through a process known as "curing" in order to develop desirable taste and aroma for

smoke products. Several different curing processes are used to produce leaf tobacco suitable for the manufacture of a variety of tobacco products (*37*).

Curing is a process during which chemical conversions take place in the tobacco leaf. During flue-curing or air-curing, chemical conversion is dominated by hydrolytic enzymes. Disaccharides and polysaccharides are hydrolyzed to simple sugars; proteins are hydrolyzed to amino acids which undergo subsequent oxidative deamination; pectins and pentosans are at least partially hydrolyzed to pectic acid, uronic acid, and methanol. A second step occurs only in air-cured tobaccos and includes conversions such as the oxidation of simple sugars to acids, the oxidation and polymerization of certain phenolic compounds, and some decrease in alkaloids and dry weight (*26*).

As a result of years of research, numerous advances have been made in the procedures used to harvest, cure, and process tobacco. One particular development in the early 1950's was the process of manufacturing reconstituted tobacco sheets (out of tobacco scrap) in a manner analogous to paper manufacture (*13*). The process will be discussed later. The significance of the process lies in the fact that tobacco need not be harvested and cured in whole leaf form, thus suggesting new mechanized approaches to harvesting and curing.

A new curing procedure called homogenized leaf curing (HLC), developed by scientists at the U.S. Department of Agriculture, involves the homogenization, incubation, and dehydration of tobacco leaf (*4, 33*). The fundamental concept is to cause the necessary chemical changes to occur in a homogenized tobacco slurry instead of in the harvested whole leaf. The process saves considerable hand labor normally required for handling whole leaf, allows a mechanism for removal of undesirable components, and permits better control and enhancement of biochemical and chemical changes. Results have shown that the HLC method may provide smoking quality that is comparable to conventionally cured leaf but with a relatively lower biological response (*33*).

Cured, unaged tobacco is still unsuitable for manufacturing into tobacco products because it has a sharp, disagreeable odor and an undesirable aroma and produces irritating smoke with unacceptably harsh flavor (*26*). To improve these conditions, cigarette tobaccos (flue-cured, Burley, Maryland and Turkish) are subjected to a further process called aging. Aging greatly improves the aroma and other qualities desirable in smoking products. The aging process can be natural or forced, depending upon time, temperature, and humidity. A 1- to 2-year aging period is not unusual for cigarette tobaccos.

The treatment of cigar tobaccos consists of two steps (*7*). The first step is storage and the second is fermentation. Current knowledge of the chemical conversions during aging and fermentation is rather limited (*26*). The most noticeable chemical changes in the aging process

are an increase in volatile acids and a decrease in α-amino nitrogen. Flue-cured and Turkish tobaccos also exhibit a loss of reducing sugars and volatile bases other than nicotine. In fermentation, new chemical reactions appear and ongoing reactions are intensified. A decrease in tobacco alkaloids, especially nicotine, is evident (*7*). Large amounts of ammonia are produced, and amide and α-amino nitrogen levels are decreased. The pH increases because of the elimination of organic acids through oxidation and decarboxylation. It is likely that enzymes, microorganisms, and catalysts all play a part in the fermentation process (*26*).

Representative analyses of aged and cured cigarette and cigar tobaccos are shown in Tables 7 and 8. These chemical variations are the results of different varieties, cultures, fertilizers, soils, climates, and post-harvesting practices as described above.

Other Factors

Leaves from different levels on the stalk possess considerably different chemical and physical properties. For example, upper leaves possess higher nicotine, lower total sugar, higher tannins and resins, lower ash, and higher total nitrogen; lower leaves tend to contain higher total acid, higher soluble ash, and higher pH. However, not all substances are at their highest or lowest concentration in the upper and lower leaves. The leaves at the middle stalk position, for example, have the highest sugar, lowest α-amino nitrogen, lowest total acid, lowest total nitrogen, and lowest soluble ash. Selecting mature leaves at various time intervals (priming) allows maximum use of tobacco leaves and selectivity in future blending.

Because of the chemical and physical differences, leaves from various stalk positions also vary in smoke characteristics, as shown in Tables 5 and 6. Lower leaves usually deliver a lighter "strength," somewhat sharper taste, and less aromatic smoke than the upper and middle leaves (*1*). These smoking properties are largely functions of chemical composition. For example, nitrogen compounds are believed to be associated with strength; tannins and resins are associated with aromaticity; sugars, starch, and oxalic acid are associated with mildness; and cell membrane substances, ash constituents, and citric acid are associated with "sharpness" (*1*). Certain physical quality factors are also related to chemical components, as all these variables are interrelated. In a recent study with bright tobaccos (*31*), many physical variables including leaf thickness, rate of burning, leaf color, moisture content, moisture equilibrium, specific volume, and trichome numbers were found to be significantly correlated with many leaf chemical variables.

The presence of radioelements, including radium-226, lead-210 and polonium-210 have been reported in tobacco and tobacco smoke (*19*) and reviewed recently by Harley and coworkers (*9*). Contents of Po^{210} in

TABLE 7.—Representative analyses of cigarette tobaccos (leaf web after aging, moisture-free basis)

Component %[a]	Flue-cured. Type 13	Burley. Type 31	Maryland. Type 32	Turkish[b]
Total volatile bases as ammonia	0.282	0.621	0.366	0.289
Nicotine	1.93	2.91	1.27	1.05
Ammonia	0.019	0.159	0.130	0.105
Glutamine as ammonia	0.033	0.035	0.041	0.020
Asparagine as ammonia	0.025	0.111	0.016	0.058
α-Amino nitrogen as ammonia	0.065	0.203	0.075	0.118
Protein nitrogen as ammonia	0.91	1.77	1.61	1.19
Nitrate nitrogen as NO_3	trace	1.70	0.087	trace
Total nitrogen as ammonia	1.97	3.96	2.80	2.65
pH	5.45	5.80	6.60	4.90
Total volatile acids as acetic acid	0.153	0.103	0.090	0.194
Formic acid	0.059	0.027	0.022	0.079
Malic acid	2.83	6.75	2.43	3.87
Citric acid	0.78	8.22	2.98	1.03
Oxalic acid	0.81	3.04	2.79	3.16
Volatile oils	0.148	0.141	0.140	0.248
Alcohol-soluble resins	9.08	9.27	8.94	11.28
Reducing sugars as dextrose	22.09	0.21	0.21	12.39
Pectin as calcium pectate	6.19	9.91	12.41	6.77
Crude fiber	7.88	9.29	21.79	6.63
Ash	10.81	24.53	21.98	14.78
calcium as CaO	2.22	8.01	4.79	4.22
potassium as K_2O	2.47	5.22	4.40	2.33
magnesium as MgO	0.36	1.29	1.03	0.69
chlorine as Cl	0.84	0.71	0.26	0.69
phosphorus as P_2O_5	0.51	0.57	0.53	0.47
sulfur as SO_4	1.23	1.98	3.34	1.40
Alkalinity of water-soluble ash [c]	15.9	36.2	36.9	22.5

[a] In % except for pH and alkalinity.
[b] Blend of Macedonia, Smyrna, and Samsun types.
[c] Milliliters of 1N acid per 100 g tobacco.
SOURCE: Harlan, W.R. (*8*).

leaf tobacco and tobacco soil vary with the origin of the sample and methods of culture and curing (*24*). Polonium seems not to be entirely derived from radium. The plant probably takes it up from the soil or air. The general range of Po^{210} in tobacco leaf varies from 0.15 to 0.48 pCi/g (10^{-12} Curies per gram); in tobacco-growing soil, it varies from 0.26 to 0.55 pCi/g. The amount of Ra-226 in tobacco-producing soil appears to be related to phosphorus fertilization. Soils having high available P continuously used for tobacco crops usually have a higher Ra-226 content, the range being 0.52 to 1.53 pCi/g (*24*). The significance of these radioelements in tobacco and tobacco smoke is being extensively studied with Pb^{210}-enriched leaf tobacco by USDA.

TABLE 8.—Representative analyses of cigar tobaccos (leaf web after fermentation, moisture-free basis)

Component[a]	Conn. shade-grown wrapper. Type 61	Northern Wisconsin binder. Type 55	Penn filler. Type 41	Puerto Rican filler. Type 46	Cuban filler. Type 81	Sumatra wrapper. Type 82
Total volatile bases as ammonia	1.293	1.055	0.874	0.707	1.478	0.670
Nicotine	1.47	2.68	2.04	0.90	2.23	1.42
Ammonia	0.914	0.575	0.495	0.348	1.012	0.313
Total amide as ammonia	0.225	0.199	0.165	0.264	0.232	0.208
Protein nitrogen as ammonia	2.20	2.14	2.88	3.26	2.81	3.01
Total nitrogen as ammonia	5.78	4.75	5.16	4.65	5.83	5.17
pH	6.27	6.33	6.10	7.21	6.56	7.25
Ash	23.79	24.94	24.50	22.45	22.57	22.34
Alkalinity of water-soluble ash[b]	90.4	45.5	47.0	62.7	43.0	93.6

[a]In % except for pH and alkalinity.
[b]Milliliters of 1N acid per 100 g tobacco.
SOURCE: Harlan, W.R. (*8*).

Aflatoxin B_1, the most toxic of the four known aflatoxins, is produced by *Aspergillus flavus* Lk. ex Fr. The binding of aflatoxin B_1 to both native and denatured deoxyribose nucleic acid (DNA) partially explains its extreme toxicity and carcinogenicity. Aflatoxins have been reported to occur in many commodities, but its presence in leaf tobacco has not been positively confirmed, although *A. flavus* was known to be present in various grades of air-cured Burley tobacco. Certain types of tobacco contain higher populations of fungi than other types (*6*). These differences probably result from culture, curing, and handling practices as well as from the chemical composition of tobacco leaf and the climate in which it is grown. An examination of samples of leaf tobacco and of cigarette smoke condensate by Tso, et al. (*26*) failed to show aflatoxin B_1. Pure aflatoxin B_1 added to cigarettes was not recovered in the smoke condensate, indicating that aflatoxin B_1, even if present, was changed or decomposed during the smoking process.

Relationships Among Tobacco Leaf, Smoke, and Biological Response

Recent reports have been published dealing with precursor-product relationships among specific leaf tobacco components and smoke constituents (*20, 26, 31, 34*). One comprehensive study was conducted to examine the relationships among leaf, smoke, and biological responses using well-defined bright tobacco samples specially produced for this

purpose. This study involved a total of 151 variables, including 102 leaf and agronomic characteristics, 42 cigarette and smoke components, and 7 biological responses (*31*). The results clearly indicated that certain leaf characteristics could be used as "markers" to predict total smoke delivery or individual smoke components. These findings demonstrated that modification of these markers through genetic, cultural, or curing procedures might lead to the development of leaf tobacco of more desirable quality and usability.

The correlations made by Tso and coworkers may be interpreted in the sense of precursor-product relationships between specific leaf and smoke components and between certain smoke components and biological responses. Table 9 gives the correlations among some selected leaf and smoke variables.

Using the same selected leaf characteristics, the correlations with the results of seven short-term bioassay systems were determined as shown in Table 10. The sebaceous gland suppression system showed many significant and interesting correlations with certain leaf characteristics (*34*). In examining all these variables, the authors commented that one significant factor appeared to be the one which affects leaf combustibility and thus the formation of components that affect suppression. Variables that promoted combustion were generally negatively associated with suppression, and variables that inhibited combustion were generally positively associated with suppression. In addition, phenolic compounds were positively associated with suppression. These compounds may serve as precursors of smoke constituents with tumor-promoting activity.

In addition to the sebaceous gland suppression system, the *E. coli.*, virus-infected quail, and mixed cell-culture systems also used cigarette smoke condensate. These three systems did not demonstrate any meaningful correlations with the variables examined. Correlations among selected smoke and biological variables are shown in Table 11. For example, static burning rate was negatively associated, whereas total phenols, benzo(*a*)pyrene (B*a*P), benz(*a*)anthracene (BaA), and smoke pH were positively associated with sebaceous gland suppression. Tso, et al. (*34*) commented that it is somewhat surprising that dry total particulate matter, cresols, acetaldehyde, acrolein, and hydrogen cyanide did not show any statistically significant correlation with the biological data employing whole smoke in these studies.

Smoke delivery and smoke composition thus seem to depend on the characteristics of leaf tobacco (*26*). The effects of genetic and stalk position differences are reflected in botanical, physical, and chemical properties of leaf tobacco, which in turn are clearly illustrated in the smoke constituents of these experimental samples. These results agree with those of parallel studies using leaf "markers" for identification of leaf quality and usability as described by Tso and Gori (*32*). Usability in their definition represents the state of being usable without adverse

TABLE 9.—Correlations among smoke and leaf variables

	Static-burning rate (mg/min.)	Nicotine in smoke (mg/100 g tobacco smoked)	Dry TPM (g/100 g tobacco smoked)	Nicotine-free dry TPM (g/100 g tobacco smoked)	Acetal-dehyde (mg/100 g tobacco smoked)	Acrolein (mg/100 g tobacco smoked)	BaP (μg/100 g tobacco smoked)	BaA (μg/100 g tobacco smoked)	HCN (mg/100 g tobacco smoked)	Phenols (mg/100 g tobacco smoked)	o, m, p-cresols (mg/100 g tobacco smoked)	Total vol. phenols (μg/g tob. smoked)	Smoke pH (last puff)
Trichoine	-.604**	.450**	.705**	.719**	-.122	-.484**	.538**	.494**	.665**	.744**	.836**	.142	.399*
Leaf thickness	-.403*	.587**	.462**	.399*	-.577**	-.594**	.353*	.308	.543**	.686**	.530**	-.088	.695**
Fire-holding capacity	.684**	-.612**	-.799**	-.792**	.407*	.663**	-.663**	-.548**	-.755**	-.827**	-.820**	-.179	-.599**
Moisture equilibrium	-.671**	.468**	.672**	.675**	.089	-.158	.594**	.587**	.488**	.668**	.725**	.712**	.340
pH (leaf tobacco)	.680**	-.538**	-.601**	-.575**	.382*	.548**	-.597**	-.571**	-.634**	-.699**	-.671**	-.688**	-.599**
K	.615**	-.754**	-.804**	-.761**	.550**	.608**	-.662**	-.566**	-.766**	-.801**	-.703**	-.775**	-.699**
Cell-wall substance	.398*	-.212	-.406*	-.425*	-.095	.144	-.460**	-.490**	.278	-.433*	-.565**	-.511**	-.199
Total N	-.662**	.905**	.884**	.81!**	-.308	-.426*	.793**	.760**	.831**	.949**	.824**	.919**	.852**
Nitrate N	.367*	-.280	-.451**	-.461**	.167	.382*	-.224	-.114	-.431*	-.498**	-.543**	.099	-.261
Total alkaloid (dist.)	-.526**	.984**	.710**	.595**	-.368	-.297	.656**	.637**	.467**	.832**	.581**	.744**	.929**
Total vol. bases	-.513**	.985**	.758**	.650**	-.359*	-.333	.672**	.650**	.723**	.864**	.626**	.781**	.924**
α amino N	.603**	.475**	.472**	.439*	-.073	-.175	.423*	.450**	.569**	.496**	.427*	-.090	.483**
Total free amino acids	-.445**	.263	.555**	.588**	.263	-.535**	.449*	.427*	.605**	.552**	.622**	.591**	.312
Arginine	-.410*	.233	.476**	.503**	.233	-.690**	.344	.302	.587**	.447*	.511**	.489**	.275
Aspartic acid	.609**	-.358*	-.529**	-.534**	.324	.459**	-.471**	-.436**	.466**	.488*	-.551**	-.528**	-.294
Proline	-.560**	.364*	.382*	.360*	-.192	-.530**	.348	.319	.356*	.425*	.580**	.508**	.121
Dimethylamine	-.559**	.573**	.497*	.444*	-.113	-.196	.523**	.522**	.468**	.541**	.460**	.523**	.548**
Total polyphenols	-.474**	.151	.507**	.560**	.161	-.169	.538**	.514**	.399*	.496**	.642**	.563**	.163
Chlorogenic acid	-.585**	.561**	.634**	.610**	-.084	-.100	.690**	.645**	.468**	.653**	.550**	.624**	.527**
Rulin	-.444*	.147	.495**	.548**	.245	-.036	.434*	.364*	.348	.452**	.610**	.529**	.077
Scopoletin	-.728**	.620**	.748**	.727**	-.456**	-.735**	.620**	.574**	.738**	.801**	.785**	.821**	.645**
Lignin	-.140	.378*	.528**	.529**	.016	-.036	.392	.393*	.570**	.396	.328	.362*	.241
Oxalic acid	.545**	.516**	.596**	.575**	-.623**	-.723**	.584**	.479**	-.739**	.646**	.618**	.626**	.578**
Malic acid	.452**	-.481**	-.748**	-.763**	.112	.412*	-.583**	-.510**	-.657**	-.729**	-.732**	-.765**	-.437*
Pentadecenoic acid	-.449*	.410*	.659**	.675**	.035	-.140	.590**	.589**	.567**	.500**	.548**	.529**	.229
Stigmasterol	.520**	-.565**	-.543**	-.501**	.761**	.820**	-.484**	-.429**	-.627**	-.596**	-.508**	-.558**	-.659**
p,p'-TDEE	-.366*	.667**	.636**	.584**	-.205	-.321	.454**	.447*	.639**	.699**	.584**	.665**	.550*
Total DDT + TDE	.228	.378*	.533**	.534**	.034	-.070	.472**	.460**	.519**	.485**	.517**	.519**	.278
Aroma	-.364	.531**	.583**	.332	.211	.096	.566**	.527**	.328	.525**	.501**	.528**	.358*
Flavor	-.221	.470**	.566**	.430*	.313	.212	.533**	.500**	.280	.509**	.512**	.533**	.284
Strength	.416*	.627**	.714**	.514**	.054	.023	.585**	.514**	.546**	.696**	.623**	.700**	.488**

* - 5 0/0 significance
** - 1 8/0 significance
SOURCE: Tso, T.C. (34).

TABLE 10.—Correlations among selected leaf and biological variables

Variable	Sebaceous gland	*E. Coli* zone inhibition	Virus-infected quail	Mixed cell culture	Cilia toxicity	Cyto-toxicity	Macro-phage
Stalk position	0.506**	-0.090	-0.009	-0.316	-0.037	-0.076	-0.023
Trichome	.391*	-.169	.007	-.327	-.158	-.111	-.038
Leaf thickness	.352*	.060	.156	-.313	.295	-.373*	-.004
Rate of burn	-.554**	.011	-.083	.193	-.034	.017	.091
Moisture equilibrium	.466**	-.100	.056	-.460**	.048	.080	-.054
pH (leaf tobacco)	-.494**	.104	-.284	.209	-.039	.154	-.152
Potassium	-.523**	-.106	-.221	.070	-.066	-.016	.043
Total nitrogen	.595**	-.086	.200	-.194	.037	-.096	.171
Nitrate nitrogen	-.473**	.015	.148	.205	.035	.083	.092
Total alkaloids	.439*	-.053	.219	-.124	.255	-.150	.166
Total volatile bases	.458**	-.081	.229	-.089	.140	-.130	.175
α-Amino nitrogen	.178	-.303	.204	.064	-.306	-.100	.247
Total free amino acids	.355*	-.239	-.012	-.087	-.304	-.111	.053
Aspartic acid	-.337	-.048	-.107	.172	-.168	.002	.134
Dimethylamine	.451**	.394*	-.042	.330	.017	-.133	.185
Total polyphenols	.382*	-.223	.148	-.353*	-.197	.001	-.046
Chlorogenic acid	.509**	-.025	.160	-.326	.086	-.050	.098
Scopoletin	.488**	-.076	.044	-.264	.077	-.181	.085
Oxalic acid	.397*	-.039	.401*	.028	-.130	-.014	.104
Malic acid	-.507**	-.117	-.072	.224	.223	.020	.105
Pentadecenoic acid	.196	-.123	.143	.064	-.375*	.274	-.106
Stigmasterol	-.361*	-.070	-.171	-.101	-.171	.225	-.043
Total DDT + TDE	.460**	.030	.180	-.186	-.271	.102	.159
Flavor	.358*	-.126	-.010	-.249	-.065	.020	-.178
Strength	.428*	.147	.048	-.272	-.126	.144	.126

* and ** — significantly different from 0 at 5 and 1 percent, respectively.
SOURCE: Tso, T.C. (*26*).

$$\text{Usability index} = \frac{A}{B}$$

If chemical, physical and botanical characteristics are considered:

$$\text{Usability index} = \frac{A}{B} + \frac{C+D}{E}$$

where

A = nitrate + K + total ash + cellulose,
B = nicotine + TVB + α-amino nitrogen + starch + polyphenols + PEE + lipid residues + waxes + phytosterols + fatty acids,
C = filling value + combustibility,
D = stem/lamina ratio,
E = thickness.

(TVB and K = total volatile bases, potassium) PEE = petroleum ether extracts

TABLE 11.—Correlations among selected smoke and biological variables

Variable[1]		Sebaceous gland	*E. Coli* zone inhibition	Virus-infected quail	Mixed cell culture	Cilia-toxicity	Cyto-toxicity	Macro-phage
Static burning rate per minute	mg	-0.465**	0.010	-0.145	0.390*	-0.128	0.030	-0.132
Dry total particulate matter[2]	g	.272	.234	.073	.104	.272	-.017	-.104
Nicotine in smoke[2]	mg	.268	.171	.204	-.013	.472**	-.152	-.196
o-, *m*-, and *p*-Cresols[3]	mg	.137	.116	-.074	.035	.293	-.167	-.314
Total volatile phenols[2]	mg	.542**	-.165	.054	-.322	.011	-.142	.080
Acetaldehyde[3]	mg	-.104	-.112	-.329	-.033	-.216	.180	-.018
Acrolein[3]	mg	.073	-.109	-.089	.109	-.308	.263	.145
Hydrogen cyanide[3]	mg	.138	.152	.280	.163	.125	-.078	-.130
Benzo[*a*]pyrene[2]	μg	.388*	.249	.205	.019	.251	-.014	.057
Benzo[*a*]anthracene[2]	μg	.446*	-.098	.291	-.024	-.170	-.064	.025
Smoke pH (last puff)	pH	.468**	-.034	.213	-.103	.345	-.362*	.228
Carbon monoxide[2]	mg	.285	.105	.373*	.002	-.444*	.264	-.128
Carbon dioxide[2]	mg	.323	.136	.312	.031	-.335	.194	-.178

[1]* and ** = significantly different from 0 at 5 and 1 percent, respectively.
[2]per gram tobacco burned
[3]per 100 grams tobacco burned
SOURCE: Tso, T.C. (*26*).

effects. Markers were used to establish a "usability index." High emphasis was placed on the chemical constituents. Physical factors were next in importance because they can be improved through reconstitution. Botanical factors were considered only when natural leaf was used and entire stems were returned for cigarette manufacture.

Thus, the potential is there to assume that modification of the markers identified in this type of analysis may lead to the improvement of the smoke products as well as the biological effects of the smoke.

Modification of Tobacco and Tobacco Products

It has been reported by Tso and coworkers (*33*) that the labor of tobacco harvest and post-harvest handling may account for 50 to 55 percent of the total required to produce the crop. Consequently, many attempts have been made to reduce use of hand labor. It is not essential that the tobacco leaf be kept whole in order to be useful to the tobacco industry (*14*). Tso and coworkers (*4*, *33*) recently reported the results of a new procedure for curing leaf tobacco through homogenization, incubation, and dehydration, called homogenized leaf curing (HLC). The objectives of the HLC process were threefold: to reduce production labor costs, to reduce or eliminate undesirable factors that may be associated with the smoking and health problem,

and to improve tobacco usability by enhancing certain physical and chemical factors. Preliminary results (*4*, *33*) suggest HLC advantages are the capability for more complete mechanization and the enhanced potential for reduction or elimination of substances found to be hazardous to health. Reductions in total volatile bases, nicotine, reducing substances, total particulate matter, and nitrosamines have been reported (*33*).

Another method of modifying tobacco and tobacco products involves development of the reconstituted tobacco sheet (RTS); this method has been reviewed by Moshey (*14*) and Mattina and Selke (*13*). The original impetus for developing a reconstitution process was purely economical. For each pound of auction weight tobacco, only about 63 percent was usable shredded leaf tobacco, although approximately 6 percent of the stem material was also blended in smoking tobacco. The remaining 31 percent, consisting of sand (2 percent), discarded stems (18 percent), manufacturing fines (1 percent), and moisture and aging loss (10 percent) was lost to the manufacturer. A process that could utilize the lost stems and fines and control moisture would increase the amount of usable tobacco from a harvest, cut costs, and offer some manufacturing control over the physical and chemical properties of the resultant product (*13*).

Several processes were developed in the early 1950's. These were of two general type groups; in one group, the tobacco is ground into fine particles, mixed with a hydrocolloid gum, and cast on an endless steel belt. The other, more widely used group of processes, involves mechanically working the insoluble portion of the tobacco into a fibrous mass and forming it, via papermaking techniques, into a web. In one variation of the paper process, the soluble portion is diverted prior to the papermaking and then added back to the self-supported web. In another variation, the soluble portion remains with the fibrous material throughout the processing. For all processes, the finished product is in the form of leaflets which are then blended with natural tobacco and shredded.

The significance of the sheet process lies in the ability to chemically and mechanically produce desired changes during the pulping process. For example, chemical extractions can be performed to reduce nicotine and other constituents. Tar-yield levels can be reduced to some extent, and additives can be put into the material. The structural modifications which can be effected through reconstituted sheet technology could result in considerable differences in the burn properties and in the smoke. Produced tobacco sheet with a 10 mg/cigarette tar yield without filtration is now available using RTS technology. Lower figures are possible but may cause the sheet to be undesirable as a tobacco product. Flavorings and other additives can also be added at selective stages during the process if necessary, depending upon the solubility and volatility of the additive.

The components of leaf tobacco can be classified into three different categories. Some components are essential for smoke quality and desirability, others have either little or no effect, and a third category consists of components that serve as precursors of undesirable smoke constituents such as HCN and aza-arenes (*5, 28*).

One class of components in the third category is fraction-1-protein (*12, 28, 29*). This and other proteins do not contribute in any significant way to smoke aroma or flavor. Removal of fraction-1-protein achieves two purposes—improved leaf quality and usability, and fraction-1-protein as a potential food source. It is estimated that up to 6 percent of the tobacco yield could be used for feed and food purposes (*28*).

Fraction-1-protein is the major soluble protein of green plants and may account for 50 percent of the soluble protein fraction and 25 percent of the total protein (*26, 28*). The protein is an enzyme called carboxydismutase (*21*) that catalyzes the first step in the transformation of CO_2 into carbohydrates during photosynthesis (*28*).

Tso (*33*) and DeJong (*4*) have reported that the fraction-1-protein can be removed for beneficial use by the above-mentioned HLC process, and could be used as a food source for millions of people annually (*28*). The protein has been evaluated as a food source (*28, 29*) and found to compare favorably with egg and human milk for essential amino acid content.

Cigarette Engineering

The tobacco blend can vary in the amount of Burley, bright (Virginia), Maryland, and oriental leaf and in the amount of reconstituted tobacco sheet used. Casing solutions are used to hold the tobacco blend together. Humectants (moisture retainers) are added to maintain the necessary body and moisture qualities and to contribute to the flavoring of the blend. Flavor-enhancing additives are used to make the smoke pleasant and more acceptable to the smoker. To maintain the physical integrity of the product, a paper wrapper is used. Each of these ingredients may affect the burn rate, puff number, pyrolysis products, and ultimately the chemical constituents of mainstream and sidestream smoke and smoke condensate.

Typical casing materials that may be used are sugars, sirups, licorice and balsams. These additives improve or change the flavor characteristics and burning qualities and impart important binding qualities to the blend. However, additives, when pyrolyzed, may yield undesirable as well as desirable products. Licorice, for instance, could be a precursor of polyaromatic hydrocarbons (PAH). Sugars used in casings cause an increase in furfural, nicotine, and tar in resulting smoke and a decrease in volatile acids (*21*).

Flavoring agents are added at different steps in the cigarette manufacturing process, depending upon volatility. Volatile flavors, such as alcohol-soluble fruit extractives, menthol oils, and aromat

materials are applied late in the process. The flavorings normally used (whether natural or chemically compounded) are usually selected from substances generally considered safe to humans even though such definitions do not guarantee that subsequent pyrolytically-produced materials are safe.

Tobacco blends can also be mechanically processed in different ways. For example, leaf tobacco can be shredded to various widths and lengths to control density, burning rates, puff resistance, and other related properties (*15*). This alteration in tobacco blends produces a cigarette or cigar with a modified chemical composition in both the tobacco product and the resulting smoke as has been described earlier in this chapter.

Cigarette paper can also be manufactured with a variety of additives and with different porosities in order to control burning qualities. High porosity citrate paper used with a standard tobacco blend delivered less tar, but the same nicotine, as a control cigarette. Acetaldehyde, acrolein, formaldehyde, carbon monoxide, and hydrogen cyanide were reduced, but the pH of the smoke was elevated slightly. Low porosity phosphate paper used with the same blend delivered greater quantities of tar and nicotine than did the control cigarettes. Increases were also found for the deliveries of acetaldehyde, acrolein, formaldehyde, carbon monoxide, and hydrogen cyanide, while the pH remained unchanged (15–18).

Most modern cigarettes use filters of various kinds. Over 80 percent of the cigarettes sold in 1977 were filtered, using charcoal filters, mentholated filters, special baffled filters, cellulose acetate, and combination filters. Charcoal filtration reduces some of the toxic gas components; cellulose with absorptive additives tends to remove acidic constituents; and magnesium silicate (when used) removes some of the aldehydes and organic vapors from smoke. Perforating the filter to allow air dilution further reduces the concentration of gas phase components of smoke (*10, 11, 22*).

Many modifications of cigarettes are possible and the precise ingredients and variations thereof are usually proprietary to manufacturers. However, experimental cigarettes have been prepared using a number of modifications, such as variation of the width of tobacco cut, the use of different parts of the tobacco itself (leaf, stems, fines, etc.), a selection of additives, and different paper porosities. These experimental cigarettes have been prepared by different methods, smoked on smoking machines under standard conditions, and the condensate collected. Subsequent mouse dermal bioassays showed such trends as the following (*15–17*): (1) Reconstituted tobacco sheets generally resulted in condensates less tumorigenic than standard control cigarettes. (2) High relative paper porosity seemed to decrease carcinogenic activity of condensate on mouse skin. (3) The addition of nitrates to aid combustion did not reduce condensate carcinogenicity as

was originally anticipated. (4) Different shred widths of tobacco did not appear to affect the carcinogenicity of condensate for mouse skin. (5) Cigarettes made from 100 percent tobacco stems resulted in condensate with the lowest carcinogenic activity for mouse skin. (6) In two cases, cigarettes made solely of tobacco leaves produced condensates so toxic that they caused the death of experimental mice before carcinogenicity could be ascertained. (7) The relative petroleum ether solubles in tobacco correlated with condensate carcinogenicity for mouse skin.

Several special processes are also possible in treating tobacco blends; for example, puffing or expanding (adding air or CO_2) and freeze drying. These methods can affect the cigarette weight, puff resistance, nicotine delivery, and in fact, the delivery of many components such as acetaldehyde and acrolein. Since puffing or expanding processes introduce air and effectively reduce the density of the cigarette, they constitute a form of dilution and tend to reduce the output of some substances. The burning rate is also affected, which in turn will change the yield and composition of some pyrolysis products. Freeze drying, for example, reduced nicotine and phenolics significantly in the experimental blend used, but produced about the same amounts of acetaldehyde, acrolein, and formaldehyde as did control blend cigarettes (*15-17*).

Possible approaches that plant scientists can take to modify tobacco leaf have been reviewed by Tso (*26*). The main objective of such research is to acquire the desired characteristics which will meet with acceptance of smokers and at the same time produce a less harmful tobacco (*25*). Modification may involve genetic and cultural modification, nitrogen fertilization technology, leaf and plant population, the physiological stage of topping, and pesticide treatments. Post-harvest modification is also possible, as leaf composition is markedly affected by the curing process, aging, or other treatment of cured leaves.

Other Tobacco Products

In contrast to cigarettes (see discussion on types and classes of tobacco) cigars are normally made of filler tobacco (bulk of cigar), binder tobacco (used to hold the shape), and wrapper tobacco (the outside layer or covering) (*30*). Wrappers are now being made increasingly from reconstituted tobacco products. Cigar tobaccos are generally air-cured, aged, and fermented. Pipe tobacco may be pure Burley or a blend of Burley with other tobaccos. A considerable amount of sweeteners and other additives is used to create a pleasing aroma and taste. Chewing tobacco is made of tobacco leaf (usually Burley, cigar, and bright) and is heavily sweetened. Snuff is powdered and flavored tobacco (usually dark air-cured and fire-cured).

Summary

Tobacco has been cultivated and consumed in the civilized world for more than 300 years. It is an important economic crop and demands high production inputs, including energy. The United States is well known for its high quality tobacco and the application of modern technology to tobacco production. Extensive knowledge in tobacco science has been accumulated by intensive research effort, especially during the past 20 years. Recent advances in various areas of research related to tobacco and tobacco smoke have provided adequate basic information for improvement of production.

In plant research, there are means available for genetic, cultural, and post-harvest modification. Also, a new homogenized leaf curing process makes it possible to extract soluble proteins and to improve the smoking material at the same time.

(1) BRUECKNER, H. Die Biochemie des Tabaks und der Tabakverarbeitung. Berlin, Verlagsbuchhandlung Paul Parey, 1936, pp. 280-330.

(2) DARKIS, F.R., HACKNEY, E.J. Range of chemical composition of tobacco being used in cigarettes. In: Wynder, E.L., Hoffmann, D. (Editors). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, p. 42.

(3) DAWSON, R.F., OSDENE, T.S. A speculative view of tobacco alkaloid biosynthesis. In: Runeckles, V.C., Tso, T.C. (Editors). Structural and Functional Aspects of Phytochemistry. Recent Advances in Phytochemistry. Volume 5. New York, Academic Press, 1972, pp. 317-338.

(4) DEJONG, D.W., LAM, J., LOWE, R., YODER, E., TSO, T.C. Homogenized leaf curing. II. Bright tobacco. Beitraege zur Tabakforschung 8(2): 93-101, May 1975.

(5) DONG, M. SCHMELTZ, I., JACOBS, E., HOFFMANN, D. Aza-arenes in tobacco smoke. Journal of Analytical Toxicology 2: 21-25, 1978.

(6) FORGACS, J., CARLL, W.T. Mycotoxicoses: Toxic fungi in tobaccos. Science 152: 1634-1635, June 1966.

(7) FRANKENBURG, W.G. Chemical changes in the harvested tobacco leaf, Part I. Chemical and enzymic conversions during the curing process. In: Nord, F.F. (Editor). Advances in Enzymology and Related Subjects of Biochemistry, Volume 6. New York, Interscience Publishers, 1946, pp. 309-387.

(8) HARLAN, W.R., MOSELEY, J.M. Tobacco. In: Encyclopedia of Chemical Technology, Volume 14. New York, Interscience Encyclopedia, Inc., 1955, pp. 242-261.

(9) HARLEY, N.H., COHEN, B.S., TSO, T.C. Polonium-210 in tobacco. Presented at the Symposium on Public Health Aspects of Radioactivity in Consumer Products, Atlanta, Georgia, February 2-4, 1977. Symposium Summaries published by the Nuclear Regulatory Commission.

(10) KEITH, C.H. Filtration as a means of reduction of tar and nicotine levels in tobacco smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 49-55.

(11) KIEFER, J.E., TOUEY, G.P. Filtration of tobacco smoke particulates. In: Wynder, E.L., Hoffmann, D. (Editors). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, pp. 545-575.

(12) LOWE, R.H. Crystallization of fraction 1 protein from tobacco by a simplified procedure. FEBS Letters 78(1): 98-100, June 1977.

(13) MATTINA, C.F., SELKE, W.A. Reconstituted tobacco sheets. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 67-72.

(14) MOSHY, R.J. Reconstituted tobacco sheet. In: Wynder, E.L., Hoffmann, D. (Editors). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, pp. 47-83.

(15) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 1. Toward Less Hazardous Cigarettes. The First Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-905, 1976, 148 pp.

(16) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 2. Toward Less Hazardous Cigarettes. The Second Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1111, 1976, 153 pp.

(17) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 3. Toward Less Hazardous Cigarettes. The Third Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1280, 1977, 152 pp.

(18) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 4. Toward Less Hazardous Cigarettes. The Fourth Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. (Unpublished preliminary results)

(19) RADFORD, E.P., JR., HUNT, V.R. Polonium-210: A volatile radioelement in cigarettes. Science 143(3603): 247-249, January 17, 1964.

(20) RATHKAMP, G., TSO, T.C., HOFFMANN, D. Chemical studies on tobacco smoke. XX: Smoke analysis of cigarettes made from bright tobaccos differing in variety and stalk positions. Beitraege zur Tabakforschung 7(3): 179-189, November 1973.

(21) SUGAWARA, S., ISHIZU, I., KOBASHI, U. Studies on casing effects on cigarettes. I. Change in chemical composition with casing additives. Scientific papers of the Central Research Institute, Japan Monopoly Corporation 105: 203-207, 1963.

(22) TIGGELBACK, D. Vapor phase modification—an under-utilized technology. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH) 76-1221, 1976, pp. 507-514.

(23) TSO, T.C. Manipulation of leaf characteristics through production—role of agriculture in health-related tobacco research. Journal of the National Cancer Institute, 48(6): 1811-1819, June 1972.

(24) TSO, T.C. Physiology and Biochemistry of Tobacco Plants. Stroudsburg, Pennsylvania, Dowden, Hutchinson & Ross, Inc., 1977, pp. 58, 91-99.

(25) TSO, T.C. The potential for producing safer cigarette tobacco. Agricultural Science Review 10(3): 1-10, 1972.

(26) TSO, T.C. Production, phytochemistry and modification of tobacco. In: Minutes of the Smoking and Health Contractors Conference, National Cancer Institute, Savannah, Georgia, March 11-14, 1979) (Minutes to be published, May 1979)

(27) TSO, T.C. Tobacco. In: Standen, A. (Editor). Encyclopedia of Chemical Technology, Volume 20, 2nd edition. New York, John Wiley & Sons, 1969, pp. 504-527.

(28) TSO, T.C. Tobacco and tobacco smoke. In: Childers, W.F., Russo, G.M. (Editors). Nightshades and Health. Somerville, New Jersey, Horticultural Publications, Somerset Press, 1975, pp. 93-121.

(29) TSO, T.C. Tobacco as potential food source and smoke material. Beitraege zur Tabakforschung 9(2): 63-66, June 1977.

(30) TSO, T.C. Tobacco composition: Potential for changes through production. Tobacco—The International Weekly: 69-72, April 25, 1969.

(31) TSO, T.C., CHAPLIN, J.F. Simple Correlation and Multiple Regression Among Leaf Characteristics, Smoke Components, and Biological Responses of Bright Tobaccos. U.S. Department of Agriculture, Agricultural Research Service, Technical Bulletin 1551, May 1977, 135 pp.

(*32*) TSO, T.C., GORI, G.B. Effect of tobacco characteristics on cigarette smoke composition. In: Schmeltz, I. The Chemistry of Tobacco and Tobacco Smoke. New York, Plenum Press, 1972, pp. 51-63.

(*33*) TSO, T.C., LOWE, R., DEJONG, D.W. Homogenized leaf curing. I. Theoretical basis and some preliminary results. Beitraege zur Tabakforschung 8(1): 44-51, January 1975.

(*34*) TSO, T.C., RATHKAMP, G., HOFFMANN, D. Chemical studies on tobacco smoke. XXI: Correlation and multiple regression among selected cigarette-smoke constituents and leaf characteristics of bright tobacco. Beitraege zur Tabakforschung 7(3): 190-194, November 1973.

(*35*) U.S. DEPARTMENT OF AGRICULTURE. Agricultural Statistics, 1976. U.S. Department of Agriculture, 1976, pp. 96-111.

(*36*) U.S. DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH SERVICE. Tobacco production. U.S. Department of Agriculture, Agricultural Research Service, Agriculture Information Bulletin No. 245, December 1976, 77 pp.

(*37*) WOLF, F.A. Tobacco production and processing. In: Wynder, E. L., Hoffmann, D. (Editors). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, pp. 5-40.

Smoke Formation

The raw material that goes into the making of a cigarette is only a prelude to what happens when the cigarette is smoked. Indeed, the lighted cigarette is a unique chemical factory generating more than 2,000 known compounds by a variety of processes responsive to thermodynamic constraints. The following sections will review the smoke generation process and the effects on smoke composition.

Physico-Chemical Nature of Cigarette Smoke

As a smoker takes a puff from a burning cigarette, he draws the mainstream smoke that issues from the butt end. The aerosol emitted from the burning cone during puff intervals is the sidestream smoke, and is chemically different from mainstream smoke. That portion of the smoke which can be retrained by a Cambridge glass fiber filter (99.9 percent efficient for particles $>0.1\ \mu$) is defined as the particulate phase, whereas the portion that passes the filter is termed the gas phase.

Smoke aerosol is a highly concentrated aerosol of liquid particles constituting the "tar." Each particle is composed of a large variety of organic and inorganic chemicals that are dispersed in a gaseous media consisting primarily of nitrogen, oxygen, hydrogen, carbon dioxide, carbon monoxide, and a large variety of volatile and semivolatile organic chemicals in equilibrium with the particulate phase of the tobacco smoke. The smoke aerosol is a continuously changing entity. Aging of the aerosol results in changes in its physical and chemical properties (*13*).

In order to generate reproducible physical and chemical data for the analysis of cigarette smoke, standard smoking conditions have been set up based on observations of patterns in human smoking. In the United States, these standard conditions prescribe 1 puff per minute, 2-second puff duration, a puff volume of 35 ml, and a butt length of 23 mm in an unfiltered cigarette, or the length of the filter tip, including the overwrap plus 3mm, whichever is greater, in a filtered cigarette. Smoking conditions for cigarettes in other countries (*9*) and for cigars (*46*) differ somewhat from the adapted standards for U.S. cigarettes.

Temperature Profiles

Several parameters determine the qualitative and quantitative smoke composition of mainstream and sidestream smoke. The major factors affecting the temperature profiles of the burning cigarette include physical form (length and circumference) of the cigarette, filler materials, tobacco type or blend, tobacco cut, packing density, additives, moisture content, quality of the cigarette paper (porosity, additives), and the filter (fiber material, plasticizer, draw resistance, construction, perforation). During puffing, temperatures in the

burning cone reach 900°C with some hot spots on the periphery of the cigarette up to 1,050°. A steep temperature gradient from 880°C to 40°C is observed away from the burning center extending over the next 3 centimeters of the tobacco column (*65*, *100*). On the basis of this temperature profile, three major reaction zones are defined: the high temperature zone (900–600°C) which is free of oxygen (immeasurable) and contains up to 8 volume percent of hydrogen and 15 volume percent of carbon monoxide, the oxygen-depleter pyrolysis-distillation zone (600–100°C), and the low-temperature zone (<100°C) with up to 12 volume percent of oxygen. Within these three zones, the actual mainstream smoke formation occurs by hydrogenation, pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation. The exit temperature of the mainstream smoke at the cigarette butt ranges from 25 to 50°C, depending on the butt length.

The sidestream smoke is generated during smoldering of the cigarette at peak temperatures inside the glowing cone of up to 800°C but reaches ambient temperatures at a distance of a few centimeters from the burning cone.

Material Balance

The amount of tobacco consumed during puffing and smoldering depends on the static burning temperature and on the same parameters which determine the mainstream smoke formation. An indicator for the release of sidestream smoke is the static burning rate between puffs which generally ranges from 5 to 7 mm of tobacco column per minute. It has been shown that between 55 and 70 percent of the tobacco of a cigarette is burned between puffs and thus serves as a source for the formation of sidestream smoke and ashes. The mainstream smoke effluent of a cigarette smoked to a 30 mm butt length amounts to about 500 mg (Tables 12 and 13, and reference *4*). Of the 55 mm tobacco column, about 300 mg is consumed for the generation of mainstream smoke (and ashes) and about 500 mg for the formation of sidestream smoke (and ashes).

The interrelationships involved in cigarette smoke may be described by the general equation described recently by Gori (*25*).

Weight of ash produced during puffs
+ Mainstream TPM weight
+ Mainstream gas phase weight
- Mainstream entrained gas weight
- Mainstream combustion oxygen weight

= Weight of cigarette burned during puffs

TABLE 12.—Percent distribution of cigarette smoke*

Material	Weight (mg/cigarette)	Weight of total effluent (%)
Particulate matter (inc. cond. H_2O)	40.6	8.2
Nitrogen (67.2 vol %)	295.4	59.0
Oxygen (13.3 vol %)	66.8	13.4
Carbon dioxide (9.8 vol %)	68.1	13.6
Carbon monoxide (3.7 vol %)	16.2	3.2
Hydrogen (2.2 vol %)	0.7	0.1
Argon (0.8 vol %)	5.0	1.0
Methane (0.5 vol %)	1.3	0.3
Water vapor (relative humidity = 0.6)	5.8	1.2
C_2–C_6 hydrocarbons	2.5	0.5
Carbonyls	1.9	0.4
Hydrogen cyanide	0.3	0.1
Other known gaseous materials	1.0	0.2
Total	505.6	101.2
Measured total effluent	500	100

*85 mm nonfilter cigarettes, 30 mm butt length, 10 puffs of 38.9 ml volume each.
SOURCE: Keith, C.H. (*52*).

TABLE 13.—Typical mainstream smoke mixture*

Material	Weight (mg/cigarette)
TPM (wet)	40.6
Nitrogen	295.4
Oxygen	66.8
Argon	5.0
Carbon dioxide	68.1
Carbon monoxide	16.2
Water vapor	5.8
C_2–C_6 hydrocarbons	2.5
Carbonyls	1.9
Other (gaseous)	3.3
	505.6

*85 mm cigarette, 30 mm butt length, 10 puffs of 38.9 ml volume each.
SOURCE: Gori, G.B. (*25*).

Mainstream Smoke Aerosol

The undiluted smoke as it leaves the cigarette butt contains up to 5 x 10^9 heterogeneous particles per ml with round and spheric forms ranging in diameter between 0.2 and 1.0 μ and a median particle diameter of about 0.4 μ (*13, 51*). The smoke aerosol is slightly charged with about 10^{12} electrons per gram of smoke; about 55 percent of the particles contain one or more charges (*51*). The pH of the total smoke effluent of a cigarette is primarily determined by the tobacco. For a

blended U.S. cigarette, the pH of the mainstream smoke varies between 5.5 and 6.2, and that of the sidestream smoke ranges between 6.5 and 7.5, depending on the puff number measured. In the case of cigarettes made exclusively from Burley or black tobacco, or in the case of cigars, the pH for mainstream smoke varies between 6.5 and 8.5 (highest values for last puffs) and for sidestream smoke between 7.5 and 8.8 (*8*). Cigarette smoke has reducing activity which increases with puff number (*79*).

Chemical Composition of Tobacco Smoke

To facilitate the analysis of the tobacco smoke, the smoke is separated into a gas phase and a particulate phase in the following way: the particulate phase is defined as that portion of the smoke collected on a conventional Cambridge filter pad (99.9 percent efficient for particles more than 0.1 μ), and the gas phase is the portion that passes through the Cambridge filter.

Gas Phase

Carbon Monoxide and Carbon Dioxide

More than 90 percent of the weight of the total mainstream smoke effluent is given by the gas phase with nitrogen and oxygen already comprising more than 70 percent. Of the remaining gas phase components, carbon dioxide and especially carbon monoxide have been studied in great detail. These compounds are primarily formed by oxidation of the tobacco constituents in the high temperature zone and by decarboxylation in the pyrolysis and distillation zone and in the low temperature zone. Both CO and CO_2 increase linearly with ascending puff number. Leaves from the lower stalk positions generate significantly less CO and CO_2 than do leaves from the upper stalk positions of the same tobacco plant (*6*). The mainstream smoke of U.S. commercial cigarettes contains between 1.8 and 17.0 mg of CO (1.5–5.5 volume percent) and between 10 and 60 mg of CO_2 (8.5–14.5 volume percent) (*6, 30, 74*). Especially low CO values have been reported for cigarettes with perforated filter tips (*27*). A study with a limited number of commercial cigarettes from England indicates that filter cigarettes without perforated filter tips may contain as much, if not slightly more, CO than nonfilter cigarettes (*98*). Levels of sidestream smoke CO may be three times as high as those levels in mainstream smoke, and CO_2 may be up to eight times as high. The CO and CO_2 values for the smoke of cigars are significantly higher than those for cigarette smoke, primarily because of the relatively unporous cigar wrapper (*6*).

Nitrogen Oxides

Tobacco smoke is known to contain nitric oxide (NO) and trace amounts of nitrogen dioxide (NO_2) and nitrous oxide (N_2O). The alkali nitrates in tobacco are the major precursors for the nitrogen oxides in the smoke (*100*). With the possible exception of the last few puffs of a cigarette, fresh mainstream smoke does not contain NO_2 (*64a*); however, upon aging, NO in the smoke is quickly oxidized to NO_2 (although the half lifetime of NO in cigarette smoke is about 10 minutes). In concentrated smoke, aging leads to the formation of nitrites (*96*). Nitrogen oxides can be reduced in the mainstream smoke of cigarettes and little cigars with the aid of charcoal-containing filter tips (*91*). The concentration of NO in the smoke of U.S. commercial cigarettes varies between 5 and 800 μg per cigarette (*1, 27, 72*).

Ammonia

The major precursors for ammonia in the mainstream and sidestream smoke of tobacco products are alkali nitrate and protein (*48*). The nitrate in tobacco is reduced to nitrogen and ammonia in the burning cone with a high yield in sidestream smoke. The mainstream smoke of U.S. commercial tobacco products contains between 22 and 130 μg ammonia (as the ammonium ion) per cigarette and between 68 and 135 μg ammonia per little cigar (*7, 33*). The ratio of ammonia in sidestream smoke to that in mainstream smoke ranges from 1:40 to 1:70. The sidestream smoke of cigars is even richer in ammonia, with amounts up to more than 1 mg per cigar.

Volatile N-Nitrosamines

Another type of compound for which the yield is largely determined by the nitrate content of the tobacco is that of nitrosamines, many of which are known animal carcinogens (*57*). To date eight volatile nitrosamines have been identified in tobacco smoke with dimethylnitrosamine (DMN), diethylnitrosamine (DEN) and nitrosopyrrolidine (NPy) as the major representatives (*76*). The unaged (freshly generated) smoke of three U.S. cigarettes without filter tips contained 13 to 65 ng of DMN, 15 to 50 ng of DEN, and 11 to 34 ng of NPy (*11*). Cellulose acetate filter tips retain volatile nitrosamines selectively, whereas charcoal filter tips do not exhibit such selective removal. Unaged sidestream smoke contains 10 to 40 times higher concentrations of volatile nitrosamines than the mainstream smoke of the same cigarette.

Hydrogen Cyanide and Cyanogen

Amino acids and protein are the major precursors for hydrogen cyanide (HCN), cyanogen, and nitriles in tobacco smoke (*49*). HCN is the major ciliatoxic agent in cigarette smoke; however, its selective

reduction by charcoal filters, among other things, diminishes the inhibition of lung clearance of the cigarette smoke to a significant degree. The concentration of HCN in the smoke of U.S. commercial cigarettes varies between 10 and 400 μg per cigarette with low values for low "tar" cigarettes and cigarettes with charcoal filter tips (*27, 72*). Sidestream smoke (SS) contains significantly less HCN than mainstream smoke (MS) with SS/MS ratios between 0.006 and 0.37 (*12, 49*). Tobacco smoke also contains small amounts of cyanogen $(CN)_2$ with concentrations varying between 10 and 20 μg/cigarette (*12*). Since $(CN)_2$ hydrolyzes easily to cyanide and cyanate, it can contribute to the hydrogen cyanide concentration in the smoke. In the case of cigar smoke, this can amount to 10 to 30 percent of the measured HCN.

Volatile Sulfur Compounds

This class of gas-phase compounds is of special interest because of its high reactivity. Sulfur-containing volatiles are highly sensitive to flame photometric detectors, and nanogram amounts of sulfur compounds can be rapidly determined even in the presence of great excesses of other gases. Guerin and Horton determined 28 sulfur compounds in the gas phase of cigarette smoke (*29, 43*). Typical cigarette deliveries of the major sulfur constituents include 85 μg of hydrogen sulfide, 35 μg of carbonylsulfide, 2 μg of carbon disulfide, and 3 μg of sulfur dioxide (*43*). The authors also observed an "aging effect" during the first 30 seconds after smoking, even when Teflon® sampling loops and columns were used instead of conventional stainless steel tubes. During "aging," the composition of the mixture of the sulfur components in the smoke shifts significantly from low molecular compounds (such as hydrogen sulfide) toward high molecular weight sulfur components.

Volatile Nitriles

The major precursors for volatile nitriles in tobacco are amino acids and protein similar to those for hydrogen cyanide (*50*). The most widely studied nitrile is acetonitrile (CH_3CN). Its concentration in the smoke of one cigarette varies between 100 and 250 μg. So far a total of 13 aliphatic nitriles and 20 aromatic nitriles have been identified in tobacco smoke, many of which occur in the gas phase (*76*). Pyridine-3-carbonitrile and possibly some aliphatic and aromatic nitriles may be formed from nicotine and other tobacco alkaloids during smoking. Recently one volatile smoke nitrile has been reported as carcinogenic in the experimental animal and is considered as a possible occupational carcinogen (*64*). Acetonitrile has been reported in much higher concentration in sidestream smoke than in mainstream smoke (1:3.9).

Other N-Containing Volatile Compounds

To date, more than 600 N-containing compounds have been identified in tobacco smoke; several of them are volatile (*76*). Of these, aliphatic and aromatic nitrohydrocarbons and nitrophenols have been studied in some detail. The concentration of the major representative, nitromethane, varies between 0.5 and 1.0 μg per cigarette and nitrobenzene between 10 and 25 ng per cigarette. These compounds are formed primarily from NO_2 and C,H-radicals in the hot zones of burning tobacco products; thus concentration of the nitro compounds is governed by the nitrate content of the tobacco. Little is known about the tumorigenic potential of nitrohydrocarbons and nitrophenols, although it should be considered that the aromatic nitrohydrocarbons and possibly nitrophenols are reduced *in vivo* to the corresponding amines, some of which are known carcinogens. Recently 2-nitropropane (0.2–2.0 μg/cigarette) has been reported to induce hepatomas in mice (*24*).

Tobacco has long been known to contain aliphatic and aromatic amines, with methylamine (4.6 μg/cigarette) and aniline (1.2 μg/cigarette), as representative examples, present in the highest concentrations. In the blended U.S. cigarette with a smoke pH around 6, the major portion of the volatile amines may be protonated and thus found in the particulate phase. In recent years, several amines, especially the volatile secondary amines including pyrrolidine, have been discussed as precursors for carcinogenic N-nitrosamines. Since nitrosamines as well as both types of their precursors, NO_{12} and amines, have been found in much higher concentrations in the smoke of nitrate-rich cigarettes (*48*), the concept of smoke amines as potential precursors for nitrosamines has been supported. Aniline and possibly other volatile amines are present in significantly higher concentration in sidestream smoke than in mainstream smoke ($1:\geq 30$) (*67*).

Three other N-compounds with tumorigenic activity in the experimental animal have been reported in tobacco smoke. These are hydrazine (30 μg/cigarette), 1,1-dimethylhydrazine (100 ng/cigarette), and urethane (20–38 ng/cigarette). The hydrazines are not formed from the maleic hydrazide, the major U.S. tobacco sucker growth inhibitor, but both are transferred from tobacco during smoking and are also pyrosynthesized. Urethane is primarily formed during smoking. As with other compounds with the amino group (ammonia and amines), more hydrazine is found in sidestream smoke than in mainstream smoke (1:3).

Volatile Hydrocarbons

The highest concentration of organic compounds found in the gas phase are the hydrocarbons (*88*). Methane (200–1,000 μg/cigarette), ethane (100–600 μg/cigarette), and propane (50–300 μg/cigarette) are

cigarettes accounted for less than 40 percent of the total market in 1957 and comprise nearly 90 percent of today's market. Several parameters influence the "tar" yields of cigarettes. These include tobacco type, use of reconstituted tobacco sheets and expanded tobacco, packing density, cigarette paper, and filter tips. The effects of these and other factors are discussed in the next section.

The sidestream smoke of cigarettes has been determined in specially designed chambers which are under constant slow airflow during the collection procedure. In this case, the particulate matter is retained and measured on Cambridge fiber filter discs (*100*). For nonfilter cigarettes, the "tar" ratio in mainstream and sidestream smoke varies from 1:1.4 to 1:1.2; for low "tar" filter cigarettes this ratio can shift considerably in favor of sidestream smoke. The quantitative compositions of the two "tars," however, differ widely (as noted later in this section).

In 1972, the FTC reported "tar" yields for U.S. little cigars to range from 16.5 to 47.8 mg (*92*). All cigars weighing less than 1.36 g are considered "little cigars." When the tobacco of little cigars is wrapped in cigarette paper, the tar yield remains the same as or only slightly lower than that of little cigars with normal wrappers. This observation is quite different from that made for the CO yield. Here, the paper wrapper leads to a 30 to 50 percent CO reduction. Large cigars puffed under standard cigar-smoking conditions generally deliver more "tar" than cigarettes and little cigars because of their higher weight. Compared on the basis of gram-to-gram tobacco consumed, the cigar "tar" yield, however, is only 20 to 30 percent that of a cigarette (*75*, *100*).

Nicotine and Minor Tobacco Alkaloids

Nicotine and the compounds derived from it contribute significantly to the organoleptic nature and toxicity of tobacco smoke and are considered a major factor in tobacco habituation. As in the case of "tar," the FTC reports the nicotine values for the smoke of U.S. cigarettes semiannually (0.05–2.50 mg)(*23*). The sales-weighted average of nicotine in the smoke of U.S. cigarettes has decreased from 2.5 mg in 1957 to 1.1 mg in 1976 (*97*). Similar observations were made for products of other countries (*99*). Figures 15 and 16 describe the trends of tar and nicotine in the United States.

The nicotine values for the smoke of U.S. little cigars were reported by the FTC in 1972 to vary between 0.52 and 3.11 mg (*92*). In general, the yield of nicotine in the smoke of a cigar is considerably higher than that in the smoke of a cigarette. However, on a per-gram-tobacco-smoked basis (or for a given smoke volume), the nicotine yield is significantly lower for cigars (20 to 40 percent) (*75*, *100*). When one considers the physiological effects of nicotine, however, the comparison of the nicotine content of cigarette smoke with that of cigar smoke can

be misleading. In cigarette smoke, with the exception of French black tobacco cigarettes, nicotine is present in a protonated form, whereas in cigar smoke, nicotine is partially present in the more easily absorbed unprotonated form (*2, 8, 34*).

Depending on the *Nicotiana tabacum* variety, the nicotine content of the processed leaf can vary between 0.2 and 5.0 percent of the dry weight. The nicotine content of smoke tobaccos, however, varies generally between 1.0 and 2.0 percent, with values below 1.0 percent reported for certain low "tar" cigarettes. Because of the pharmacological effect of nicotine and its relatively high concentration in the tobacco, it is important to study the fate of tobacco nicotine during smoking. Studies with ^{14}C-labelled nicotine have shown that, in the case of the blended U.S. cigarette, 14 to 22 percent of the nicotine was transferred unchanged into mainstream smoke and 20 to 30 percent was found unchanged in the sidestream smoke (*47, 80*). Four to eight percent of the radioactivity in the mainstream smoke particulate matter was given by decomposition products of ^{14}C-nicotine. The major decomposition products identified were myosmine, bipyridyl (Figure 3), and pyridines. Despite the high transfer rate of intact nicotine into mainstream smoke and the low yield of (non-tumorigenic) decomposition products, one cannot exclude a contributory role of the thermal decomposition of nicotine towards the tumorigenicity of cigarette smoke. So far, it has been shown that nicotine may yield traces of the carcinogenic dibenzacridines, a dibenzocarbazole (*93, 100*), and tobacco specific nitrosamines (*38*).

The structural formulas of nicotine and of other tobacco alkaloids and of tobacco specific nitrosamines are presented in Figure 3, together with their concentrations in the mainstream smoke of cigarettes.

Nonvolatile N-Nitrosamines

During curing and fermentation of tobacco, specific nitrosamines can be formed by nitrosation of alkaloids, as was shown by identification of N′-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosoanatabine (NAtB) in processed tobacco leaves. The yield of these compounds depends on the concentration of the nitrate and alkaloids in the leaf. In the case of cigarette tobacco, NNN and NNK were found in concentrations between 0.3 and 7.0 ppm and 0.1 and 0.4 ppm, respectively. The reported values for cigar tobacco were for NNN, 3 to 45 ppm, and for NNK, 2 to 36 ppm. Since chewing of tobacco has been associated with an increased risk of cancer of the oral cavity and esophagus, high values of nitrosamines in chewing tobacco and snuff are of more than academic interest (NNN 2 to 90 ppm) (*35, 38*).

NNN, NNK, and NAtB have also been identified in the mainstream smoke of cigarettes (NNN, 0.14 to 3.70 μg/cigarette; NNK, 0.11 to 0.42

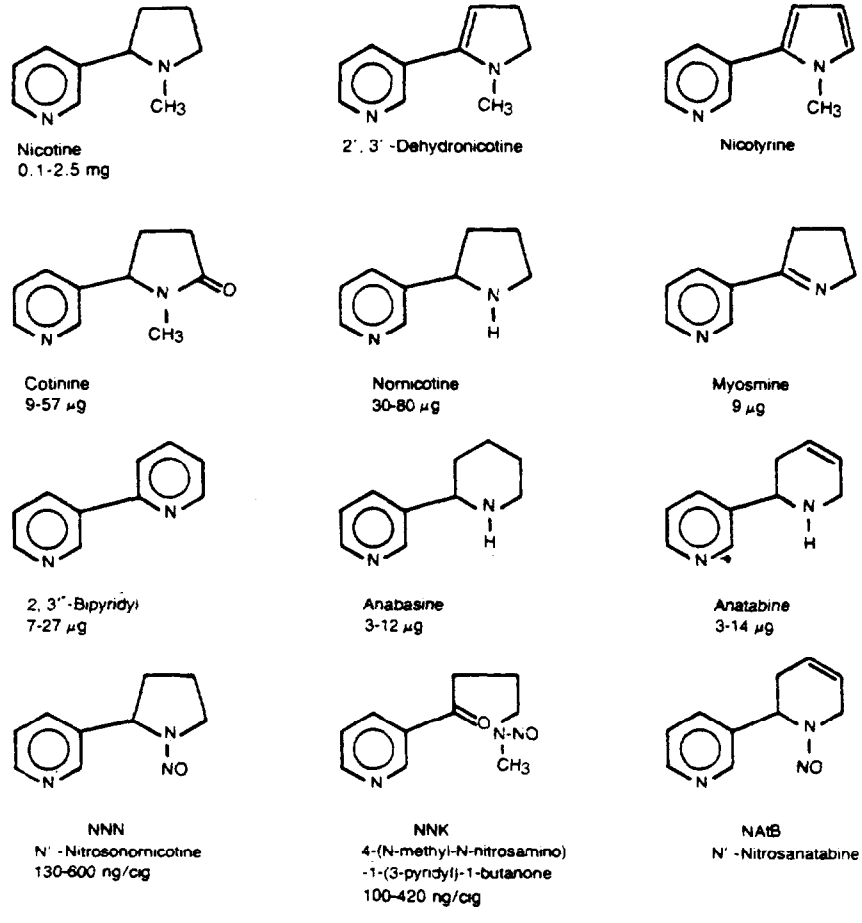


FIGURE 3.—Common tobacco alkaloids and tobacco-specific nitrosamines in cigarette smoke. (Numbers are values for mainstream smoke of a cigarette).

μg/cigarette) and cigars (NNN, 3.2 to 5.5 μg/cigarette; NNK, 1.9 to 4.2 μg/cigarette), as well as in the sidestream smoke of cigarettes (NNN, 1.7 to 6.1 μg; NNK, 0.41 to 0.60 μg) and cigars (NNN, 0.9 to 17.0 μg; NNK, 0.8 to 16.0 μg). Again, as for other smoke compounds depending on the reduction of nitrogen oxides in the burning cone, tobacco-specific nitrosamines are found in higher amounts in sidestream than in mainstream smoke (*38*).

The transfer rate of ^{14}C-labelled NNN into mainstream smoke was determined for a U.S. blended nonfilter cigarette and was found to be about 11 percent (*38a*). This finding indicates that about 50 percent of the NNN in the smoke originates by transfer from tobacco and the other half was pyrosynthesized from nicotine during smoking. The nonvolatile nitrosamines are of special interest because they are the only tobacco-specific carcinogens thus far identified.

In the United States, about 70 to 80 percent of all tobaccos are treated during cultivation with the sucker growth inhibitor, maleic hydrazide (MH-46). Since this chemical is water-insoluble, it is solubilized as a diethanolamine formulation. During curing, the diethanolamine residue on tobacco is nitrosated to the carcinogenic N-nitrosodiethanolamine (*74, 76*). As an alternative, the potassium salt of MH has been used to impart water solubility. Although no data are presently available, it is possible that residues of pesticides with amino groups give rise to nitrosamines in tobacco and its smoke (e.g., carbaryl)(*20*). This area needs to be investigated.

Aromatic Amines

Aromatic amines have been discussed as one possible factor in the association of cigarette smoking with bladder cancer (*16*). So far, two known human bladder carcinogens have been identified in trace amounts in cigarette smoke. These are β-naphthylamine (1–2 ng/cigarette) and 4-aminobiphenyl (0.8–2.4 ng/cigarette). These amines may serve as indicators of the concentration of other potential carcinogens in tobacco smoke, since most aromatic amines are pyrosynthesized by the same mechanism and have been isolated from tobacco smoke, although not yet fully identified (*66, 67*). Furthermore, a safe level of exposure for human bladder carcinogens has not been established (*73, 93*). Tobacco smoke also contains a number of alkylated o-toluidines, of which only the parent compound has been tested so far and found to be carcinogenic in the experimental animal (*73*).

Sidestream smoke of cigarettes contains significantly higher amounts of aromatic amines than mainstream smoke. For example, the mainstream smoke of a nonfilter cigarette was found to contain 160 ng of o-toluidine, 1.7 ng of β-naphthylamine, and 4.6 ng of 4-aminobiphenyl. The amounts of these amines in the sidestream smoke of the same cigarette were 3,000 ng, 67 ng and 140 ng, respectively (*67*). Since tobacco smoke may also contain the highly mutagenic amino-β-

carbolines which can be pyrosynthesized from tryptophan (*87*), further studies are needed before one can evaluate the contribution of aromatic amines to tobacco carcinogenesis.

Alkanes and Alkenes

The coating of leaves with "waxes" is an almost universal phenomenon throughout the plant kingdom (*100*). The waxy layer of tobacco leaves is primarily composed of alkanes, alkenes, terpenes, esters, phytosterols, and alkaloids (*85*). The tobacco specific alkane fraction of the wax layer is made up of n-, iso-, anteiso-$C_{24}H_{50}$ to $C_{34}H_{70}$ paraffin hydrocarbons. The most abundant hydrocarbon is n-(and iso-) hentriacontane ($C_{31}H_{64}$), which amounts to 30 to 40 percent of the total alkanes. Trace amounts of hydrocarbons have also been found from $C_{12}H_{26}$ to $C_{23}H_{48}$. The content of the crystalline alkanes amounts to 0.24 to 0.43 percent of the dry weight of the leaves.

Mainstream smoke of nonfilter cigarettes contains between 0.7 and 1.2 mg of nonvolatile alkanes, depending on the type of tobacco leaves used as cigarette filler. When diluents such as reconstituted tobacco sheets, stems, or expanded tobacco are incorporated into the cigarette blend, the content of nonvolatile alkanes decreases accordingly. These nonvolatile hydrocarbons are retained by filter tips to the same degree as "tar" in general.

Studies with ^{14}C-labelled n-dotriacontane have shown that about 25 percent of the radioactivity is recovered in the mainstream smoke and 75 percent in the sidestream smoke. Of the radioactivity in the mainstream smoke, about 95 percent was given by the unchanged C_{32}-hydrocarbon and 0.7 percent by $CO + CO_2$ and the rest by C_1 to C_{10} compounds. N-dotriacontane did not contribute in any measurable degree to the benzo(*a*)pyrene content in mainstream and sidestream smoke (*47*).

So far, only a limited number of studies have been concerned with the unsaturated hydrocarbons (C_{10} to C_{32}) in the mainstream smoke particulate matter, because they amount to less than 0.02 percent of the "tar." It appears that the nonvolatile acids, esters, and ketones in the leaf serve as precursors for the alkenes in the smoke.

The alkanes and alkenes appear to play no major role in tobacco toxicity and carcinogenesis other than to influence the resorption of smoke carcinogens. In studies on mouse skin, this effect was seen as an inhibition of resorption, which delayed latency of tumor development and diminished tumor yield.

Tobacco Isoprenoids

Tobacco and its smoke contain a large spectrum of isoprenoids; many of them can be regarded as tobacco-specific constituents (*85*). They are important because they contribute to the organoleptic nature of

tobacco smoke and thereby add to the consumer acceptability of specific tobacco products. The increasing volume of cigarettes with reduced and low "tar" yield and the desire to produce tobacco substitutes have given renewed impetus to chemical research on tobacco flavor components, especially on tobacco isoprenoids, during the last decade.

Primarily four types of terpenoids are found in tobacco: the carotenoids and acyclic isoprenoids; the cytoplasmic triterpenoids and phytosterols; the diterpenoids, which are biosynthesized in the trichomes; the glandular hair of the leaves; and the cyclic sesquiterpenoids and monoterpenoids (Figure 4) (*85*). The concentration and nature of these terpenoids in the leaf are not just dependent on plant genetic factors and growth conditions but also on the curing and fermentation processes that lead to the final tobacco product.

For the details on the chemistry and organoleptic nature of individual tobacco terpenes, the reader should refer to the specific scientific literature (*21*, *82*, *85*, *100*). At present, several hundred isoprenoids have been isolated from tobacco. During smoking, some of these compounds, especially the more volatile ones, are transferred partially intact and appear also in the mainstream smoke as thermally rearranged or oxidized decomposition products. Although it has been demonstrated that the tobacco terpenoids represent an important part of smoke flavor, little is known about their contribution to the toxicity or tumorigenic properties of tobacco products. Some authors have considered it possible that certain cyclic tobacco isoprenoids may be active as tumor promoters (*36*), while others have shown that cyclic terpenes, upon pyrolysis, form relatively high concentrations of carcinogenic polycylic hydrocarbons (*100*). At best, the data at hand are inconclusive. Therefore, intensified research is needed on the possible contribution of isoprenoids to smoke toxicity and tumorigenicity. The importance of such a program is underscored by the fact that, today, flavoring agents derived from tobacco and mixtures of plant extracts are added to tobacco in order to make low "tar" cigarettes acceptable to the consumer.

Benzenes and Naphthalenes

During all incomplete combustions of organic matter, small amounts of aromatic hydrocarbons are formed. Like other plant materials, tobacco already contains a number of compounds with the benzene ring structure, such as hemicellulose, plant phenols and polyphenols, certain amino acids, and a few terpenes (e.g., aromatized menthanes) (*82*, *85*, *100*). In addition, benzenes are pyrosynthesized from C,H-radicals and by diene-synthesis reactions with subsequent dehydrogenation during burning of the tobacco. It is, therefore, not surprising that cigarette smoke contains more than two dozen benzene hydrocarbons, with toluene (20 to 150 μg/cigarette) and benzene itself (10 to 100 μg) as the

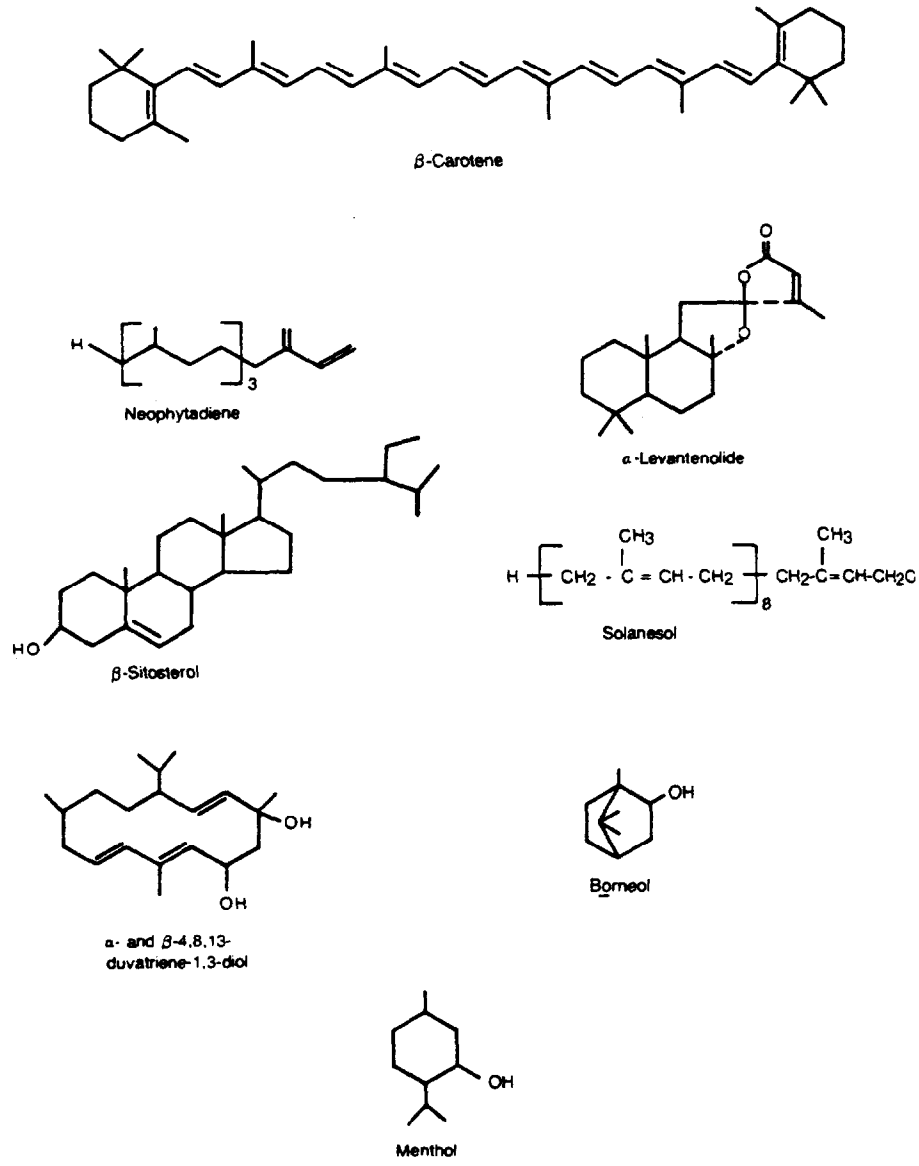


FIGURE 4.—Tobacco isoprenoids.

most abundant compounds of this type. Most benzene compounds are considered to be semivolatile and thus are present in both the gaseous and the particulate phase.

Concern has been expressed in recent years about the possible risk of leukemia for workers who have been exposed to benzene. This concern has led to a standard of 10 ppm as a threshold limit for benzene in the working atmosphere. Although some prospective and retrospective studies have reported a somewhat higher risk of leukemia for cigarette smokers, these data remain unconfirmed and no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked.

In model studies with ^{14}C-labelled precursors, Badger and his group showed that the probability of pyrosynthesis of polycyclic aromatic hydrocarbons decreases with the number of condensed rings (*3*); thus, tobacco smoke contains less naphthalene (2.0 to 3.5 μg/cigarette) than toluene (20 to 150 μg/cigarette) (*6, 85, 100*). Other naphthalenes identified in cigarette smoke are ethylnaphthalenes, dimethylnaphthalenes, and trimethylnaphthalenes . Neutral tobacco smoke condensate fractions, which contain naphthalene and methylnaphthalenes and are free of three-ring and higher polycyclic hydrocarbons, are inactive as carcinogens, co-carcinogens, and tumor initiators, as are the pure compounds (*77, 78*). There has been some indication that naphthalenes may induce lymphomas in mice; however, this finding needs confirmation.

Polynuclear Aromatic Hydrocarbons (PAH)

Fractionation studies with tobacco "tar" have shown that only those neutral fractions and subfractions in which the PAH are enriched induce tumors on mouse skin and the bronchial epithelium of rats and sarcomas in the connective tissues of rats (*40, 83, 100*). Minute subfractions (<0.002 percent) of the "tar," containing only four-, five-, and six- ring PAH, are the only fractions which show activity as tumor initiators upon application in low doses. PAH alone, however, account for only a small portion of the carcinogenicity of tobacco "tar." These observations, and the fact that a significant reduction of PAH in the smoke leads to a concomitant reduction of the tumorigenicity of the total "tar" on mouse skin, are the major reasons for the extensive chemical analytical studies and identification of tumorigenic PAH (*83, 100*). More than 100 individual four-ring and higher polycyclic hydrocarbons have been identified to date. These include the classical carcinogens benzo(*a*,)pyrene, dibenz(*a,h*)anthracene, and dibenzo(*a,h*)pyrene as well as other PAH. The levels of carcinogenic PAH in tobacco smoke are well below their practical threshold as complete mouse skin carcinogens, but their role in tobacco smoke condensate is definitely that of a tumor initiator.

Certain PAH are not active when tested as complete carcinogens, but they are active as tumor initiators or as co-carcinogens when applied as such. A major characteristic for a tumor initiator is that it merely induces a dormant tumor cell, thus not eliciting tumors in epithelial tissues unless the tissue is exposed to a promoting agent. Promotors are active only in tissues previously treated with a tumor initiator. A co-carcinogen is a chemical which is neither a tumor initiator nor a complete carcinogen; it is, however, typically capable of significantly increasing the carcinogenic response towards a low dose of a carcinogen. Figure 5 presents the structural formulas of several carcinogenic PAH, tumor-initiating PAH and co-carcinogenic PAH. Table 15 lists the concentrations of some of the active PAH in cigarette smoke. Since it has been demonstrated that most, though not all, of the PAH are pyrosynthesized from C,H-radicals by the same mechanism and from unspecific precursors, carcinogenic B*a*P has often been used as an indicator of the concentration of tumorigenic PAH in the smoke of a given cigarette and cigar. The concentration of B*a*P in "tar" of cigarettes made primarily from tobacco lamina has served as an indicator of the carcinogenic potential of the smoke particulates on mouse skin.

N-Heterocyclic Hydrocarbons (Aza-Arenes)

Although the nicotine-free basic portion of tobacco smoke is inactive as a complete carcinogen, it contains traces of carcinogenic aza-arenes. This group includes dibenz(*a*,*h*)acridine and dibenz(*a*,*j*)acridine (Figure 6). Another aza-arene with carcinogenic activity is dibenzo(*c*,*g*)carbazole, which is found in the neutral portion (*100*). Van Duuren and coworkers have shown in model studies that nicotine can serve as precursor for these carcinogenic aza-arenes (*94*). So far, the basic portion of tobacco smoke has not been found to be carcinogenic (*40*). Mutagens thus far identified in cigarette smoke are: quinoline (MS 1.7 μg/cigarette; SS 18 μg/cigarette), all seven isomeric methylquinolines (MS 0.7 μg/cigarette; SS 8 μg/cigarette), benzo(*f*)quinoline (MS 0.01 μg/cigarette; SS 0.1 μg/cigarette), phenanthridine (MS 0.01 μg/cigarette; SS 0.01 μg/cigarette), and benzo(*h*)quinoline (MS 0.01 μg/cigarette; SS 0.1 μg/ cigarette) (*84*, *88*). Quinoline induces hepatomas when fed in high doses to rats (*19*, *37*, *83*).

Phenols

The weakly acidic fraction of cigarette smoke condensate is active as both a tumor promoter and co-carcinogen (*13*, *100*). It contains volatile phenols, polyphenols, cyclopentenols, fatty acids, and pyridinols (Figure 7). Among these, the catechols are of special interest as co-carcinogens (*95*). At present, however, the major tumor promoters and co-carcinogens in the weakly acidic fraction need identification.

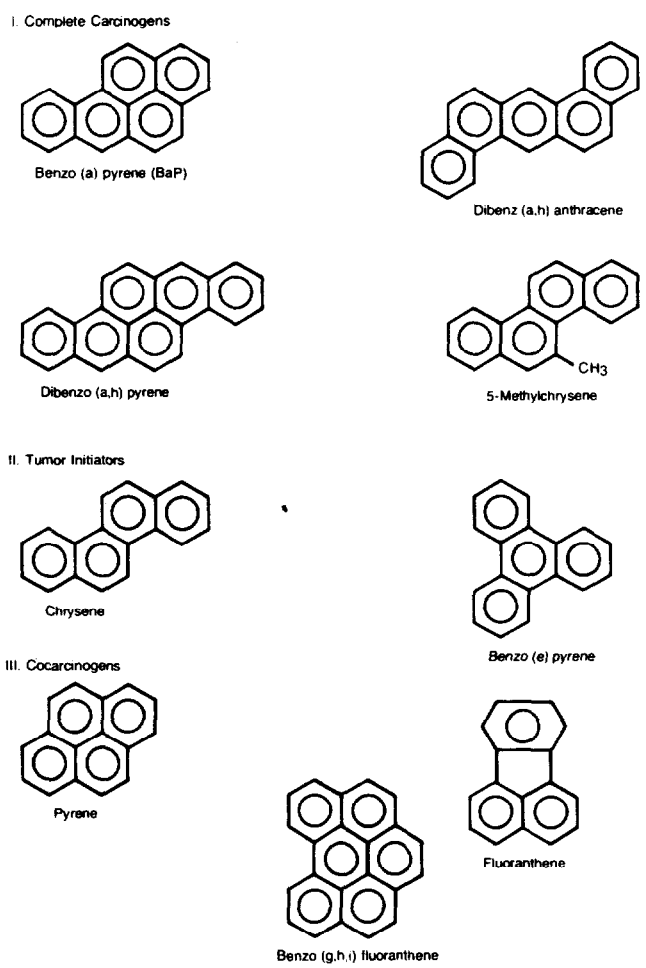


FIGURE 5.—Some tumorigenic PAH in tobacco smoke.

TABLE 15.—Tumorigenic PAH in cigarette smoke[1]

PAH	Relative activity as complete carcinogen[2]	ng/cig
I. *Active as tumor initiators*		
Benzo(*a*)pyrene	+ + +	10–50
5–Methylchrysene	+ + +	0.6
Dibenz(*a,h*)anthracene	+ +	40
Benzo(*b*)fluoranthene	+ +	30
Benzo(*j*)fluoranthene	+ +	60
Dibenzo(*a,h*)pyrene	+ +	pr[3]
Dibenzo(*a,j*)pyrene	+ +	pr[3]
Indeno(1, 2, 3–cd)pyrene	+	4
Benzo(*c*)phenanthrene	+	pr[3]
Benz(*a*)anthracene	+	40–70
Chrysene	- (+?)	40–60
Benzo(*e*)pyrene	- (+?)	5–40
2–, 3–Methylchrysene	+	7
1–, 6–Methylchrysene	-	10
2–Methylfluoranthene	+	30
3–Methylfluoranthene	?	40
Dibenz(*a,c*)anthracene	?	pr[3]
II. *Active as co-carcinogens*		
Pyrene	-	50–200
Methylpyrenes	-	50–300
Fluoranthene	-	100–260
Benzo(*g,h,i*)perylene	-	60

[1]Incomplete list.
[2]Relative carcinogenic activity on mouse skin.
[3]Present, but no quantitative data available.
SOURCE: Hoffman, D. (*40*).

Catechol is the phenol with the highest concentration in the smoke of cigarettes. In the mainstream smoke of a plain cigarette it varies from 160 to 500 μg, and in the mainstream smoke of a filter cigarette it ranges from 60 to 200 μg (*10, 100*). Smoke also contains a number of alkylated catechols, hydroquinone, resorcinol, and volatile phenols. The latter group appears to contribute only to a minor extent to the tumor-promoting activity of the weakly acidic portion. Compared to mainstream smoke, sidestream smoke of cigarettes contains less catechol (SS/MS 0.7–0.8) and more volatile phenols (SS/MS 2–3). It appears that the major precursors for the smoke catechols reside in the "wax" layer of the tobacco leaf and that the major precursors for the smoke phenols are the tobacco carbohydrates.

Extensive investigations in several laboratories have demonstrated highly selective filtration of semi-volatile phenols from cigarette smoke by cellulose acetate filter tips (*52, 61*). Because of their low

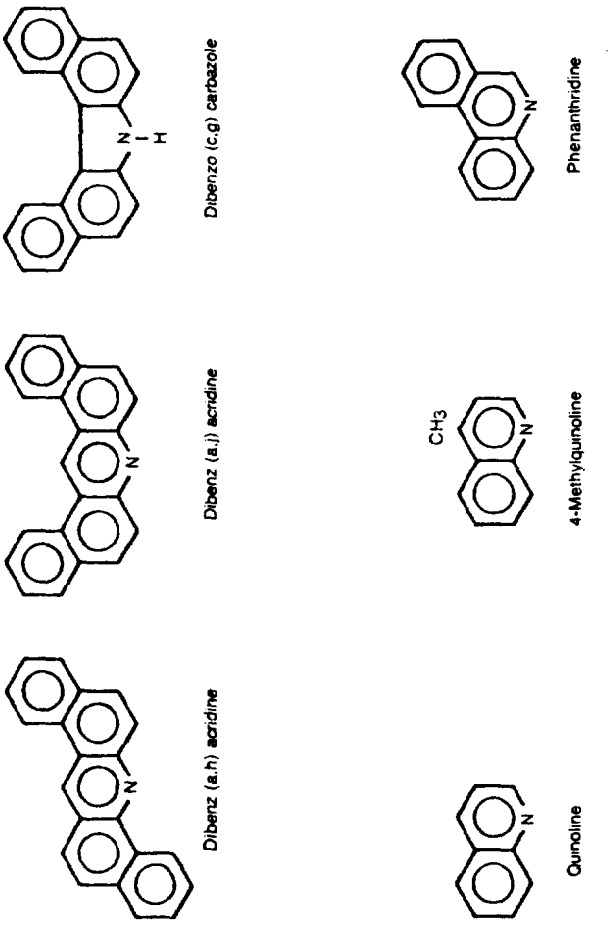


FIGURE 6.—Carcinogenic aza-arenes in tobacco smoke.

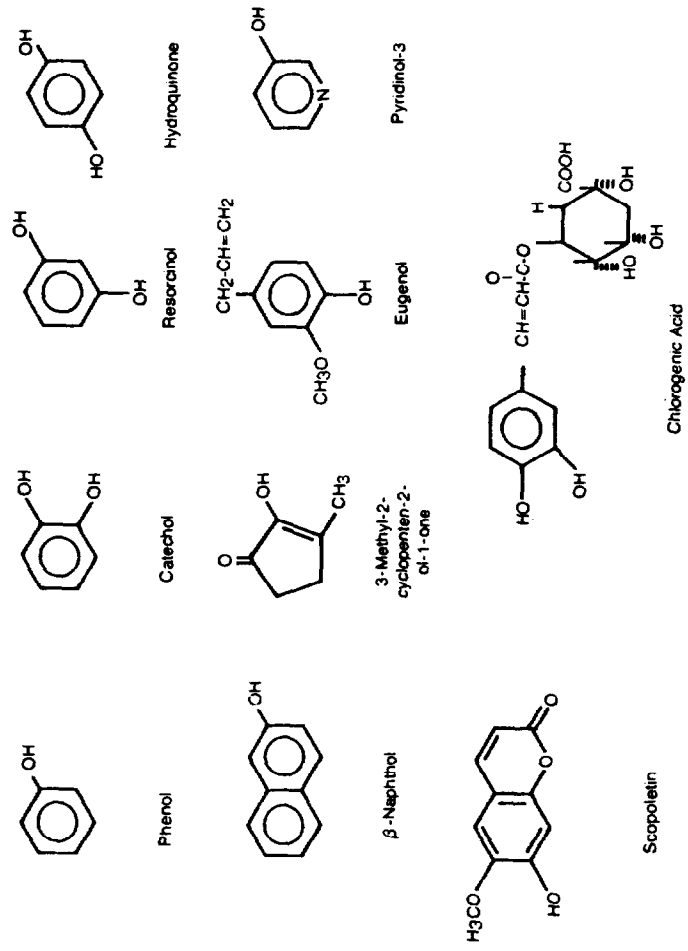


FIGURE 7.—Weakly acidic compounds in cigarette smoke.

TABLE 16.—Major phenols in cigarette smoke

Phenol	μg/cigarette		Remarks[1]
	Nonfilter	Filter	
Phenol	50–130	10–50	1
o-Cresol	20–40	7–20	1
m- + p-Cresol	40–70	15–25	1
2,4-Dimethylphenol	15–25	5–12	1
Catechol	160–500	60–200	2
3-Methylcatechol	15–25	10–20	2
4-Methylcatechol	15–25	10–20	2
Hydroquinone	50–120	N.D.[2]	-
Resorcinol	15–20	N.D.	-
Eugenol	3–10	N.D.	-
Isoeugenol	8–20	N.D.	-
Scopoletin	140–280	N.D.	-
Chlorogenic Acid	N.D.	N.D.	-
Rutin	N.D.	N.D.	-
β-Naphthol	0.5–2	N.D.	-

[1]Remarks: 1 = Tumor promoting agent on mouse skin
2 = Cocarcinogen on mouse skin;
- = Inactive or not tested.
[2]N.D. = Quantitative data not determined.
SOURCE: Keith, C.H. (*52*), Morie, G.P. (*61*).

vapor pressure, no selective reduction by filter tips was observed for catechols (Table 16).

Cyclopentanediones found as constituents of the weakly acidic portion of tobacco smoke are considered important flavor compounds in tobacco smoke. Their concentrations are highest in the smoke of Oriental tobaccos, less in Burley and the least in flue-cured varieties (9:2:1) (*26*). It appears that these compounds are not toxic.

Carboxylic Acids

A considerable number of carboxylic acids are present in tobacco and tobacco smoke. More than 50 of these have been identified thus far in smoke, accounting for 4 to 7 percent of the particulate matter. The composition of the fraction of volatile carboxylic acids (C_1 to C_6) is a determining factor in the flavor of tobacco varieties. Oriental tobaccos, for example, have a high proportion of β-methylvaleric acid and also contain hydroxyderivatives of valeric- and β-methylvaleric acid. Flue-cured tobaccos are often high in acetic acid, whereas benzoic acid predominates in Burley tobaccos. The non-volatile fatty acids in tobacco range from C_8–C_{24} with highest concentrations of palmitic acid (C_{16}), C_{18}-acids, stearic, oleic, linoleic and linolenic acids. These range from 0.01 to 0.7 percent in dry tobacco leaf and from 1 to 3 percent in the tar. The highest fatty acid concentrations are found for Turkish tobacco and its smoke.

TABLE 17.—Free fatty acids in cigarette smoke

Acid	μg/l g Tobacco smoked[1]				
	Turkish 1	Bright	Maryland	Burley	Blend
Palmitic	284	197	107	55	152
Stearic	90	74	43	33	75
Oleic	108	39	32	21	58
Linoleic	146	113	52	50	96
Linolenic	329	310	66	52	240
Total (mg)	0.96	0.73	0.30	0.21	0.62
Wet TPM (mg)	37.2	37.6	26.4	20.1	32.3
5 fatty acids % of TPM (wet)	2.6	1.95	1.14	1.05	1.9

[1]Moisture content of the tobaccos varied between 11.5 and 12.0%.
SOURCE: Hoffman, D. (*40a*).

Transfer rates of unchanged fatty acids from tobacco into mainstream smoke can be up to 20 percent, especially for the saturated fatty acids of C_{16}-C_{18} chain length. Lower transfer rates are observed for the C_{18} unsaturated fatty acids—oleic, linoleic, and linolenic acid. Comparative concentrations of the major fatty acids in the smoke of various cigarettes are presented in Table 17.

Although high concentrations of fatty acids play a role as tumor promoters in model studies with B*a*P it appears that these fatty acids are of lesser importance in tobacco carcinogenesis. About two dozen hydroxy-γ-lactones of C_4 to C_6-acids have been identified in tobacco smoke. They probably arise from tobacco leaf carbohydrates by thermal degradation (*81*). γ-Lactones have not been fully examined for their biological significance in tobacco carcinogeneis. However, several of these compounds are known alkylating agents and as such induce sarcomas in rats (*54*).

Metallic Constituents

Minerals and other inorganic compounds in the tobacco plant derive from soil, fertilizers, or agricultural sprays. The most prominent metal ions in tobacco are Ca++, Mg++, K+, and Na+. During combustion, the bulk of metallic constituents remain in the ashes, but some compounds are vaporized or transferred into the smoke stream. With the growing sophistication of analytical techniques, the list of trace amounts of metals is increasing. Presently, 76 metals, including Bi, Si, As, Se, and Te, excluding the post-uranium metals, have been detected in cigarettes. Of these, 30 have been identified in the smoke (Table 18) (*63*).

TABLE 18.—Metals in cigarette smoke particulate

Metal	(μg/cig)	Metals for which good quantitative data are not available
K	70	
Na	1.3	
Zn	0.36	
Pb	0.24	Si
Al	0.22	Ca
Cu	0.19	Ti
Cd	0.12[1]	Sr
Ni	0.080[1]	Tl
Mg	0.070	Po[2]
Sb	0.052	
Fe	0.042	
As	0.012[1]	
Te	0.006	
Bi	0.004	
Hg	0.004	
Mn	0.003	
La	0.0018	
Sc	0.0014	
Cr	0.0014	
Ag	0.0012	
Se	0.001	
Co	0.0002	
Cs	0.0002	
Au	0.00002	

[1]Cigarettes other than the University of Kentucky Reference cigarette
[2]Levels expressed in terms of radioactivity
SOURCE: Norman, V. (*63*).

With respect to tobacco carcinogenesis, special interest has focused on As and Ni. The continued trend toward replacement of arsenical sprays with other pesticides has been reflected in progressively lower arsenic contents of leaf and smoke. Between 1940 and 1950, arsenic values in the dry leaf of up to 50 to 60 ppm were reported for U.S. tobaccos (*31*). The last published data for U.S. tobaccos range between 0.5 and 0.9 ppm (*28*). Between 7 and 18 percent of the total arsenic in tobacco reappears in the mainstream smoke of cigarettes. Studies with ^{74}As-labelled cigarettes have shown that, depending on the individual's smoking patterns, 2.2 to 8.6 percent of the arsenic in cigarette tobacco is transferred into the respiratory tract. About 50 percent of the inhaled arsenic is eliminated within 10 days, primarily in urine; the remainder is either deposited in body tissues or is exhaled or otherwise eliminated (*41*).

All forms of nickel (metal, oxide, sulfide, salts, and carbonyl) tested in the experimental animal were found to be carcinogenic. In nickel factories, primarily in those converting nickel sulfide to nickel oxide,

workers have a high risk for cancer of the nasal cavity and cancer of the lung. In cigarette tobacco, 2.0 to 6.2 μg Ni per cigarette were reported; other tobacco products contained between 0.5 and 8.5 μg per gram. In South Africa, nickel values of 52 and 88 μg per gram of Swazi snuff were reported as a possible contributing factor in the high incidence rate of cancer of the nose and in accessory sinuses in male Bantus (*5*). During smoking, 10 to 20 percent of the nickel in the tobacco is transferred into the mainstream smoke (*62*). In one study, tentative evidence indicated that most of the nickel transferred into the mainstream smoke (≅10) is present in the gas phase (≅8 percent) (*90*). This and a model study suggest that nickel is present in the gas phase of tobacco smoke as nickel carbonyl. $Ni(CO)_4$ is highly carcinogenic in the respiratory tract of rats. It induces epidermoid carcinomas and adenocarcinomas of the lung (*89*).

Several forms of cadmium are carcinogenic in the experimental animal. Two studies suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer (*45*). In mainstream smoke, concentrations are 9–70 ng Cd per cigarette (*45*). It has been suggested that a heavy smoker retains about 1.5 μg of Cd per day and that he may accumulate up to 0.5 mg through inhalation.

Radioactive Compounds

Two types of radioactive compounds have been reported in tobacco and tobacco smoke. These are the α-particle emitting elements of the disintegrating radium and thorium series and the β-emitters. In the latter group, potassium-40 is the most abundant in tobacco products (*100*). A sample of 100 U.S. and Canadian cigarettes was found to contain 2,120 and 2,295 pCi of ^{40}K-derived β-activity, respectively. The β-activity from ^{40}K in the mainstream smoke of 100 cigarettes was 15.9 and 9.4 pCi, corresponding to a transfer rate of 0.75 percent and .41 percent, respectively. ^{40}K is a soft emitter with E_{max} of 1.3 meV.

The presence of radioelements ^{226}Ra, ^{210}Pb, and ^{210}Po in tobacco products (e.g., from fallout, natural background) have been of special interest and concern (*69*). The general range of ^{210}Po in 1 g of U.S. tobacco leaf varies from 0.15 to 0.45 pCi. In the smoke of one U.S. cigarette, ^{210}Po values of between 0.03 and 0.07 pCi were reported. The average ^{210}Po content was ≅0.036 PCi per cigarette or ≅2.6 pCi of ^{210}Po per 1 g smoke condensate with a ^{210}Pb: ^{210}Po ratio of 0.66 ± 0.23 (*42*). $^{210}_{82}Pb$ has a half-lifetime of 22 years and decays by emission of two β-particles to $^{210}_{84}Po$; the latter decays by α-emission with a half-lifetime of 138.4 days. Preliminary studies indicate that most of the ^{210}Pb is concentrated in the nonvolatile and insoluble portion of the particulate matter of cigarette smoke (*58*).

Analysis of human tissues demonstrated that the lung, blood, and liver of smokers contain a higher concentration of ^{210}Po than do those of nonsmokers. It has been calculated that a smoker's intake of ^{210}Po is

reflected within several days by the observed excess burden of 3–10 pCi of ^{210}Pb and ^{210}Po in the lungs. Based on the measured concentration of ^{210}Po in epithelial samples, Little and Radford estimated a maximum radiation dose of $\cong$200 rem per 25 years to the lower lobe bifurcations of the lung (*56*); however, others have estimated a far lower effective radiation dose (*14, 70*).

After multiple intratracheal installations of ^{210}Po in Syrian golden hamsters, a dose-dependent increase was observed in epidermoid carcinoma and adenocarcinoma in the peripheral lung fields (*55*). Simultaneous and multiple intratracheal instillation of benzo(a)pyrene (total dose 4.5 mg) and ^{210}Po (total dose 50,000 pCi) on the same carrier induced twice the number of tumors expected from the additive effect of either carcinogen alone (*59*).

Agricultural Chemicals

As in the case of arsenical pesticides, a significant reduction in the use of chlorinated hydrocarbon insecticides on tobacco has occurred during the last decade. This is reflected in the reduction of such insecticide residues as DDD, DDT, endrin, and endosulfan on tobacco (Figure 8). Whereas in 1968 70.2 percent of all U.S. flue-cured auction-marketed tobaccos contained more than 10 ppm of DDT, in 1972 there was no tobacco of the same type containing levels above 10 ppm of DDT. In the latter year, 73.1 percent of the tobaccos marketed contained only 0.1 to 0.49 ppm of DDT (*17*). DDD values declined from levels of $\geq$ 10 ppm in 97.6 percent of the 1968 crop to levels no higher than 0.1 to 0.49 percent in 63.9 percent of the tobaccos marketed in 1972. Again, there was no tobacco with levels of DDD above 10 ppm in 1972. Similar reductions of insecticide residues on tobacco were reported for endrin, dieldrin, and endosulfan (*17, 30*). A further gradual decrease of these pesticides in tobacco is expected. During smoking, 11 to 18 percent of DDT and DDD are transferred without change of structure from tobacco into the mainstream smoke of cigarettes. DDE, DDM, and 4,4′-dichlorostilbene (Figure 8), an immediate decomposition product of DDT and DDM resulting from elimination of HCL and molecular rearrangement, are also detected in mainstream smoke (*39*). One study showed that levels of chlorinated hydrocarbon insecticides in adipose tissues of smokers were not elevated above those in nonsmokers (*18*). Other pesticide residues found on some U.S. tobaccos are parathion (up to 0.03 ppm), carbaryl (up to 1.5 ppm), endosulfan (up to 2.9 ppm), and toxaphene (0.7 to 3.4 ppm) (*30*).

Some of the chlorinated hydrocarbon insecticides and the isomeric impurities present in the technical preparations, e.g., o,p′-DDD, are possible or known carcinogens in experimental animals. One of the co-carcinogens is 4,4′-dichlorostilbene, formed by pyrolysis from DDT and DDD (*40*). As discussed earlier, the carbaryl residue on tobacco may give rise to a carcinogenic nitrosamine. Similarly, maleic hydrazide and

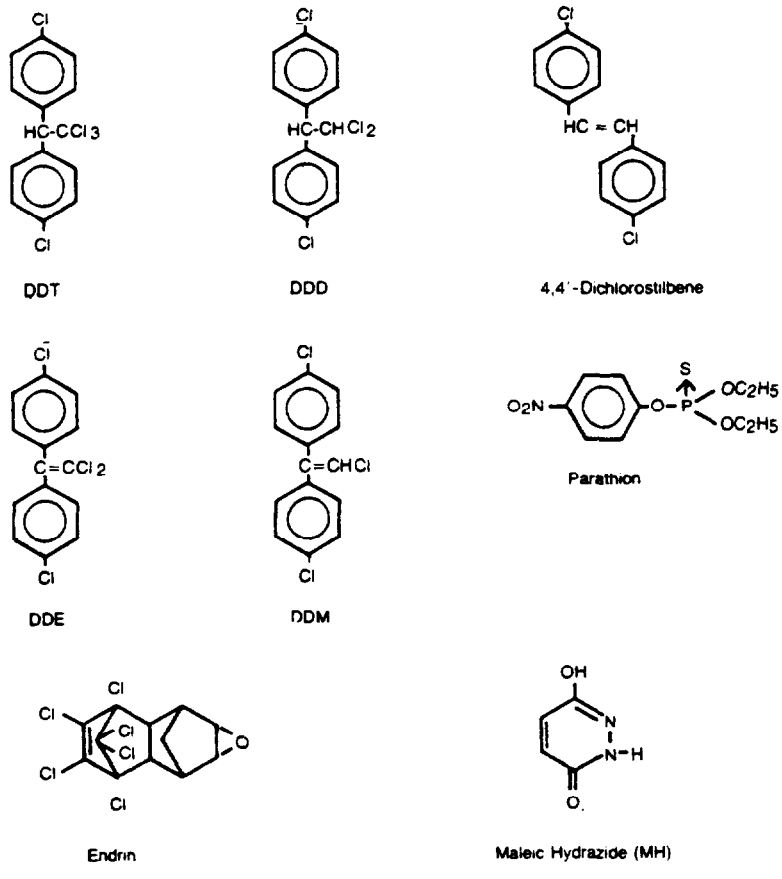


FIGURE 8.—Residues of agricultural chemicals in tobacco and cigarette smoke.

its soluble salts have been mentioned. Present evidence is not uniformly clear as to whether pure MH is mutagenic or carcinogenic, though the weight of the evidence suggests it is mutagenic. (*22, 32*).

Tobacco Additives

Tobacco products are refined by the addition of additives, humectants, tobacco casings, and flavor-enhancing compounds. The most widely used humectants are propanediol, glycerol, diethylene glycol, triethylene glycol, and D-sorbitol (*100*). Humectants amount to 2 to 4 percent of the original tobacco weight for cigarettes. Analyses of 18 U.S. cigarette brands showed ranges of 0.46 to 2.24 percent of propylene glycol and 1.7 to 3.15 percent of glycerol in the tobaccos (*15*). Smoke analyses demonstrated that in filter cigarettes 9.9 percent and in nonfilter cigarettes 12.6 percent of the propylene glycol in tobacco reappear unchanged in the mainstream smoke. The glycerol transfer rate into the mainstream smoke of filter and nonfilter cigarettes was 12 and 14 percent, respectively. The smoke of humectant-treated cigarettes had increased amounts of acetaldehyde and acetone (*53*). Transfer of humectants into the mainstream smoke is probably significantly greater in pipe smoking than in cigarette smoking because of the former's higher puff frequency (*60*).

The use of humectants in tobacco products has raised concern as to their effects on smoke toxicity. Formation of volatile aldehydes and ketones, including acrolein, from combustion of such humectants would add to the ciliatoxicity of tobacco smoke. The glycols, especially diethylene glycol, are suspected to influence the smoker's risk for bladder cancer (*44*).

Pipe tobaccos may contain up to 30 percent of casing agents. These are primarily sugars, starches, humectants, and plant extracted isoprenoids. These casing agents influence the flavor of the tobacco smoke, as well as the burning rate of the tobacco, and thus affect smoke toxicity. When cigarette tobacco contained 5 percent or higher levels of sugar additives, the resulting smoke was higher in furfural, nicotine, and tar content than the smoke from an identical cigarette without the sugar casing (*86*).

The flavor of cigarette smoke is also affected by the curing, aging, and blend of tobaccos used. Considerations such as acreage yield and tobacco prices during the last decade have resulted in changes of leaf aroma affecting the tobacco blends and thus the smoke flavor. More importantly, however, the trend toward low-tar, low-nicotine cigarettes and toward a reduction of undesirable volatile smoke compounds has brought about major changes in the smoke flavor of cigarettes. The use of rolled stems and reconstituted tobacco sheet admixed with leaf lamina and the use of effective filter tips are major factors inducing changes in smoke flavor. All of these developments have led to increased use of flavor additives, especially for low-tar, low-nicotine

TABLE 19.—Harmful constituents of cigarette smoke particulate matter

I. Compounds judged most likely to contribute to the health hazards of smoking[1]:		
Nicotine 50–2,500 μg/cig		"Tar"[2] 500–35,000 μg/cig
II. Compounds judged as probable contributors to the health hazards of smoking:		
Cresols (all 3 isomers) 68–97 μg/cig		Phenol 9–202 μg/cig
III. Compounds judged as suspected contributors to the health hazards of smoking:		
DDT	0–0.77 μg/cig	Endrin 0–0.06 μg/cig
Hydroquinone	83 μg/cig	Nickel compounds 0–0.58 μg/cig
Pyridine	25–218 μg/cig	

[1]Values from May 1978 FTC list

[2]"Tar" contains the polynuclear aromatic hydrocarbons which are "generally accepted as being responsible for a substantial portion of the carcinogenic activity of the total "tar". "Tar" also contains β-naphthylamine, a known human bladder carcinogen for which there is no known safe level of human exposure.

SOURCE: U.S. Public Health Service (*93*).

cigarettes. In fact, these new cigarettes require flavor corrections by additives in order to be acceptable to the consumer. Tobacco extracts as well as nontobacco flavors, such as licorice, coca, fruit, spices, and floral compositions, are used. More recently, suggestions for synthetic flavor additives for cigarette tobaccos are increasing in the patent literature. At present, the selection of tobacco flavor additives from the GRAS (Generally Regarded As Safe) List or from natural extracts and the screening of their smoke decomposition products for toxicity or other biological activity are not required by law and are done voluntarily by manufacturers.

Toxic and Carcinogenic Agents—A Summary

The report of an expert panel on the "harmful constituents of cigarette smoke" classified the harmful and possibly harmful smoke compounds into the following categories: (1) contributors, (2) probable contributors, and (3) suspected contributors to the health hazard of smoking (*93*).

The constituents of the particulate matter are listed according to this classification in Table 19. Since 1970, when the harmful smoke constituents were so defined, much progress has been made toward the identification of toxic and especially of tumorigenic agents in cigarette smoke. The identified tumorigenic agents and their quantities in cigarette smoke are listed in Table 20. The majority of co-carcinogenic agents in cigarette smoke remain to be identified.

The increased risk for cigarette smokers of cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette

TABLE 20.—Known tumorigenic agents in cigarette smoke particulates

Compound	μg/cig	Compound	μg/cig
I. *Tumor Initiators*		II. *Co-carcinogens*	
Benzo(*a*)pyrene	0.01–0.05	Pyrene	0.05–0.2
Other PAH[1]	0.3–0.4	Other PAH[2]	0.5–1.0
Dibenz(*a,j*)acridine	0.003–0.01	1-Methylindoles	0.8–
Other Aza Arenes	0.01–0.02	9-Methylcarbazoles	0.14–
Urethane	0.035	4, 4-Dichlorostilbene	0.5–1.5
		Catechol	200–500
		Alkylcatechols	10–30
III *Organ Specific Carcinogens*			
N'-Nitrosonornicotine	0.14–3.70		
4-(N-Methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone	0.11–0.42		
N'-Nitrosoanatabine	+[3]		
Polonium-210	0.03–0.07pCi		
Nickel Compound	0–5.8		
Cadmium compounds	0.01–0.07		
β-Naphthylamine	0.001–0.022		
4-Aminobiphenyl	0.001–0.002		
O-Toluidine	0.16		

[1]For details see Table 15
[2]For details see Table 15
[3]Concentrations unknown
SOURCE: U.S. Public Health Service (*93*).

smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic amines and N-nitrosamines.

Smoke Formation: References

(1) ADAMS, J.D., BRUNNEMANN, K.D., HOFFMANN, D. Determination of nitric oxide in unaged smoke by GSC-TEA. Abstract No. 36. Presented at the 32nd Tobacco Chemists' Research Conference, Montreal, Canada, October 30-November 1, 1978, p. 19.

(2) ARMITAGE, A.K., TURNER, D.M. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. Nature 226: 1231-1232, June 27, 1970.

(3) BADGER, G.M. The Chemical Basis of Carcinogenic Activity. Springfield, Illinois, Charles C. Thomas, 1962, pp. 16-19.

(4) BATTISTA, S.P. Cilia toxic components of cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 517-534.

(5) BAUMSLAG, N., KEEN, P., PETERING, H.G. Carcinoma of the maxillary antrum and its relationship to trace metal content of snuff. Archives of Environmental Health 23: 1-5, July 1971.

(6) BRUNNEMANN, K.D., HOFFMANN, D. Chemical studies on tobacco smoke. XXIV. A quantitative method for carbon monoxide and carbon dioxide in cigarette and cigar smoke. Journal of Chromatographic Science 12: 70-75, February 1974.

(7) BRUNNEMANN, K.D., HOFFMANN, D. Chemical studies on tobacco smoke. XXXIV. Gas chromatographic determination of ammonia in cigarette and cigar smoke. Journal of Chromatographic Science 13(4): 159-163, April 1975.

(8) BRUNNEMANN, K.D., HOFFMANN, D. The pH of tobacco smoke. Food and Cosmetics Toxicology 12: 115-124, 1974.

(9) BRUNNEMANN, K.D., HOFFMANN, D., WYNDER, E.L., GORI, G.B. Determination of tar, nicotine, and carbon monoxide in cigarette smoke. A comparison of international smoking conditions. XXXVII of chemical studies on tobacco smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 441-449.

(10) BRUNNEMANN, K.D., LEE, H.-C., HOFFMANN, D. Chemical studies on tobacco smoke. XLVII. On the quantitative analysis of catechols and their reduction. Analytical Letters 9(10): 939-955, 1976.

(11) BRUNNEMANN, K.D., YU, L., HOFFMANN, D. Assessment of carcinogenic volatile N-nitrosamines in tobacco and in mainstream and sidestream smoke from cigarettes. Cancer Research 37(9): 3218-3222, September 1977.

(12) BRUNNEMANN, K.D., YU, L., HOFFMANN, D. Chemical Studies on Tobacco Smoke. XLIX. Gas chromatographic determination of hydrogen cyanide and cyanogen in tobacco smoke. Journal of Analytical Toxicology 1(1): 38-42, January/February 1977.

(13) CARTER, W.L., HASEGAWA, I. Fixation of tobacco smoke aerosols for size distribution studies. Journal of Colloid and Interface Science 53(1): 134-141, October 1975.

(14) CASARETT, L.J. Role of radioactive substances in effects of smoking. Toward a less harmful cigarette. National Cancer Institute Monograph No. 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, June 1968, pp. 199-209.

(15) CUNDIFF, R.H., GREENE, G.H., LAURENE, A.H. Column elution of humectants from tobacco and determination by vapor chromatography. Tobacco 159(26): 58-65, December 25, 1964.

(16) DOLL, R. Cancers related to smoking. In: Richardson, R.G. (Editor). Proceedings of the Second World Conference on Smoking and Health, London, September 20-24, 1971. London, Pitman Medical, 1971, pp. 10-23.

(17) DOMANSKI, J.J., HAIRE, P.L., SHEETS, T.J. Insecticide residues on 1972 U.S. auction-market tobacco. Beitraege zur Tabakforschung 8(1): 39-43, January 1975.

(18) DOMANSKI, J.J., NELSON, L.A., GUTHRIE, F.E., DOMANSKI, R.E., MARK, R., POSTLETHWAIT, R.W. Relation between smoking and levels of DDT and dieldrin in human fat. Archives of Environmental Health 32: 196-199, September/October 1977.

(19) DONG, M., SCHMELTZ, I., LAVOIE, E., HOFFMANN, D. Aza-arenes in the respiratory environment: Analysis and assays for mutagenicity. In: Jones, P.W., Freudenthal, R.I. (Editors). Carcinogenesis, Volume 3. Polynuclear Aromatic Hydrocarbons. New York, Raven Press, 1978, pp. 97-108.

(19a) DUPONT COMPANY. Corporate news release. Acrylonitrile may cause cancer in man. Wilmington, Delaware, Dupont Company, May 23, 1978, 4 pp.

(20) ELESPURU, R., LIJINSKY, W., SETLOW, J.K. Nitrosocarbaryl as a potent mutagen of environmental significance. Nature 247: 386-387, February 8, 1974.

(21) ENZELL, C.R., WAHLBERG, I., AASEN, A.J. Isoprenoids and alkaloids of tobacco. Fortschritte der Chemie Organischer Naturstoffe 34: 1-79, 1977.

(22) EPSTEIN, S.S., ANDREA, J., JAFFE, H., JOSHI, S., FALK, H., MANTEL, N. Carcinogenicity of the herbicide maleic hydrazide. Nature 215: 1388-1390, September 23, 1967.

(23) FEDERAL TRADE COMMISSION. Report of "tar" and nicotine content of the smoke of 167 varieties of cigarettes. Federal Trade Commission, May 1978, 17 pp.

(24) FISHBEIN, L. Potential industrial carcinogens and mutagens. Environmental Protection Agency, Office of Toxic Substances, EPA 560/5-77-005, May 5, 1977, pp. 311-312.

(25) GORI, G.B. Approaches to the reduction of total particulate matter (TPM) in cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, pp. 451-461, 1976.

(26) GREEN, C.R. Neutral oxygenated compounds in cigarette smoke and their possible precursors. Tobacco Smoke: Its Formation and Composition. Recent Advances in Tobacco Science 3: 94-120, 1977.

(27) GRIEST, W.H., QUINCY, R.B., GUERIN, M.R. Selected Constituents in the Smoke of Domestic Low Tar Cigarettes. Tennessee, Oak Ridge National Laboratory, Report ORNL/TM-6144/P1, December 1977, 20 pp.

(28) GRIFFIN, H.R., HOCKING, M.B., LOWERY, D.G. Arsenic determination in tobacco by atomic absorption spectrometry. Analytical Chemistry 47(2): 229-233, February 1975.

(29) GUERIN, M.R. Detection of sulfur-containing compounds in the gas phase of cigarette smoke. Analytical Letters 4(11): 751-759, 1971.

(30) GUTHRIE, F.E. Pending legislative restrictions on the use of agricultural chemicals on tobacco. Beitraege zur Tabakforschung 7(3): 195-202, November 1973.

(31) GUTHRIE, F.E., BOWERY, T.G. Pesticide residues on tobacco. Residue Reviews 19: 31-56, 1967.

(*32*) HAEBERER, A.F., CHORTYK, O.T. Free and bound maleic hydrazide residues in Burley and U. S. cigarette tobacco. Abstract No. 11. Presented at the 31st Tobacco Chemists' Research Conference, Greensboro, North Carolina, October 5-7, 1977, p. 6.

(*33*) HARRELL, T.G., RUSH, K.L., SENSABAUGH, A.J., JR. Colorimetric method for the determination of ammonia in tobacco smoke. Tobacco Science 19: 145-147, 1975.

(*34*) HARRIS, J.L., HAYES, L.E. A method for measuring the pH value of whole smoke. Tobacco Science 21: 58-60, 1977.

(*35*) HECHT, S.S., SCHMELTZ, I., HOFFMANN, D. Nitrogenous compounds in cigarette smoke and their possible precursors. Recent Advances in Tobacco Science 3: 59-93, 1977.

(*36*) HECKER, E. Structure-activity relationships in diterpene esters irritant and co-carcinogenic to mouse skin. In: Slaga, T.J., Sivak, A., Boutwell R.K. (Editors). Carcinogenesis, Volume 2. Mechanisms of Tumor Promotion and Carcinogenesis. New York, Raven Press, 1978, pp. 11-48.

(*37*) HIRAO, K., SHINOHARA, Y., TSUDA, H., FUKUSHIMA, S., TAKAHASHI, M., ITO, N. Carcinogenic activity of quinoline on rat liver. Cancer Research 36: 329-335, February 1976.

(*38*) HOFFMANN, D., ADAMS, J.D., BRUNNEMANN, K.D. Non-volatile N-nitrosamines: Analysis in tobacco and tobacco smoke by HPLC-TEA. Abstract No. 52. Presented at the 31st Tobacco Chemists' Research Conference, Greensboro, North Carolina, October 5-7, 1977, p. 27.

(*38a*) HOFFMANN, D., DONG, M., HECHT, S.S. Origin in tobacco smoke of N'-nitrosonornicotine, a tobacco-specific carcinogen: Brief communication. Journal of the National Cancer Institute 58(6): 1841-1844, June 1977.

(*38b*) HOFFMANN, D., RATHKAMP, G. Chemical studies on tobacco smoke. III. Primary and secondary nitroalkanes in cigarette smoke. Beitraege zur Tabakforschung 4(3): 124-134, February 1968.

(*39*) HOFFMANN, D., RATHKAMP, G., WYNDER, E.L. Chemical studies on tobacco smoke. IX: Quantitative analysis of chlorinated hydrocarbon insecticides. Beitraege zur Tabakforschung 5(3): 140-148, December 1969.

(*40*) HOFFMANN, D., SCHMELTZ, I., HECHT, S.S., WYNDER, E.L. Chemical studies on tobacco smoke. XXXIX. On the identification of carcinogens, tumor promoters, and co-carcinogens in tobacco smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 125-145.

(*40a*) HOFFMANN, D., WOZIWODZKI, H. Chemical studies on tobacco smoke. IV. The quantitative determination of free nonvolatile fatty acids in tobacco and tobacco smoke. Beitraege zur Tabakforschung 4(4): 167-175, May 1968.

(*40b*) HOFFMANN, D., WYNDER, E.L. Identifizierung und reducktion von respirationskarzinogenen (Identification and reduction of carcinogens in the respiratory environment). Zentralblatt fuer Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene, Abteilung 1, Originale B, 166: 113-135, 1978.

(*41*) HOLLAND, R.H., MCCALL, M.S., LANZ, H.C. A study of inhaled arsenic-74 in man. Cancer Research 19: 1154-1156, December 1959.

(*42*) HOLTZMAN, R.B., ILCEWICZ, F.H. Lead-210 and polonium-210 in tissues of cigarette smokers. Science 153: 1259-1260, September 9, 1966.

(*43*) HORTON, A.D., GUERIN, M.R. Quantitative determination of sulfur compounds in the gas phase of cigarette smoke. Journal of Chromatography 90: 63-70, 1974.

(44) HUEPER, W.C. Environmental carcinogenesis in man and animals. Annals of the New York Academy of Sciences 108(3): 963-1038, November 4, 1963.

(45) INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. Cadmium and inorganic cadmium compounds. In: World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Volume 2. Some Inorganic and Organometallic Compounds. Lyon, International Agency for Research in Cancer, 1973, pp. 74-94.

(46) INTERNATIONAL COMMITTEE FOR CIGAR SMOKE STUDY. Machine smoking of cigars. Coresta Information Bulletin 1974 (1): 31-34, 1974.

(47) JENKINS, R.W., JR., COMES, R.A., BASS, R.T. The use of carbon-^{14}-labelled compounds in smoke precursor studies—A review. Recent Advances in Tobacco Science 1: 1-30, 1975.

(48) JOHNSON, W.R., HALE, R.W., CLOUGH, S.C., CHEN, P.H. Chemistry of the conversion of nitrate nitrogen to smoke products. Nature 243(5404): 223-225, May 25, 1973.

(49) JOHNSON, W.R., HALE, R.W., NEDLOCK, J.W., GRUBBS, H.J., POWELL, D.H. The distribution of products between mainstream and sidestream smoke. Tobacco Science 17: 141-144, 1973.

(50) JOHNSON, W.R., KANG, J.C. Mechanisms of hydrogen cyanide formation from the pyrolysis of amino acids and related compounds. Journal of Organic Chemistry 36(1): 189-192, 1971.

(51) KEITH, C.H., DERRICK, J.C. Measurement of the particle size distribution and concentration of cigarette smoke by the "conifuge." Journal of Colloid Science 15(4): 340-356, August 1960.

(52) KEITH, C.H., TESH, P.G. Measurement of the total smoke issuing from a burning cigarette. Tobacco Science 9: 61-64, 1965.

(53) KOBASHI, U., DOIHARA, T., SUGAWARA, S., KABURAKI, Y. Changes in chemical composition of smoke from cigarettes imparted with several polyols. Scientific Papers of the Central Research Institute, Japan Monopoly Corporation 107: 319-323, 1965.

(54) LAWLEY, P.D. Carcinogenesis by alkylating agents. In: Searle, C.E. (Editor). Chemical Carcinogens. ACS Monograph No. 173. Washington, D.C., American Chemical Society, 1976, pp. 83-244.

(55) LITTLE, J.B., KENNEDY, A.R. Evaluation of alpha radiation-induced respiratory carcinogenesis in Syrian hamsters: Total dose and dose-rate. Progress in Experimental Tumor Research 24: April/May 1979. (To be published)

(56) LITTLE, J.B., RADFORD, E.P., JR. Polonium-210 in bronchial epithelium of cigarette smokers. Science 155: 606-607, February 3, 1967.

(57) MAGEE, P.N., MONTESANO, R., PREUSSMANN, R. N-nitroso compounds and related carcinogens. In: Searle, C.E. (Editor). Chemical Carcinogens. ACS Monograph No. 173. Washington, D.C., American Chemical Society, 1977, pp. 491-625.

(58) MARTELL, E.A. Radioactivity of tobacco trichomes and insoluble cigarette smoke particles. Nature 249: 215-217, May 17, 1974.

(59) MCGANDY, R.B., KENNEDY, A.R., TERZAGHI, M., LITTLE, J.B. Experimental respiratory carcinogenesis: Interaction between alpha radiation and benzo(a)pyrene in the hamster. In: Karbe, E., Park, J.F. (Editors). Experimental Lung Cancer. New York, Springer-Verlag, 1974, pp. 485-491.

(60) MILLER, J.E. Determination of the components of pipe tobacco and cigar smoke by means of a new smoking machine. Proceedings of the Third World Tobacco Scientific Congress, Salisbury, Southern Rhodesia, 1963, pp. 584-595.

(61) MORIE, G.P. Selective filtration of tobacco smoke components: A review. Proceedings of the American Chemical Society Symposium. Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke. New Orleans, Louisiana, March 20-25, 1977, pp. 553-583.

(62) NATIONAL ACADEMY OF SCIENCES, NATIONAL RESEARCH COUNCIL, COMMITTEE ON MEDICAL AND BIOLOGIC EFFECTS OF ENVIRONMENTAL POLLUTANTS. Nickel. Washington, D.C., National Academy of Sciences, 1975, pp. 178-188.

(62a) NEURATH, G. Stickstoffverbindungen des tabakrauches (Nitrogenous compounds in tobacco smoke). Beitraege zur Tabakforschung 5(3): 115-113, December 1969.

(63) NORMAN, V. An overview of the vapor phase, semivolatile and nonvolatile components of cigarette smoke. Recent Advances in Tobacco Science 3:28-51, 1977.

(64) OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION. Carcinogenic Chemicals. U.S. Department of Labor, Occupational Safety and Health Administration, July 13, 1978, 62 pp.

(64a) NORMAN, V., KEITH, C.H., Nitrogen oxides in tobacco smoke. Nature 205(4974): 915-916, February 27, 1965.

(65) OSDENE, T.S. Reaction mechanisms in the burning cigarette. In: Fina, N.J. (Editor). The Recent Chemistry of Natural Products, Including Tobacco. Proceedings of the Second Philip Morris Science Symposium, Richmond, Virginia, October 30, 1975. New York, Philip Morris, Inc., 1976, pp. 42-59.

(66) PAILER, M., HUEBSCH, W.J., KUHN, H. Untersuchungen der aliphatischen und aromatischen primaeren und sekundaeren amine des zigarettenrauches mit hilfe der gaschromatographie und massenspektrometrie (Investigations on the aliphatic and aromatic primary and secondary amines of cigarette smoke aided by gas chromatography and mass spectrometry). Fachliche Mitteilungen der Oesterreichischen Tabakregie 7: 109-118, April 1967.

(67) PATRIANAKOS, C.D., BRUNNEMANN, K.D., HOFFMANN, D. Aromatic amines in cigarette smoke. Abstract No. 44. Presented at the 31st Tobacco Chemists' Research Conference, Greensboro, North Carolina, October 5-7, 1977, p. 23.

(68) PILLSBURY, H.C., BRIGHT, C.C., O'CONNOR, K.J., IRISH, F.W. Tar and nicotine in cigarette smoke. Journal of the Association of Official Analytical Chemists 52(3): 458-462, 1969.

(69) RADFORD, E.P., JR., HUNT, V.R. Polonium-210: A volatile radioelement in cigarettes. Science 143(3603): 247-249, January 17, 1964.

(70) RAJEWSKY, B., STAHLHOFEN, W. Polonium-210 activity in the lungs of cigarette smokers. Nature 209(5030): 1312-1313, March 26, 1966.

(71) ROSS, W.S. Poison gases in your cigarettes: Carbon monoxide. Reader's Digest, October 1976, pp. 114-118.

(72) ROSS, W.S. Poison gases in your cigarettes. Part II: Hydrogen cyanide and nitrogen oxides. Reader's Digest, December 1976, pp. 92-98.

(73) RUSSFIELD, A.B., HOMBURGER, F., WEISBURGER, E.K., WEISBURGER, J.H. Further studies on carcinogenicity of environmental chemicals including simple aromatic amines. Toxicology and Applied Pharmacology 25: 446-447, 1973. (Abstract)

(74) SCHMELTZ, I., ABIDI, S., HOFFMANN, D. Tumorigenic agents in unburned processed tobacco: N-nitrosodiethanolamine and 1,1-dimethylhydrazine. Cancer Letters 2: 125-131, 1977.

(75) SCHMELTZ, I., BRUNNEMANN, K.D., HOFFMANN, D., CORNELL, A. On the chemistry of cigar smoke: Comparisons between experimental little and large cigars. Beitraege zur Tabakforschung 8(6): 367-377, June 1976.

(76) SCHMELTZ, I., HOFFMANN, D. Nitrogen-containing compounds in tobacco and tobacco smoke. Chemical Reviews 77(3): 295-311, June 1977.

(77) SCHMELTZ, I., TOSK, J., HILFRICH, J., HIROTA, N., HOFFMANN, D, WYNDER, E.L. Bioassays of naphthalene and alkylnaphthalenes for co-carcinogenic activity. Relation to tobacco carcinogenesis. In: Jones, P.W., Freudenthal, R.I. (Editors). Carcinogenesis, Volume 3. Polynuclear Aromatic Hydrocarbons. New York, Raven Press, 1978, pp. 47-60.

(78) SCHMELTZ, I., TOSK, J., HOFFMANN, D. Formation and determination of naphthalenes in cigarette smoke. Analytical Chemistry 48(4): 645-650, April 1976.

(79) SCHMELTZ, I., TOSK, J., JACOBS, G., HOFFMANN, D. Redox potential and quinone content of cigarette smoke. Analytical Chemistry 49(13): 1924-1929, November 1977.

(80) SCHMELTZ, I., WENGER, A., HOFFMANN, D., TSO, T.C. Chemical Studies on Tobacco Smoke. LXIII. On the fate of nicotine during pyrolysis and in a burning cigarette. (Submitted for 1979 publication to the Journal of Agricultural and Food Chemistry)

(81) SCHUMACHER, J.N., GREEN, C.R., BEST, F.W., NEWELL, M.P. Smoke composition. An extensive investigation of water-soluble portion of cigarette smoke. Journal of Agricultural and Food Chemistry 25(2): 310-320, 1977.

(82) SENKUS, M. (Symposium Chairman). Leaf composition and physical properties in relation to smoking quality and aroma. The 30th Tobacco Chemists' Research Conference, Nashville, Tennessee. Recent Advances in Tobacco Science 2: 1-135, 1976.

(83) SEVERSON, R.F., SNOOK, M.E., AKIN, F.J., CHORTYK, O.T. Correlation of biological activity with polynuclear aromatic hydrocarbon content of tobacco smoke fractions. In: Jones, P.W., Freudenthal, R.I. (Editors). Carcinogenesis, Volume 3. Polynuclear Aromatic Hydrocarbons. New York, Raven Press, 1978, pp. 115-130.

(84) SIMONS, P.J., LEE, P.N., ROE, F.J.C. Squamous lesions in lungs of rats exposed to tobacco-smoke-condensate fractions by repeated intratracheal instillation. British Journal of Cancer 37(6): 965-973, 1978.

(85) STEDMAN, R.L. The chemical composition of tobacco and tobacco smoke. Chemical Reviews 68(2): 153-207, April 1968

(86) SUGAWARA, S., ISHIZU, I., KOBASHI, U. Studies on casing effects on cigarettes. I. Change in chemical composition with casing additives. Scientific Papers of the Central Research Institute, Japan Monopoly Corporation 105: 203-207, 1963

(87) SUGIMURA, T., NAGAO, M., KAWACHI, T., HONDA, M., YAHAGI, T., SEINO, Y., SATO, S., MATSUKURA, N., MATSUSHIMA, T., SHIRAI, A., SAWAMURA, M., MATSUMOTO, H. Mutagen-carcinogens in food, with special reference to highly mutagenic pyrolytic products in broiled foods. In: Hiatt, H.H., Watson, J.D., Winsten, J.A., (Editors). Origins of Human Cancer. New York, Cold Spring Harbor Laboratory, 1977, pp. 1561-1577.

(88) SUGIMURA, T., SATO, S., NAGAO, M., YAHAGI, T., MATSUSHIMA, T., SEINO, Y., TAKEUCHI, M., KAWACHI, T. Over-lapping of carcinogens and mutagens. In: Magee, P.N., Takayama, S., Sugimura, T., Matsushima, T. (Editors). Fundamentals in cancer prevention. Baltimore, University Park Press, 1976, pp. 191-215.

(89) SUNDERMAN, F.W., DONNELLY, A.J. Studies of nickel carcinogenesis metastasizing pulmonary tumors in rats induced by the inhalation of nickel carbonyl. American Journal of Pathology 46(6): 1027-1041, 1965.

(90) SZADKOWSKI, D., SCHULTZE, H., SCHALLER, K.-H., LEHNERT, G. Zur oekologischen bedeutung des schwermetallgehaltes von zigaretten. blei-, cadmium- und nickelanalysen des tabaks sowie der gas- und partikelphase (On the ecological importance of the content in heavy metal of cigarette smoke. Lead-, cadmium-, and nickel analysis of tobacco and its gas and particulate phases). Archiv fuer Hygiene 153: 1-8, 1969.

(91) TIGGELBECK, D. Vapor phase modification—an under-utilized technology. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 507-514.

(92) TOBACCO REPORTER. FTC comes out with its first report on little cigar tar and nicotine content. Tobacco Reporter 99(8): 35-36, August 1972.

(93) U. S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7516, 1972, pp. 141-150.

(94) VAN DUUREN, B.L., BILBAO, J.A., JOSEPH, C.A. The carcinogenic nitrogen heterocyclics in cigarette-smoke condensate. Journal of the National Cancer Institute 25(1): 53-61, July 1960.

(95) VAN DUUREN, B.L., KATZ, C., GOLDSCHMIDT, B.M. Brief communication: Cocarcinogenic agents in tobacco carcinogenesis. Journal of the National Cancer Institute 51(2): 703-705, August 1973.

(96) VILCINS, G., LEPHARDT, J.O. Ageing processes of cigarette smoke: Formation of methyl nitrite. Chemistry and Industry (London), November 15, 1975, pp. 974-975.

(97) WAKEHAM, H. Sales weighted average "tar" and nicotine deliveries of U.S. cigarettes from 1957 to present. In: Wynder, E.L., Hecht, S.S. (Editors). Lung Cancer. A Series of Workshops on the Biology of Human Cancer. Report No. 3. UICC Technical Report Series—Volume 25. Geneva, International Union Against Cancer, 1976, pp. 151-152.

(98) WALD, N.J., HOWARD, S., EVANS, J. Smoking tables for carbon monoxide. British Medical Journal 1(6007): 434-435, February 21, 1976.

(99) WEBER, K.H. Recent changes in tobacco products and their acceptance by the consumer. Proceedings of the Sixth International Tobacco Scientific Congress, Tokyo, Japan, 1976, pp. 47-63.

(100) WYNDER, E.L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, 730 pp.

Physiological Responses to Cigarette Smoke

Previous editions of this report have examined acute and chronic effects of cigarette smoke. Starting with epidemiological evidence and buttressed by clinical and pathological findings, the role of cigarette smoke has been implicated in numerous disease processes in humans.

Since smoke is such a complex mixture of elements, experimental work in humans must be augmented by animal studies in order to define the specific role of particular smoke components. Inhalation studies (*33*) must be designed to closely mimic smoke exposure in the human population and provide data relating to: (1) understanding the physiological or biochemical mechanism of action of whole cigarette smoke or individual smoke components, (2) understanding of pathogenesis and early identification of endpoints which are predictive in nature, and (3) screening potentially less hazardous cigarette models to differentiate their relative influence on physiological or pathological endpoints.

Bioassays must be designed with appropriate exposure modes, since cigarette smoke-related diseases in man are usually chronic and involve a history of prolonged interaction between smoke components and target tissue.

Animal Smoke Inhalation Exposure Methodology

Smoke Generation

Exposure systems for tobacco smoke can be classified as active or passive, depending upon the system used for generating cigarette smoke.

Active exposure systems require the animal to generate the smoke by drawing air through a lighted cigarette to simulate what happens to the human smoker. McGill, et al. (*30*) used a water-reward system to train baboons to puff on lighted cigarettes and to inhale cigarette smoke. Once the animals were trained to take puffs of a specific duration, it was possible to control the animal's smoking behavior by manipulating the water reward per puff. The effectiveness of this system was shown by the fact that the animals remained in good health throughout the period of training and were able to achieve blood carboxyhemoglobin levels similar to those of human smokers.

However, since most experimental animals will not cooperate as well as baboons, passive devices in which smoke is generated by a machine are commonly used. Passive exposure systems can then be further classified as continuous or intermittent. A continuous system is one which smokes a series of cigarettes at one time by using one or two rotating discs or turrets to position the cigarettes at a smoking port where the puff is usually drawn by a vacuum pump. By designing the system so that a cigarette on one turret is being smoked while a

cigarette on the other turret is being rotated into position, it is possible to generate a nearly continuous stream of smoke (*24*).

In the intermittent system, smoke is generated either by applying positive pressure to a chamber containing a cigarette and forcing smoke out through the cigarette (*36*) or by a cam-activated plunger which draws a puff of smoke and injects it into a holding tube (*4*) where it is allowed to stand. The smoke generated by the piston is a closer approximation of the human smoke generation process than earlier mechanical smokers. It can be more accurately controlled as to puff volume, duration, and frequency and thus is the currently preferred system.

Methods of Inhalant Delivery

A great number of different exposure systems are available for tobacco smoke inhalation experimentation. Since the goal of much of the inhalation research currently being done is intended to simulate human experience, some degree of compromise is usually involved in selecting an inhalation system. The basic systems for delivering tobacco smoke inhalants include:

(1) complete chamber exposure—the entire animal is exposed to the inhalant (*6, 36*).

(2) partial chamber exposure—only the nose of the animal is exposed to the inhalant (*29*).

(3) face mask or mouth piece exposure—the inhaled smoke is delivered to the nose or mouth through a mask or mouthpiece, with a means of allowing expired smoke and air to be exhausted (*8, 35*).

(4) tracheal exposure—the inhalant is delivered directly into the trachea via a cannula inserted into a permanent tracheotomy (*12*).

The decision to use a particular exposure system is made after considering factors such as selection of a suitable animal model; the ability to control exposure levels, including delivery of smoke as a bolus in a fresh air stream; system wash-in and wash-out times; the ability to sample inhalant and/or test gases from the system inlet or outlet; and the ability of the exposure system to deliver smoke to the experimental animal while offering the least alteration of normal respiratory function.

Dosimetry

Administration of experimental inhalants via the pulmonary route requires a description of the concentration, duration, and pattern of inhalant exposure. Unfortunately, there is no simple relationship among these variables that will determine the dose delivered to a specific site of interest in the experimental animal. Prime attention must be given to the definition of real-life human exposure conditions so that appropriate parameters can be incorporated into the experi-

ment, although as noted by Nettesheim, et al. (*33*), the investigator determines the smoke exposure conditions but the animal determines smoke uptake or dose.

Periodic measurements to determine the amounts of cigarette smoke components received by experimental animals can be just as complex and equally as important as the endpoints used in the characterization and evaluation of the effects of tobacco smoke exposure.

Among the indicators which have been used for monitoring smoke uptake are blood levels of nicotine (*20*), urinary nicotine and cotinine (*11*), and tracers such as decachlorobiphenyl (*6*, *7*) and ^{14}C-dotriacontane (*15*). Each of these indicators has problems associated with it, such as the need for lengthy extractions for nicotine and cotinine and the requirements for homogenation of tissue samples prior to determining decachlorobiphenyl content.

Blood carboxyhemoglobin (COHb) levels have often been given to indicate that animals have inhaled the smoke, since carbon monoxide absorption occurs primarily in the lungs. In a study of total particular matter (TPM) deposition in the lungs of small mammals, Binns, et al. (*6*) also examined COHb levels to determine the correlation between these tests. They found that TPM could only be predicted from COHb levels within fairly wide levels in a particular species and showed no clear relationship when comparing different species.

Limiting Factors in Smoke Exposure

The major factor limiting the size of the dose in cigarette smoke inhalation studies is the acute toxicity of carbon monoxide and nicotine (*33*). In developing exposure regimens, it is important to consider acute toxicity of these two substances as well as the irritant nature of smoke when it is delivered to animals in high concentrations (*7*).

Excessive carbon monoxide buildup in blood, which can alter the transport of oxygen of the experimental animal, is a common problem in continuous exposure systems. To prevent toxicity of smoke, such systems require excessive dilution or intermittent exposure, which can lead to exposures of animals to smoke of different chemical and physical properties. Although the same situation is true for acute toxicity of nicotine, its half life is much shorter than that of carbon monoxide.

Intermittent systems have also been found to be advantageous in smoke exposure studies. These systems operate on a puff-hold-purge cycle with a holding period which can be adjusted to prevent major chemical and physical changes in the smoke. Rylander (*38*) has reviewed some of the contradictory results which occurred with varied smoke exposure conditions and has stressed the need to monitor smoke dilution, exposure duration, and selective absorption of volatile water-soluble smoke constituents.

Selected Animal Studies

Pulmonary Studies

Since Cahan and Kirman (*12*) published a method of delivering smoke to dogs in a controlled manner, the dog has been widely used as an animal model. While their report was primarily a technique paper, the authors noted increases in hematocrits and cardiac hypertrophy along with pulmonary fibrosis and emphysema in the smoking group.

A further description of pulmonary morphologic changes induced by smoking was published by Frasca, et al. (*22*). Their electronmicroscopic findings included a complete loss or marked reduction in the number of capillaries and a marked thickening of the septa due to increased amounts of collagen in the lung parenchyma. They also found large numbers of macrophages in both the pleura and parenchyma, occurring singly and in clumps. Many of these macrophages contained crystalline-like structures in membrane-bound inclusions.

Male cynomolgus monkeys trained to smoke an average of 12 cigarettes a day for 5 days a week over 6 months showed no changes in their epithelia of large airways but did exhibit aggregation of a large number of macrophages in the alveoli (*8*). These macrophages were clumped, pigmented with black/brown granules, and had foamy cytoplasm. Pulmonary physiological changes were limited to increases in pulmonary resistance, while tidal volume, respiratory rate, dynamic compliance, and nitrogen washout were normal throughout the test period.

Park, et al. (*35*) found that pulmonary mechanics and arterial blood gases of dogs which smoked eight cigarettes per day showed no significant differences until after 11 months of smoking, when functional residual capacity fell slightly and respiratory resistance rose. They attributed these changes, in part, to the smaller lung size of the smoking dogs. As in earlier studies, an increased number of alveolar macrophages were harvested from the lungs of smokers. Functional changes in macrophages included an increased initial latex uptake and a decreased bacteriosuppressive activity in smoking dogs.

Cardiovascular Studies

Chronic changes in cardiovascular functions due to tobacco smoke have not been extensively investigated in intact animals. A study by Ahmed, et al. (*1*) compared hemodynamics and left ventricular microscopic structural changes after beagle dogs smoked seven cigarettes per day or were given an equivalent intramuscular dose of nicotine daily for 22 months. They reported that both experimental groups had smaller left ventricular ejection fractions and lower left ventricular dP/dt values, both of which reflect a deficit in the contractile function of left ventricular muscle. Mean aortic blood pressure was elevated in both groups, indicating an increased peripheral resistance. Since the left

ventricular contractility indices were still lower after acute phlebotomy, it appeared that the left ventricular function was compromised independently of the increased afterload. The only histological change was an increased amount of collagen in the interstitium.

Armitage (*2*) administered puffs of smoke to anesthetized or spinal cats and demonstrated transient increases in blood pressure. By comparing these pressure changes with those observed when intravenous injections of nicotine were given, he was able to obtain an estimation of the pharmacologic "dose" of nicotine-like substance(s) contained in a puff of smoke. The study demonstrated that the source of the pressor response was in the particulate phase of the smoke although it may not have been nicotine per se, since smoke from low-nicotine cigarettes caused increased blood pressure similar to smoke from a cigarette with a standard nicotine level.

The role of tobacco smoke in altering myocardial oxygen partial pressure (MP_{O2}) was studied by Rink (*37*) in a series of experiments in open-chested cats with implanted oxygen electrodes. Intravenous injections of nicotine or intratracheal puffs of smoke resulted in transitory increases of blood pressure and slight increases in MP_{O2}. It was postulated that the effect of lower oxygen availability due to CO in tobacco smoke was overshadowed by the actions of nicotine in increasing myocardial blood supply.

The preceding studies have all indicated the adaptive nature of the animal or organ system under study. While compensatory mechanisms may serve to minimize the acute or chronic insult of tobacco smoke or its specific components, the underlying assumption has been that the system is "normal" or "healthy" and thus able to respond.

To examine the effect of tobacco smoke on an impaired cardiovascular system, Bellet, et al. (*5*) produced myocardial infarcts in dogs by ligating the anterior descending branch of the left coronary artery. After allowing four days for recovery, ventricular fibrillation threshold (VFT) was determined in control and smoking dogs with and without infarcts. As expected, VFT was lower in dogs with myocardial infarcts. In both control dogs and in dogs with acute myocardial infarction, inhalation of cigarette smoke decreased VFT for up to 90 minutes after exposure. The authors noted that the effects of myocardial infarction and cigarette smoke on the VFT were additive.

Exercise Tolerance

To investigate smoke-related impairments in physical exertions, animals have been subjected to exercise programs involving swimming or running on a treadmill before and after smoking. Hrubes and Battig (*26*) trained rats to swim to the point of exhaustion. As the animals became adapted to the program, endurance times rose from 5 to 7 or 8 minutes, but after acute smoke exposure, the endurance times fell to 5 minutes.

Reece and Ball (*36*) examined electrocardiographic, blood enzyme, and hematological data on dogs which ran on a treadmill for 10 minutes a day for a year. In the smoking group, electrocardiographic change indicated cardiac enlargement, suggestive of left ventricular hypertrophy. Of the enzymes studied, postexercise lactate concentrations rose after smoke exposure began, reflecting a deficiency in oxygen transfer, transport, or utilization, all of which occur with carbon monoxide exposure. Other enzymes altered during smoke exposure included glutamic oxaloacetic transaminase and creatine phosphokinase. While there was no histopathological basis for these changes, the authors noted the potential for the combination of hypoxia and nicotine to inhibit the production of certain enzymes.

Toxicity of Specific Smoke Components

Since the list of harmful constituents in cigarette smoke was published in 1972 in the report *The Health Consequences of Smoking*, there has not been a notable increase in knowledge regarding the pathophysiological role of many specific smoke components.

Rylander (*38*) reviewed experimental work dealing with aerosol and volatile components of smoke and listed three requirements for determining relative toxicity: (1) realistic dilution of the smoke as drawn from cigarettes, (2) selective absorption of volatile, water-soluble compounds from the smoke, and (3) realistic exposure duration.

These same criteria should apply to examination of specific components of tobacco smoke. Many studies such as those which determined LD_{50} levels or reported results of continuous exposures were considered not to represent smoke-related results.

Nicotine

In an early study to determine how nicotine in cigarette smoke could cause an increase in heart rate, Burn and Rand (*10*) administered nicotine to isolated rabbit atria. By comparing normal and reserpine-treated atria, they found that nicotine caused increases in rate and amplitude of contraction by releasing epinephrine and norepinephrine from stores in the heart. Interest in the role of nicotine in cardiovascular diseases processes has continued from that time, aided in part by the availability and ease of administration of pure nicotine solutions.

Ilebekk and Lekven (*27*) used a continuous infusion of nicotine to examine the mechanical efficiency of the left ventricle during the administration of approximately 2.1 mg of nicotine over a 5-minute period. They found that nicotine increased cardiac contractility and elevated left-ventricular-systolic and end-diastolic pressures. Thus, even though peripheral vasoconstriction occurred, stroke volume was increased by nicotine during these short-term studies.

By comparing chronic smoke exposure and daily intramuscular injections of nicotine, Ahmed, et al. (*1*) were able to demonstrate that left ventricular performance did deteriorate over the course of 22 months. Ahmed reported that aortic blood pressure rose in both test groups, so that nicotine appeared to be involved in the increased peripheral resistance. Since both the smoking and nicotine groups exhibited similar interstitial fibrosis in the middle layers of myocardial tissue, nicotine appears to have a cardiotoxic effect which has previously been ascribed to carbon monoxide.

The association between nicotine and hypertension is not as clearcut as the two preceding reports may suggest. Fisher, et al. (*21*) investigated the role of nicotine in atherosclerosis and experimental hypertension in rabbits and found nicotine had no effect on either disease process over a 90-day period. While others had reported no link between nicotine and atherosclerosis, the authors noted that the dose of nicotine may not have been optimal to allow comparison with previous work in the area of hypertension.

A report by Hansson and Schmiterlow (*25*) examined the distribution of nicotine in various tissues and noted that the metabolism of nicotine in isolated tissue slices was oxygen-dependent. In a study of nicotine conversion rates in intact rats, Miller, et al. found that, while plasma nicotine clearance rates were independent of peak plasma levels (*31*), dose-dependent differences of nicotine distribution in tissues resulting from changes in regional perfusion may have effected total plasma clearance of nicotine. It thus appears likely that selective oxygen availability as well as plasma nicotine levels may influence nicotine catabolism in experimental animals.

Carbon Monoxide

When pregnant rats were maintained in a CO atmosphere that produced carboxyhemoglobin levels averaging 15 percent saturation, their offspring exhibited reduced birth weights, decreased weight gains, and lower brain protein levels than air-breathing controls (*19*). While this study might be criticized for using continuous rather than intermittent exposures, the data do suggest a highly sensitive indicator of CO toxicity.

Additional study of carbon monoxide toxicity also pointed out another case of relative susceptibility, again using the rat bioassay. When comparing tracheal pressure, blood pressure, and heart rate responses in guinea pigs and rats exposed to 2.84 percent carbon monoxide, Mordelet-Dambrine, et al. (*32*) noted that rats appeared to be more sensitive, since they had lower survival times. These differences may be due to differences in CO sensitivities, or they may be due to anesthetic variables that are hard to quantitate across species.

To avoid anesthetic problems, Cramlet, et al. (*13*) used conscious dogs that were chronically instrumented to provide continuous cardiovascular data with cannulae for blood sampling from left and right atria while the dogs inhaled carbon monoxide. Measurements were made when COHb reached 10, 20, and 30 percent saturation. The only significant cardiac changes were heart rate increases at 20 and 30 percent saturation; arterial oxygen saturation was reduced at all levels. The authors concluded that cardiac compensation was adequate to prevent tissue hypoxia up to 30 percent COHb in healthy dogs.

In an effort to study the effects of carbon monoxide in dogs with impaired hearts, DeBias, et al. (*18*) produced myocardial infarcts by injecting latex spheres into the left coronary artery. Control and infarcted dogs were exposed to carbon monoxide continuously for 14 weeks with serial electrocardiograms and hematologic evaluation. Although COHb averaged 14 percent in exposed animals, the animals remained in good health throughout the study.

Repeating the same protocol in cynomologus monkeys, DeBias, et al. (*17*) found hematocrit, RBC, and hemoglobin levels altered by 3 weeks of exposure to 100 ppm CO, with recognizable electrocardiographic changes. The authors concluded that the sensitivity to CO was species-related as well as dose-related.

Carrying these results one step further, the DeBias group (*16*) examined the effect of carbon monoxide on ventricular threshold in cynomologus monkeys. Animals with and without myocardial infarcts produced by latex bead injections into the coronary artery were exposed to 100 ppm CO for 6 hours. This CO level produced COHb values of 9.3 percent compared to 1.1 percent in air-breathing animals. It was noted that infarcted and CO-breathing animals both had lower ventricular fibrillation thresholds, and that the effects were additive.

The lack of chronic studies on CO effects in animals and humans suggests that such studies be undertaken to fill this void in our knowledge, especially as it relates to smoking and related diseases.

Nitric Oxide

While nitric oxide is found in cigarette smoke in concentrations of zero to 600 μg/cigarette (*39*), blood levels for humans, monkeys, and rats have only recently been reported (*23*). Their data indicate that a consistently low level of NO was maintained in the blood of both smokers and nonsmokers. The lack of a significant difference between smokers and nonsmokers sugggsts that a mechanism exists in mammals to rapidly detoxify NO, and that exogenous NO appears to have little effect on its steady state in blood.

Examining the role of NO at the cellular level, Arnold, et al. (*3*) exposed tubes containing rat and bovine tissue to the gas phase of cigarette smoke, nitric oxide, and room air and determined changes in guanylate cyclase activity. This enzyme is involved in the formation of

guanosene 3',5-monophosphate (cyclic GMP) and may play a role in tissue proliferation and tumoregenesis, as well as exert effects on ciliary function and mucosal secretion in lung tissue.

Nitrogen Dioxide

Acute lung damage resulting from exposure to nitrogen dioxide at levels of 80 ppm for 3 hours has been reported by Langloss, et al. (*28*). Blank, et al. (*9*) exposed rats to levels of 15 to 40 ppm for up to 5 hours. Both of these groups reported alveolar damage with subsequent edema followed by hyperplasia or increased biosynthesis. The relevance of these types of exposure to smoking-related disease processes is unclear, however, since Norman and Keith (*34*) reported that nitrogen dioxide is present in cigarette smoke only in trace quantities.

Phenol

Little is known about the effects of phenol in smoke. Dalhamn (*14*), however, administered puffs of smoke from cigarettes with high and low phenol concentrations (18.8 and 2.7 mg/100 cigarettes versus a "normal" cigarette concentration of 7 mg/100 cigarettes) and found a clear correlation between ciliostasis and the phenol level in smoke. This area is one that should also be explored in more detail.

Physiological Responses to Cigarette Smoke: References

(1) AHMED, S.S., MOSCHOS, C.B., LYONS, M.M., OLDEWURTEL, H.A., COUMBIS, R.J., REAGAN, T.J., JENKINS, B. Cardiovascular effects of long-term cigarette smoking and nicotine administration. American Journal of Cardiology 37: 33-40, January 1976.

(2) ARMITAGE, A.K. Effects of nicotine and tobacco smoke on blood pressure and release of catecholamines from the adrenal glands. British Journal of Pharmacology 25: 515-526, 1965.

(3) ARNOLD, W.P., ALDRED, R., MURAD, F. Cigarette smoke activates guanylate cyclase and increases guanosine 3', 5'-monophosphate in tissues. Science 198: 934-936, December 2, 1977.

(4) BATTISTA, S.P., GUERIN, M.R., GORI, G.B. KENSLER, C.J. A new system for quantitatively exposing laboratory animals by direct inhalation. Archives of Environmental Health 27: 376-382, December 1973.

(5) BELLET, S., DEGUZMAN, N.T., KOSTIS, J.B., ROMAN, L., FLEISCHMANN, D. The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. American Heart Journal 83(1): 67-76, January 1972.

(6) BINNS, R., BEVEN, J.L., WILTON, L.V., LUGTON, W.G.D. Inhalation toxicity studies on cigarette smoke. II. Tobacco smoke inhalation dosimetry studies on small laboratory animals. Toxicology 6: 197-206, 1976.

(7) BINNS, R., BEVEN, J.L., WILTON, L.V., LUGTON, W.G.D. Inhalation toxicity studies on cigarette smoke. III. Tobacco smoke inhalation dosimetry study on rats. Toxicology 6: 207-217, 1976.

(8) BINNS, R., CLARK, G.C. An experimental model for the assessment of the effects of cigarette smoke inhalation on pulmonary physiology. Annals of Occupational Hygiene 15: 237-247, 1972.

(9) BLANK, M.L., DALBEY, W., NETTESHEIM, P., PRICE, J., CREASIA, D., SNYDER, F. Sequential changes in phospholipid composition and synthesis in lungs exposed to nitrogen dioxide. American Review of Respiratory Disease 117: 273-280, 1978.

(10) BURN, J.H., RAND, M.J. Action of nicotine on the heart. British Medical Journal 1: 137-139, January 18, 1958.

(11) BURROWS, I.E., CORP, P.J., JACKSON, G.C., PAGE, B.F.J. The determination of nicotine in human blood by gas-liquid chromatography. Analyst 96: 81-84, January 1971.

(12) CAHAN, W.G., KIRMAN, D. An effective system and procedure for cigarette smoking by dogs. Journal of Surgical Research 8(12): 567-575, December 1968.

(13) CRAMLET, S.H., ERICKSON, H.H., GORMAN, H.A. Ventricular function following acute carbon monoxide exposure. Journal of Applied Physiology 39(3): 482-486, September 1975.

(14) DALHAMN, T. Effect of different doses of tobacco smoke on ciliary activity in cat. Variations in amount of tobacco smoke, interval between cigarettes, content of "tar," nicotine, and phenol. Toward a Less Harmful Cigarette. National Cancer Institute Monograph No. 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, 1968, pp. 79-87.

(15) DAVIS, B.R., HOUSEMAN, T.H., RODERICK, H.R. Studies of cigarette smoke transfer using radioisotopically labelled tobacco constituents. Beitraege zur Tabakforschung 7(3): 148-153, November 1973.

(16) DEBIAS, D.A., BANERJEE, C.M., BIRKHEAD, N.C., GREENE, C.H., SCOTT, S.D., HARRER, W.V. Effects of carbon monoxide inhalation on ventricular fibrillation. Archives of Environmental Health 31: 42-46, January/February 1976.

(17) DEBIAS, D.A., BANERJEE, C.M., BIRKHEAD, N.C., HARRER, W.V., KAZAL, L.A. Carbon monoxide inhalation effects following myocardial infarction in monkeys. Archives of Environmental Health 27: 161-167, September 1973.

(18) DEBIAS, D.A., BIRKHEAD, N.C., BANERJEE, C.M., KAZAL, L.A., HOLBURN, R.R., GREENE, C.H., HARRER, W.V., ROSENFELD, L.M., MENDUKE, H., WILLIAMS, N., FRIEDMAN, M.H.F. The effects of chronic exposure to carbon monoxide on the cardiovascular and hematologic systems in dogs with experimental myocardial infarction. Internationales Archiv fuer Arbeitsmedizin 29: 253-267, 1972.

(19) FECHTER, L.D., ANNAU, Z. Toxicity of mild prenatal carbon monoxide exposure. Science 197: 680-682, August 12, 1977.

(20) FEYERABEND, C., LEVITT, T., RUSSELL, M.A.H. A rapid gas-liquid chromatographic estimation of nicotine in biological fluids. Journal of Pharmacy and Pharmacology 27: 434-436, 1975.

(21) FISHER, E.R., ROTHSTEIN, R., WHOLEY, M.H., NELSON, R. Influence of nicotine on experimental atherosclerosis and its determinants. Archives of Pathology 96: 298-304, November 1973.

(22) FRASCA, J.M., AUERBACH, O., PARKS, V.R., JAMIESON, J.D. Electron microscopic observations on pulmonary fibrosis and emphysema in smoking dogs. Experimental and Molecular Pathology 15(1): 108-125, August 1971.

(23) FREEMAN, G., DYER, R.L., JUHOS, L.T., ST. JOHN, G.A., ANBAR, M. Identification of nitric oxide (NO) in human blood. Archives of Environmental Health 33: 19-23, January/February 1978.

(24) GUERIN, M.R., MADDOX, W.L., STOKELY, J.R. Tobacco smoke inhalation exposure: concepts and devices. In: Gori, G.B. (Editor). Proceedings of the Tobacco Smoke Inhalation Workshop. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 75-906, 1975, pp. 31-44.

(25) HANSSON, E., SCHMITERLOW, C.G. Metabolism of nicotine in various tissues. In: von Euler, U.S. (Editor). Tobacco Alkaloids and Related Compounds. Oxford, Pergamon Press, 1965, pp. 87-99.

(26) HRUBES, V., BAETTIG, K. Effects of inhaled cigarette smoke on swimming endurance in the rat. Archives of Environmental Health 21: 20-24, July 1970.

(27) ILEBEKK, A., LEKVEN, J. Cardiac effects of nicotine in dogs. Scandinavian Journal of Clinical and Laboratory Investigation 33: 153-159, 1974.

(28) LANGLOSS, J.M., HOOVER, E.A., KAHN, D.E. Diffuse alveolar damage in cats induced by nitrogen dioxide or feline calicivirus. American Journal of Pathology 89(3): 637-644, December 1977.

(29) MADDOX, W.L., DALBEY, W.E., GUERIN, M.R., STOKELY, J.R., CREASIA, D.A., KENDRICK, J. A tobacco smoke inhalation exposure device for rodents. Archives of Environmental Health 33: 64-71, March/April 1978.

(30) MCGILL, H.C., JR., ROGERS, W.R., WILBUR, R.L., JOHNSON, D.E. Cigarette smoking baboon model: Demonstration of feasibility (40119). Proceedings of the Society for Experimental Biology and Medicine 157: 672-676, 1978.

(31) MILLER, R.P., ROTENBERG, K.S., ADIR, J. Effect of dose on the pharmacokinetics of intravenous nicotine in the rat. Drug Metabolism and Disposition 5(5): 436-443, 1977.

(32) MORDELET-DAMBRINE, M., STUPFEL, M., DURIEZ, M. Comparison of tracheal pressure and circulatory modifications induced in guinea pigs and in rats by carbon monoxide inhalation. Comparative Biochemistry and Physiology 59A: 65-68, 1978.

(*33*) NETTESHEIM, P., GUERIN, M.R., KENDRICK, J., RUBIN, I., STOKELY, J., CREASIA, D., MADDOX, W., CATON, J.E. Control and maximization of tobacco smoke dose in chronic animal studies. In: Gori, G.B. (Editor). Proceedings of the Tobacco Smoke Inhalation Workshop. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 75-906, 1975, pp. 17-26.

(*34*) NORMAN, V., KEITH, C. H. Nitrogen oxides in tobacco smoke. Nature 205(4974): 915-916, February 27, 1965.

(*35*) PARK, S.S., KIKKAWA, Y., GOLDRING, I.P., DALY, M.M., ZELEFSKY, M., SHIM, C., SPIERER, M., MORITA, T. An animal model of cigarette smoking in beagle dogs. American Review of Respiratory Disease 115: 971-979, 1977.

(*36*) REECE, W.O., BALL, R.A. Inhaled cigarette smoke and treadmill-exercised dogs. Archives of Environmental Health 24: 262-270, April 1972.

(*37*) RINK, R. D. The acute effects of nicotine, tobacco smoke and carbon monoxide on myocardial oxygen tension in the anaesthetized cat. British Journal of Pharmacology 62: 591-597, 1978.

(*38*) RYLANDER, R. Relative role of aerosol and volatile constituents of cigarette smoke as agents toxic to the respiratory tract. Toward a Less Harmful Cigarette. National Cancer Institute Monograph No. 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, 1968, pp. 221-229.

(*39*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

Pharmacology of Cigarette Smoke

For the habitual smoker, the smoking of a cigarette is a rewarding experience, evidenced by the consumption of over 600 billion cigarettes annually in the United States. It is a reward which is highly anticipated by smokers, one that seems to satisfy a smoker's physiological and psychological needs.

Because of the myriad compounds present in cigarette smoke, it should be kept in mind that the pharmacological effects of smoking are not related solely to nicotine; rather, it is the combined effect of the whole smoke. Nevertheless, nicotine is generally accepted as the principal constituent responsible for cigarette smokers' pharmacologic response (*6, 20*), and will be reviewed on this criterion.

Nicotine is a powerful, quick-acting, ganglionic stimulant, eliciting its effects initially by depolarizing the ganglionic cells, stimulating both the sympathetic and parasympathetic ganglia (*15*).

Nicotine Absorption

Clearly, before any pharmacologic response can be elicited by nicotine from cigarette smoke, absorption must occur. The phenomenon of cigarette smoke absorption has been addressed by several investigators (*2, 4, 6, 9, 16*).

Some absorption takes place in the oral cavity. Based on monitoring carotid blood levels and radiolabeled nicotine cigarettes, estimates from three studies (*2, 4, 6*) show that less than 30 percent of the inhaled dose is absorbed. Further, Artho and Grob (*6*) observed that there were striking differences in nicotine absorption that are largely determined by the pH of the total smoke. The pK_b values of nicotine are 6.16 and 10.96 (*9*). From these data, the portions of the diprotonated nicotine and monoprotonated nicotine as well as the free nicotine can be calculated for a given pH. Because cigarette smoke typically has a pH of 5–7, the diprotonated form need not be considered in this discussion. The percentage of nicotine present as the free base is 0.40 at pH 5.35, 1.7 at pH 6, 15 at pH 7, 64 at pH 8, and 85 at pH 8.5.

The basic, lipid-soluble, uncharged nicotine is the form absorbed by the oral muscosa (*8*). A contributing factor to its absorption is that nicotine, as the free base, is volatile, which allows for rapid absorption from the gas phase. The relationship of the effects of pH are described in Figure 9 (*9*). Figure 10 (*4*) describes the oral absorption of nicotine from an identical dose of a buffered nicotine solution at pH 6, 7, and 8.

Nicotine which passes the oral cavity, as in cases of deep inhalation, is absorbed to a much greater extent than in the oral cavity. It is estimated that more than 90 percent of the inhaled nicotine is absorbed in the lungs (*2, 6, 16*). It should be noted also that retention of other cigarette smoke components by absorption is approximately 82 to 99

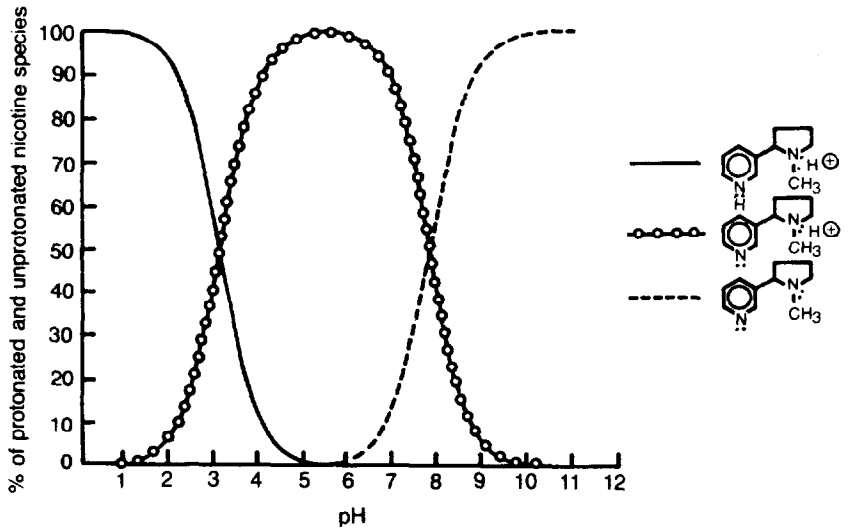


FIGURE 9.—Degree of protonation of nicotine in relation to pH (pH = pKa 10g 1 - α/α (Henderson/Hasselbach)).
SOURCE: Aviado, D.M., (7).

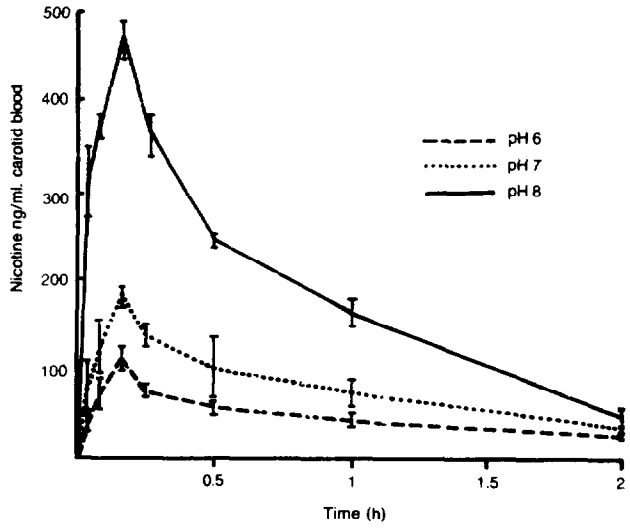


FIGURE 10.—Carotid blood levels of nicotine in ng/ml, after the presence in the mouth for 10 minutes of buffered solutions of nicotine at pH 6, pH 7, and pH 8. The bars show standard error of the mean.
SOURCE: Artho, A.A. (6).

percent, depending on the study. In any case, it is clear that the lung uptake of the nicotine in cigarette smoke is very efficient.

Whether cigarette smoke or a nicotine aerosol is used seems to make little difference on nicotine absorption in the lung. Herxheimer (*28*) found that inhalation from smoke and inhalation from a nicotine aerosol in approximately equivalent amounts (about 100 μg every 30 seconds) produced similar increases in pulse rate and blood pressure in healthy volunteers. The equivalence is only approximate, however, because the nicotine delivered per puff increases as the cigarette is smoked. This increase could explain why, although similar, the peak effects occurred later with cigarette smoking than with inhalation of the aerosol.

Although pH of the smoke is a major factor in nicotine absorption, other factors such as tobacco smoke contact time with mucus membranes, pH of the mucus membrane, pH of body fluids, depth and degree of inhalation, degree of habituation of the smoker, nicotine and moisture content, and puff frequency must be considered (*12, 20*).

Armitage, et al. (*3*) recently studied the effects of nicotine absorption in humans, comparing nicotine levels obtained in arterial blood. They found that arterial blood plasma concentrations of nicotine were comparable; however, the level rose more slowly in the smokers of small cigars. This may be due to a greater amount of the small cigar smoke being absorbed via the oral cavity as compared to cigarette smoke, which is primarily absorbed via the lung.

Alteration of Enzyme Systems

The nature of tolerance to nicotine and tobacco smoking has received attention and a complex picture has emerged (*25*). Studies with humans using high and low doses of nicotine presented apparently conflicting results regarding nicotine-cotinine metabolism. The authors suggested that acute high doses of nicotine produced inhibition of nicotine metabolism while lower daily doses on chronic exposure produced induction of the enzyme systems. These results are not uniformly accepted, however (*51*).

Gorrod and Jenner (*25*) concluded that the effect of nicotine is complex, but that the data suggest the importance of dosage, length of administration, and stress-induced effects. They also stated that a component of cigarette smoke other than nicotine may be responsible for the changes in nicotine metabolism observed in humans. In any case, tobacco smoke is a known inhibitor of enzyme systems, including dehydrogenases and oxygenases, so that inhibition of nicotine metabolism or other metabolic products is a distinct possibility (*27*).

Catecholamine Responses

Since nicotine is a ganglionic stimulant on both the sympathetic and parasympathetic nervous systems, it is not surprising that investiga-

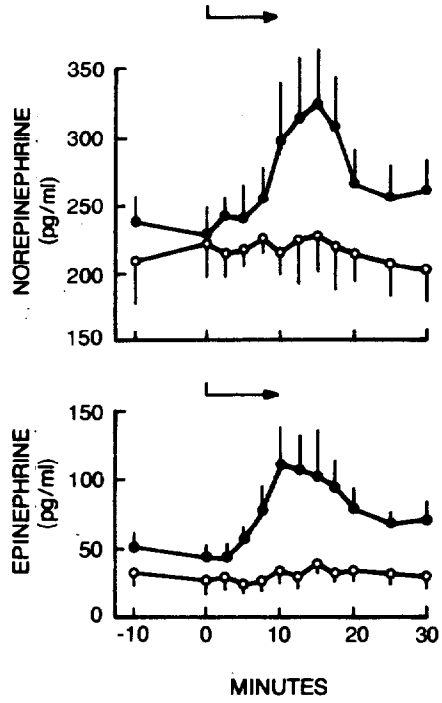


FIGURE 11.—Mean (± S.E.) plasma norepinephrine and epinephrine concentrations in association with smoking (closed symbols) and sham smoking (open symbols). The arrows indicate the period of smoking (or sham smoking).
SOURCE: Cutting, W.C. (*15*).

tors have looked at catecholamines as possible indicators of the nicotine-induced effects. Moreover, the catecholamines are usually considered to be released in stress-related responses. The source of the catecholamines is reported to be in the myocardial chromaffin tissue and the adrenal gland (*11, 29, 34*), and therefore consistent with this hypothesis.

Armitage (*1*) claims that the amount of nicotine inhaled during smoking is sufficient to cause release of catecholamines, but there is not uniform agreement on this subject (*60, 63*). Timing may be a critical factor in determining any catecholamine response because the response is likely to be transient. Cryer and coworkers (*14*) have graphically shown the rapid response of nonepinephrine and epinephrine as a consequence of cigarette smoking (see Figure 11).

Naquira and coworkers (*48*) studied the chronic administration (14 days) of nicotine in rats. They observed increased tyrosine hydroxylase

and dopamine-β-hydroxylase in the hypothalamus and adrenal medulla, but did not observe changes in tyrosine hydroxylase in the striatum. The data suggest that chronic nicotine administration can produce similar long-term alterations in both catecholamine-forming enzymes in the hypothalamus and adrenal medulla.

Catecholamines, released as a consequence of the nicotine-induced response, have been associated with or implicated in several biological responses. Cardiovascular-related diseases, bronchoconstriction and related pulmonary manifestations, fat metabolism, hyperglycemic effects, and the patellar reflex response have implicated catecholamines as being either directly or indirectly involved in these biological endpoints.

In the United States, more people die from coronary heart disease than from any other disease, and heart disease is the single most important cause of death among cigarette smokers(*62*). Epidemiological studies such as those reported by Mulcahy, et al. (*45*) who found a positive association between coronary heart disease mortality rate and the calculated per capita cigarette consumption in 21 countries, the Framingham study (*19, 23, 33, 50*), and reviews by Aronow (*5*) and Kannel (*32*) leave little doubt as to the consequences of cigarette smoking with respect to heart disease.

Cardiovascular and Related Effects

It is generally agreed that the acute cardiovascular effects of tobacco smoking can be attributed to the nicotine content of the cigarette and the amount absorbed (*14, 20*); similar effects have been observed by Irving and Yamamoto on administration of a comparable amount of nicotine by injection (*31*). The responses observed are those expected from stimulation of the sympathetic nervous system (*15*), including stimulation of the sympathetic ganglia, adrenal medulla, and the release of endogenous catecholamines (*14*). Responses are known to include increased heart rate and blood pressure (*2, 28*), cardiac output stroke volume, velocity of contraction, myocardial contractile force and oxygen consumption, and coronary blood flow and arrythmias (*15, 20*). Activation of the chemoreceptors of the carotid and aortic bodies results in vasoconstriction, tachycardia, and elevated blood pressure. Nadeau and James (*47*) have shown that the cardiac/stimulating effect of nicotine can be attributed to vagal stimulation. The possible role of elevated serum corticoids, following smoking of high nicotine cigarettes, in sensitizing the myocardium to the effects of the catecholamine has been suggested (*5, 29*) as also possibly contributing to ventricular arrythmias and myocardial infarctions. Further research has been suggested to resolve this issue (*5*).

Armitage and coworkers (*3*) have graphically described the dose-response effects of nicotine intravenous injection and cigarette

smoking as they affect blood pressure and heart rate. These results are described in Figure 12.

Pulmonary Effects

The respiratory effects of nicotine from smoke exposure are more difficult to quantify than cardiovascular effects because respiratory function may also be influenced by the solid particles or gases in cigarette smoke (i.e., CO and CO_2). For example, Reintjes and coworkers (*50*) were able to show that airway resistance values obtained immediately after smoking were elevated, but they did not identify the response as being caused by the nicotine in cigarette smoke. Aviado and coworkers (*7*) demonstrated that cigarette smoke causes acute bronchoconstriction by release of histamine and by stimulation of the parasympathetic nervous system in the lungs. Similar responses were shown to occur with arterial injections of nicotine. The effect is followed, however, by bronchodilation attributed to sympathetic stimulation.

Fat Metabolism

Changes in free fatty acids and mobilization of free fatty acids (FFA) have also been reviewed (*40*) as secondary effects of catecholamine stimulation. Kershbaum and coworkers (*35*) were led to the conclusion that nicotine had no direct lipolytic effect on cat or dog adipose fat tissue. Their findings lent support to the concept that mobilization of FFA by nicotine and cigarette smoke was a result of their stimulation of sympathetic nervous system activity and catecholamine secretion. In a related study (*36*) comparing 4 mg of nicotine in intravenously- and intratracheally-administered cigarette smoke, the authors suggested that tobacco smoking and nicotine caused an increased utilization of FFA in addition to their known effect of FFA mobilization. It was suggested that the greater FFA utilization was caused by increased cardiac output due to nicotine. The authors further suggested that nicotine changes the ratio of FFA incorporated into neutral lipid and phospholipids.

Hyperglycemic Effects

Another secondary response to the catecholamines present in the blood stream is believed to be a hyperglycemic condition as described in a recent review (*40*). Such a response would be consistent with a stress-related situation requiring an energy source for quick response. Milton (*44*) has suggested that in cats the hyperglycemic mobilizing action of smoking doses of nicotine is due entirely to stimulation of the adrenal gland, while the hyperglycemic effect at high doses is presumably due to stimulation of ganglia throughout the body resulting in the release of more epinephrine.

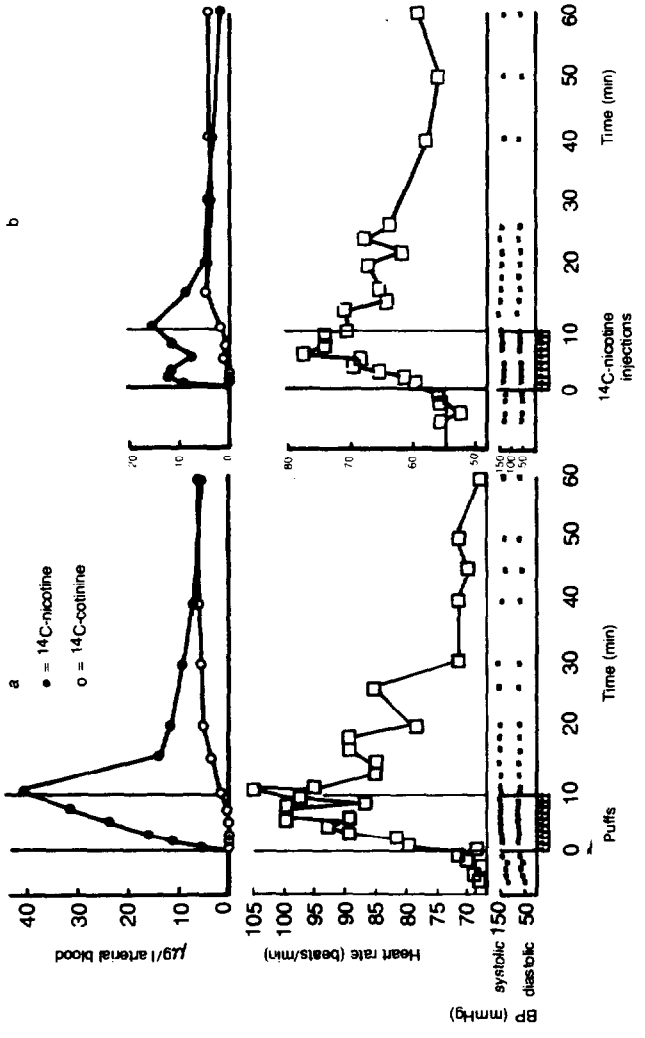


FIGURE 12.—Arterial blood levels of ^{14}C-nicotine (●) and ^{14}C-cotinine (○), heart rate (□), and blood pressure (■) during and after smoking a cigarette labeled with ^{14}C-nicotine (a), and during and after intravenous administration of 1 mg ^{14}C-nicotine in 10 divided doses (b).

SOURCE: Beckett, A.H. (*8*).

Other Central Nervous System Effects

It has recently been reported that nicotine also causes a diminution in the monosynaptic patellar reflex (*18*). This reduction in the patellar reflex was not seen after smoking nontobacco cigarettes. The effect thus appears to be closely related to nicotine. This was later confirmed by Domino and Baumgarten (*18*) after studying the response to an inhaled nicotine aerosol.

Metabolism of Nicotine

The metabolism of nicotine has been examined and reviewed by several investigators (*25, 27, 61*). The major part of the absorbed nicotine is metabolized rapidly in the body, and studies have established the liver as the major organ of detoxication. McKennis, et al. (*20a–20d*) have demonstrated that cotinine is the major metabolite of nicotine in human and animal urine. Other detected metabolites are summarized in Figure 13. Hansson and Schmiterlow (*27*), using radiolabeled nicotine, were able to detect radiolabeled products only in cotinine and CO_2. In studying tissue slices, they determined that nicotine is metabolized in the kidney and lung as well as in the liver, but not in the brain, diaphragm, spleen, stomach, small intestine, or adrenal glands.

Armitage (*2*), in comparing the effects of injected nicotine and innaled cigarette smoke, found that the half-life of nicotine in the arterial blood of smokers ranged from 24 to 84 minutes, with a mean value of 40 minutes when only the inhalation experiments were taken into account.

In examining the relationship between intravenous injections of nicotine and subsequent metabolism, Miller, et al. (*43*) found nicotine had a $t^1/_2$ of 55 to 64 minutes, with peak levels in the range of 297 ng/ml of plasma. While there was no effect of the administered dose on disappearance rate, there was a suggestion that the dose affected the distribution of nicotine. This would appear reasonable, in view of the known vasoconstrictive properties mentioned earlier, and could explain some of the conflicts in characterizing nicotine's pharmacologic properties.

Tsujimoto and coworkers (*59*) studied the tissue distribution of nicotine in dogs and rhesus monkeys. Five minutes after injection the adrenal medulla and cerebral cortex contained the highest concentration of nicotine. Other tissues containing significant quantities of nicotine included the spleen, adrenal cortex, kidney, and pancreas.

The effect of urinary pH on the excretion of nicotine and its metabolites has been studied by Beckett, et al. (*8*), Gorrod and Jenner (*25*), and Feyerabend and Russell (*21*). They determined that the amount of unchanged nicotine excreted in the urine after oral administration was dependent on pH, while cotinine was dependent on

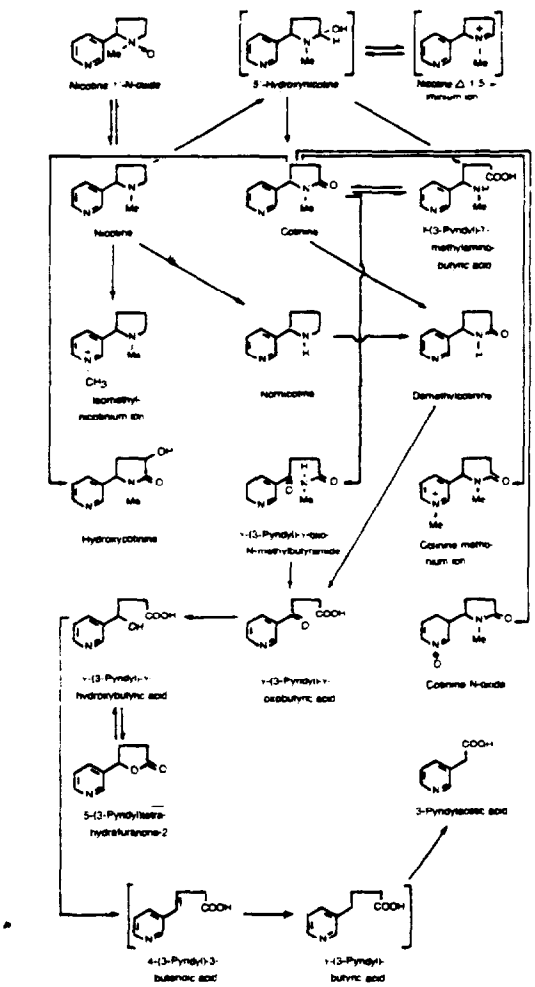


FIGURE 13.—Nicotine metabolism.
SOURCE: Hansson, E. (*27*).

urinary pH and flow rate. Specifically, the more acidic the urine, the larger the amount of unchanged nicotine. Similar results were obtained by Schachter and coworkers in reviewing the effect of urine pH as a result of stress-related factors (*55, 56*).

Metabolic Products in Test Animals from Nicotine in Cigarette Smoke

Investigations of nicotine metabolites from cigarette smoke, using various animal systems including man (*25, 27*), has led to the identification of several metabolites. An extensive investigation of

nicotine metabolites has been performed by Gorrod and Jenner (*25*). In the mouse, the metabolic products identified were cotinine, hydroxycotinine, γ-(3-pyridyl)-γ-oxo-N-methylbutyramide, CO_2 and two unidentified products separated by chromatography (*27*). The primary metabolites identified by Gorrod and Jenner include nicotine-1'-N-oxide, 5'-hydroxycotinine, cotinine, nornicotine, and isomethylnicotinium ion (*25*). Other metabolic products (Figure 13) are considered to be derived from those mentioned above. Only cotinine and nornicotine have been examined for their pharmacologic activity in any detail; these will be discussed below.

The complex mechanism by which cotinine, the major metabolite, is formed involves at least two enzyme systems. Both 5' hydroxynicotine and nicotine $\Delta N^{1'}(5')$ iminium ion have been implicated as intermediates (*30, 46*). Cotinine is further metabolized by pyrrolidone ring hydroxylation; all other metabolites of nicotine are thought to arise by cleavage of the phrrolidone ring of cotinine.

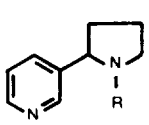
Related Alkaloids and Their Metabolites in Cigarette Smoke

It is difficult to generalize regarding the amount of various alkaloids other than nicotine in cigarettes because of differences in the alkaloid content and composition of the various tobacco strains employed in cigarette manufacture. However, nicotine is usually considered to account for about 95 percent of the alkaloids in tobacco. The remainder consists of varying proportions of nornicotine, anabasine, myosmine, anatabine, nicotyrine, and other alkaloids described in Figure 14 (*38*).

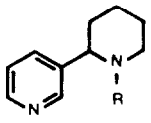
As stated above, nicotine is considered to be primarily responsible for eliciting the pharmacologic effects in cigarette smoke. Nevertheless, Using a battery of tests, Clark and coworkers (*13*) compared the pharmacological activity of a number of the minor alkaloids known or suspected to occur in tobacco smoke. Their results are summarized in Table 21. It should be noted, however, that only nicotine was optically pure. Others either were prepared synthetically, yielding racemic products, or were isolated under conditions resulting in optically inactive forms; therefore, the pharmacological responses reported may be less than would have been obtained had the optically active compounds (where appropriate) been tested. The LD_{50} values of several alkaloids in various species have been tabulated (*57*). Extrapolation of these data to other species and to the effects of multiple dosing, however, may not be useful because of variation in metabolic pathways among species.

Pharmacodynamics

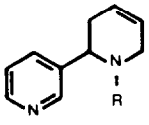
Until recently, relatively little attention was devoted to the pharmacodynamics of cigarette smoke. However, with increasing interest in smoking cessation techniques (*42*), tobacco industry emphasis on



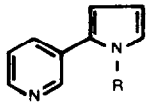
R = H, Nornicotine
R = CH_3, Nicotine



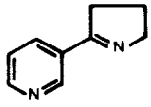
R = H, Anabasine
R = CH_3, N-Methyl-anabasine



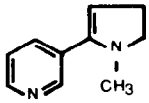
R = H, Anatabine
R = CH_3, N-Methyl-anatabine



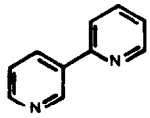
R = H, Nornicotyrine
R = CH_3, Nicotyrine



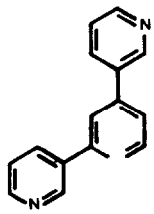
Myosmine



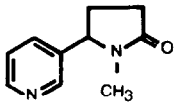
N-Methylmyosmine



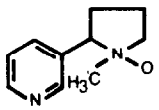
2,3-Dipyridyl



Nicotelline



Cotinine



Nicotine 1'-N-oxide

FIGURE 14.—Structural formulas of some tobacco alkaloids.
SOURCE: Larson, P.S. (*40*).

TABLE 21.—Relative molar potency of nicotine and other cigarette smoke alkaloids

Alkaloid	Contraction of guinea pig ileum	Pressor action in pithed rat	Release of catechol-amines from cat adrenal	Contraction of frog rectus	Blockade of contraction of diaphragm	Inhibition of cat knee jerk	Inhibition of cat flexor reflex	Inhibition of chick flexor reflex	Inhibition of chick crossed extensor reflex
Nicotine	100	100	100	100	100	100	100	100	100
Nornicotine	4.5	22	55	61	73	54	54	36	27
Metanicotine	4	3	20	–	<0.8	0.4	<0.6	–	12.5
Anabasine	17.5	20	75	28	50	17	33	33	20
Myosmine	0.2	5.5	–	3	12	3	<3	13	3
Nicotyrine	0.3	2.5	–	0.4	<0.08	17	<10	51	10
2:3-Dipyridyl	0.2	–	–	–	4	<0.1	<0.1	–	–
Dihydrometanicotine	<0.025	0.5	–	–	<0.8	<0.4	<0.6	–	–
N-Methylanabasine	<0.023	4.6	–	3	3.5	2	<5	–	12
Cotinine	<0.001	<0.1	0.03	–	<0.8	<0.05	<0.5	–	–
Nornicotyrine	<0.028	2	–	–	<0.9	–	–	–	–

SOURCE: Clark, M.S.G. (*15*).

lowering tar and nicotine in cigarette smoke (*49*), and major efforts undertaken in the research sector to develop and evaluate a less hazardous cigarette (*24*), the interactions between the physical/chemical characteristics of the cigarette and the behavioral/physiological characteristics of the smoker are being given increasing attention.

As discussed elsewhere in this report, there are many theories about why people smoke. While in most cases the explanation is not simple, nicotine is a generally agreed-upon factor. Nicotine has long been considered as habitual at least and, by some persons, as an addictive drug (*22, 37, 54*). The Third Report of the Royal College of Physicians of London (1977) is quite explicit in stating that "Tobacco smoking is a form of drug dependence different from but no less strong than that in other drugs of addiction" (*50a*). The pharmacodynamic implications of smoking have generated detoxification techniques in smoking-cessation programs, the search for nicotine substitutes or antinicotine drugs (e.g., lobeline (*26*)), the presentation of nicotine in an alternate vehicle (e.g., chewing gum (*52*)), and the evaluation of nicotine aerosol techniques in terms of their impact on modifying smoking behavior (*28*).

Because of the role of nicotine in creating a dependency for the smoker, it is appropriate to consider smoking patterns and the effects these patterns have on response to cigarette smoke components. There are many ways to characterize smoking patterns:

Type of cigarette smoked. Cigarette brands vary radically today in terms of nicotine and tar delivery and somewhat less in terms of CO, acrolein, HCN and NOx's.

Number of cigarettes smoked. This ranges from none to a maximum of about 100 cigarettes a day.

Amount of cigarette smoked. Smoking patterns range from smoking only the first few millimeters to smoking down to a few millimeters from the butt end. Inasmuch as the tobacco at the butt end of the cigarette acts as a filter and builds up nicotine and tar as the cigarette is smoked, the last few puffs on a cigarette smoked all the way down will have a much higher nicotine and tar delivery than the first puffs.

Number of puffs. This can range from one or two puffs up to about 20.

Depth of inhalation. Again, this can vary from the pattern of the noninhaler to deep inhalation.

Length of inhalation. The longer the cigarette smoke is held in the lungs, the greater the absorption and thus, the deposition of smoke.

Since it would be possible for an individual smoking 10 cigarettes per day to absorb more of the components of cigarette smoke than one who smoked many times that number, realistic evaluation of smoking impact calls for the development of dosimetric techniques applicable to research, screening, and smoking-pattern modification programs.

As might be expected, the smoking pattern affects absorption of the content of cigarette smoke, and consequently the toxic effects, differentially. Some of the contents and characteristics of the smoke also modify smoking patterns.

Since nicotine is absorbed through the mucus membranes and the skin as well as the alveoli, it will be absorbed, to a lesser degree, even by the noninhaler. (The nicotine from snuff and chewing tobacco is absorbed only through the mucus membrane route as is the case for most noninhaling cigar smokers.) Although the absorption of nicotine is to some degree independent of smoking patterns, there is significant evidence, not uniformly accepted, that a number of dimensions of smoking patterns are to a large degree dependent on nicotine content of the cigarette. Increasing evidence indicates that chronic "nicotine-dependent" smokers tend to titrate or compensate their inhalation profile in order to develop a desirable blood level of nicotine (*41*). This is done by modifying the number of cigarettes smoked, the number of puffs, the amount of cigarette smoked, or the depth of inhalation (*9*, *39*). The implication of this apparent compensatory modification of smoking pattern to assure a preestablished nicotine titration level in the smoker has broad ramifications when considered in the context of the increasingly popular lower-nicotine cigarettes designed to give low delivery. Since this is an area to which major attention has been devoted only recently, a serious research effort should be mounted in order to better understand this "titration" phenomenon. The implications for differential tax sanctions based upon nicotine delivery, as well as for the direction of development of less hazardous cigarettes, need exploration in depth. Since the pH of the urine affects the rate of elimination of nicotine from the blood stream, it might be expected to have an impact on the nicotine titration process with accompanying modification of smoking patterns (*53*); hence it should also be examined in greater detail.

Another characteristic of cigarette smoke which modifies smoking patterns is the pH (*9*). As has been mentioned earlier, cigarette smoke of the bright type or U.S. blending formula is mildly acidic, which results in relatively little irritation to the mucosa as compared to mildly basic smoke, and can accordingly be inhaled without unpleasant effects by many smokers. Cigar smoke, on the other hand, is mildly basic and is quite irritating to the mucosal tissues; for this reason, cigar smokers are less apt to inhale, or to inhale deeply, than are cigarette smokers. It has also been suggested that cigars are satisfying without being inhaled.

The remaining major toxic elements of cigarette smoke (CO and NO_x's) are absorbed primarily through the alveoli (acrolein and HCN are water soluble gases and are readily absorbed in the upper respiratory tract), and accordingly the inhalation characteristics of the smoker will have a direct impact on the short- and long-range effects

of these substances. Further, the ciliatoxic effects of HCN and the ciliastatic effects of acrolein will depend to a major extent on the inhalation pattern of the smoker. Lastly, the contribution of the NO_x's to chronic obstructive pulmonary disease depends to a major extent on the presentation of these substances at the alveolar site; as a result, inhalation practices will strongly affect the pathological sequelae of the NO_x compounds.

Thus, the consequences of cigarette smoking would appear to be dependent not only on the composition of the smoke itself, but also on the smoking patterns of the individual smoker. More extensive effort is needed to develop dosimetric and puff-analysis tools and techniques as a basis for better understanding of the pharmacokinetic and smoking behavioral dimensions of cigarette smoking.

Summary

The smoking of a cigarette seems to satisfy a smoker's physiological and psychological needs, and it is generally accepted that nicotine is the principal constituent responsible for cigarette smokers' pharmacologic responses.

Nicotine is rapidly absorbed in both the oral cavity and lungs, especially at basic pH. It is a quick-acting ganglionic stimulant on both the sympathetic and parasympathetic ganglia.

Nicotine causes the release of catecholamines, epinephrine, and norepinephrine. Several physiological responses have been attributed to nicotine and/or catecholamines, such as increased heart rate and blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, oxygen consumption, coronary blood flow and arrythmias, bronchoconstriction and related pulmonary manifestations, increased mobilization and utilization of free fatty acids, hyperglycemic effects, and a decreased pateller reflex response.

Considering the nicotine metabolites in cigarette smoke and the presence of minor amounts of related alkaloids, nicotine exerts the strongest response in a variety of biochemical and physiological tests.

Considerable evidence exists, although it is not uniformly accepted, that smoking patterns of chronic smokers are dependent on the nicotine content of the cigarette and dependent on what the nicotine delivery would be when measured by the standard methodology. Smoking patterns are dependent, to varying degrees, on the type of cigarette smoked, the number of cigarettes smoked, the length of the cigarette rod burned, the number of puffs, the depth of inhalation, and the length of inhalation. Nicotine absorption is also dependent on the above-mentioned parameters as well as on urine pH, which affects the rate of elimination of unmetabolized nicotine.

Pharmacology of Cigarette Smoke: References

(1) ARMITAGE, A.K. Effects of nicotine and tobacco smoke on blood pressure and release of catecholamines from the adrenal glands. British Journal of Pharmacology 25: 515-526, 1965.

(2) ARMITAGE, A.K., DOLLERY, C.T., GEORGE, C.F., HOUSEMAN, T.H., LEWIS, P.J., TURNER, D.M. Absorption and metabolism of nicotine from cigarettes. British Medical Journal 4: 313-316, November 8, 1975.

(3) ARMITAGE, A., DOLLERY, C.T., HOUSEMAN, T., KOHNER, E., LEWIS, P.J., TURNER, D. Absorption of nicotine from small cigars. Clinical Pharmacology and Therapy 23(2): 143-151, February 1978.

(4) ARMITAGE, A.K., TURNER, D.M. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. Nature 226: 1231-1232, June 27, 1970.

(5) ARONOW, W.S. Introduction to smoking and cardiovascular disease. In: Wynder, E.L., Hoffmann, D. Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 231-236.

(6) ARTHO, A.J., GROB, K. Nicotine absorption from cigarette smoke. Zeitschrift fuer Praeventivmedizin 9: 14-25, 1964.

(7) AVIADO, D.M., SAMANEK, M., FOLLE, L.E. Cardiopulmonary effects of tobacco and related substances. 1. The release of histamine during inhalation of cigarette smoke and anoxemia in the heart-lung and intact dog preparation. Archives of Environmental Health 12: 705-711, June 1966.

(8) BECKETT, A.H., GORROD, J.W., JENNER, P. A possible relation between pKa_1 and lipid solubility and the amounts excreted in urine of some tobacco alkaloids given to man. Journal of Pharmacy and Pharmacology 24: 115-120, 1972.

(9) BRUNNEMANN, K.D., HOFFMANN, D. The pH of tobacco smoke. Food and Cosmetics Toxicology 12: 115-124, 1974.

(10) BURN, J.H. Action of nicotine on the heart. Annals of the New York Academy of Sciences 90: 70-73, 1960.

(11) BURN, J.H., RAND, M.J. Action of nicotine on the heart. British Medical Journal 1(37): 137-139, January 18, 1958.

(12) BUSH, L.P., GRUNWALD, C., DAVIS, D.L. Influence of puff frequency and puff volume on the alkaloid content of smoke. Journal of Agricultural and Food Chemistry 20(3): 676-678, 1972.

(13) CLARK, M.S.G., RAND, M.J., VANOV, S. Comparison of pharmacological activity of nicotine and related alkaloids occurring in cigarette smoke. Archives of Internal Pharmacodynamics 156(2): 363-379, 1965.

(14) CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. New England Journal of Medicine 295(11): 573-577, September 9, 1976.

(15) CUTTING, W.C. Handbook of Pharmacology. Fourth Edition. New York, Appleton-Century-Crofts, 1969, pp. 559-562.

(16) DALHAMN, T., EDFORS, M.-L., RYLANDER, R. Retention of cigarette smoke components in human lungs. Archives of Environmental Health 17(5): 746-748, November 1968.

(17) DOMINO, E.F. Neuropsychopharmacology of nicotine and tobacco smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V. H. Winston & Sons, 1973, pp. 5-31.

(18) DOMINO, E.F., VON BAUMGARTEN, A.M. Tobacco cigarette smoking and patellar reflex depression. Clinical Pharmacology and Therapeutics 10(1): 72-79, 1969.

(19) DOYLE, J.T., DAWBER, T.R., KANNEL, W.B., KINCH, S.H., KAHN, H.A. The relationship of cigarette smoking to coronary heart disease. The second report on the combined experience of the Albany, New York and Framingham, Massachusetts studies. Journal of the American Medical Association 190(10): 886-890, December 7, 1964.

(20) EMELE, J.F. Pharmacology of nicotine. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. 77-1413, 1977, pp. 561-567.

(21) FEYERABEND, C., RUSSELL, M.A.H. Effect of urinary pH and nicotine excretion rate on plasma nicotine during cigarette smoking and chewing nicotine gum. British Journal of Clinical Pharmacology 5: 293-297, 1978.

(22) FINNEGAN, J.K., LARSON, P.S., HAAG, H.B. The role of nicotine in the cigarette habit. Science 102(2639): 94-96, July 27, 1945.

(23) GORDON, T., KANNEL, W.B. Predisposition to atherosclerosis in the head, heart, and legs. The Framingham study. Journal of the American Medical Association 221(7): 661-666, August 14, 1972.

(24) GORI, G.B. Low-risk cigarettes: A prescription. Science 194: 1243-1246, December 17, 1976.

(25) GORROD, J.W., JENNER, P. The metabolism of tobacco alkaloids. In: Essays in Toxicology. Volume 6. New York, Academic Press, 1975, pp. 35-78.

(26) GRITZ, E.R., JARVIK, M.E. Pharmacological aids for the cessation of smoking. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. 77-1413, 1977, pp. 575-591.

(27) HANSSON, E., SCHMITERLOW, C.G. Metabolism of nicotine in various tissues. In: Von Euler, U.S. (Editor). Tobacco Alkaloids and Related Compounds. Oxford, Pergamon Press, 1965, pp. 87-99.

(28) HERXHEIMER, A., GRIFFITHS, R.L., HAMILTON, B., WAKEFIELD, M. Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man. Lancet: 754-755, October 7, 1967.

(29) HILL, P., WYNDER, E.L. Smoking and cardiovascular disease. American Heart Journal 87(4): 491-496, April 1974.

(30) HUCKER, H.B., GILLETTE, J.R., BRODIE, B.B. Enzymatic pathway for the formation of cotinine, a major metabolite of nicotine in rabbit liver. Journal of Pharmacology and Experimental Therapeutics 129: 94-100, May 1960.

(31) IRVING, D.W., YAMAMOTO, T. Cigarette smoking and cardiac output. British Heart Journal 25(1): 126-132, January 1963.

(32) KANNEL, W.B. Epidemiologic studies on smoking in cerebral and peripheral vascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76-1221, 1976, pp. 257-274.

(33) KANNEL, W.B., SHURTLEFF, D. The Framingham study. Cigarettes and the development of intermittent claudication. Geriatrics 28: 61-68, February 1973.

(34) KERSHBAUM, A., KHORSANDIAN, R., CAPLAN, R.F., BELLET, S., FEINBERG, L.J. The role of catecholamines in the free fatty acid response to cigarette smoking. Circulation 28: 52-57, July 1963.

(35) KERSHBAUM, A., OSADA, H., SCRIABINE, A., BELLET, S., PAPPAJOHN, D.J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue in vitro and in the isolated perfused dog limb. Circulation 35 and 36(4, Supplement II): 20, October 1967.

(36) KERSHBAUM, A., PAPPAJOHN, D.J., BELLET, S. Effect of nicotine and tobacco smoke on the disappearance and distribution of administered palamitic acid-1-C^{14}. Circulation 33 and 34(4, Supplement III): 17, October 1966.

(37) KNAPP, P.H., BLISS, C.M., WELLS, H. Addictive aspects in heavy cigarette smoking. American Journal of Psychiatry 119(10): 966-972, April 1963.

(38) KUHN, H. Tobacco alkaloids and their pyrolysis products in the smoke. In: von Euler, U.S. (Editor). Tobacco Alkaloids and Related Compounds. Oxford, Pergamon Press, 1965, pp. 37-51.

(39) LADER, M. Nicotine and smoking behaviour. British Journal of Clinical Pharmacology 5: 289-292, 1978.

(40) LARSON, P.S., SILVETTE, H. Tobacco Experimental and Clinical Studies. Supplement II. Baltimore, Williams & Wilkins Company, 1971, pp. 147-167.

(41) MAHAJAN, V., HUBER, G., SORNBERGER, G., SHEA, J., HINDS, W., FIRST, M. The acute effects of tobacco smoke and synthetic smoking materials on pulmonary antibacterial defenses. Clinical Research 26: 451, 1978. (Abstract)

(42) MCABEE, N.K., JR. Smoking control programs aimed at adult audiences. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 231-236.

(43) MILLER, R.P., ROTENBERG, K.S., ADIR, J. Effect of dose on the pharmacokinetics of intravenous nicotine in the rat. Drug Metabolism and Disposition 5(5): 436-443, 1977.

(44) MILTON, A.S. The effect of nicotine on blood glucose levels and plasma non-esterified fatty acid levels in the intact and adrenalectomized cat. British Journal of Pharmacology 26: 256-263, 1966.

(45) MULCAHY, R., MCGILVRAY, J.W., HICKEY, N. Cigarette smoking related to geographic variations in coronary heart disease mortality and to expectation of life in the two sexes. American Journal of Public Health 60(8): 1515-1521, August 1970.

(46) MURPHY, P.J. Enzymatic oxidation of nicotine to nicotine $\Delta^{1'(5')}$iminium ion. Journal of Biological Chemistry 248(8): 2796-2800, April 25, 1973.

(47) NADEAU, R.A., JAMES, T.N. Effects of nicotine on heart rate studied by direct perfusion of sinus node. American Journal of Physiology 212(4): 911-916, April 1967.

(48) NAQUIRA, D., ZUNINO, E., ARQUEROS, L., VIVEROS, O.H. Chronic effects of nicotine on catecholamine synthesizing enzymes in rats. European Journal of Pharmacology 47: 227-229, 1978.

(49) OWEN, T.B. Tar and nicotine from U.S. cigarettes: Trends over the past twenty years. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 73-80.

(50) REINTJES, M., SWIERENGA, J., BOGAARD, J.M. Effect of smoking one cigarette on airway resistance. Scandinavian Journal of Respiratory Diseases 53(3): 129-134, 1972.

(50a) ROYAL COLLEGE OF PHYSICIANS. Smoking or Health. London, Pitman Medical, 1977, pp. 98-112.

(51) RUDDON, R.W., COHEN, A.M. Alteration of enzyme activity in rat liver following the acute and chronic administration of nicotine. Toxicology and Applied Pharmacology 16: 613-625, 1970.

(52) RUSSELL, M.A.H., WILSON, C., FEYERABEND, C., COLE, P.V. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. British Medical Journal 2: 391-395, August 14, 1976.

(53) RYLANDER, R. Tobacco smoke toxicity—The experimental evaluation. Reviews on Environmental Health 1(1): 53-74, 1972.

(54) SCHACHTER, S. Pharmacological and psychological determinants of smoking. Annals of Internal Medicine 88: 104-114, 1978.

(55) SCHACHTER, S., KOZLOWSKI, L.T., SILVERSTEIN, B. 2. Effects of urinary pH on cigarette smoking. Journal of Experimental Psychology: General 106(1): 13-19, 1977.

(56) SCHACHTER, S., SILVERSTEIN, B., KOZLOWSKI, L.T., HERMAN, C.P., LIEBLING, B. 4. Effects of stress on cigarette smoking and urinary pH. Journal of Experimental Psychology: General 106(1): 24-30, 1977.

(57) SCHIEVELBEIN, H.VON. Nikotin, rauchen und organismus (Nicotine, smoke and organisms). Beitraege zur Tabakforschung 6(4): 199-274, 1972.

(58) SHURTLEFF, D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham study, 18-year follow-up. In: Kannel, W.B., Gordon, T. (Editors). The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 74-599, 1974, 311 pp.

(59) TSUJIMOTO, A., NAKASHIMA, T., TANINO, S., DOHI, T., KUROGOCHI, Y. Tissue distribution of [^{3}H] nicotine in dogs and rhesus monkeys. Toxicology and Applied Pharmacology 32: 21-31, 1975.

(60) TUCCI, J.R., SODE, J. Chronic cigarette smoking. Effect on adrenocortical and sympathoadrenomedullary activity in man. Journal of the American Medical Association 221(3): 282-285, July 17, 1972.

(61) TURNER, D.M., ARMITAGE, A.K., BRIANT, R.H., DOLLERY, C.T. Metabolism of nicotine by the isolated perfused dog lung. Xenobiotica 5(9): 539-551, 1975.

(62) U.S. PUBLIC HEALTH SERVICE. Harmful constituents of cigarette smoke. In: U.S. Public Health Service. The Health Consequences of Smoking. Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7516, 1972, pp. 139-150.

(63) WATTS, D.T. The effect of nicotine and smoking on the secretion of epinephrine. Annals of the New York Academy of Sciences 90: 74-80, 1960.

Reductions of the Toxic Activity of Cigarette Smoke

Gas Phase

During the last decade there has been a reduction in the concentration of toxic and tumorigenic agents in cigarette smoke. Measured on experimental animals, these reductions of harmful smoke constituents are reflected in diminished ciliatoxicity, overall toxicity, and tumorigenicity of low-tar, low-nicotine cigarettes.

Carbon Monoxide

Carbon monoxide is one of the compounds in cigarette smoke judged most likely to contribute to the health hazards of smoking. Certain modifications in the makeup and fillers of cigarettes, as well as the use of special preparations of charcoal in filter tips, can lead to a slight reduction of carbon monoxide in cigarette smoke (*32*); however, selective filtration of CO does not seem to be feasible. For certain filter cigarettes (those without perforated filter tips) the CO yield has remained comparable to that of nonfilter cigarettes or has even increased slightly (*40*). The major, and possibly the only, significant reduction of CO in cigarette smoke can be achieved by air dilution with perforated filter tips and/or perforated cigarette paper (*33*). With increasing air dilution, CO is selectively reduced as compared to tar and CO_2 (*27, 29*). This CO reduction occurs because the air dilution holes permit rapid diffusion out of the smoke stream and because lowering the effective puff volume through the fire cone alters the combustion process and lowers the CO:CO_2 ratio. As Table 22 shows, the CO reduction is greater with ventilation than the decrease in tobacco burned during puffing, as indicated by percent ventilation. For example, where the ventilation of a cigarette is 52 percent, the CO reduction is 67 percent. However, the smoker of cigarettes with perforated wrappers and/or ventilated filter tips may compensate for air dilution by taking increased puff volumes when he inhales. Overall, though, ventilated filters do improve the CO/nicotine ratio. At present, data on the carboxyhemoglobin levels of long-term smokers of these types of cigarettes are not available for comparison.

As expected, the smoke of cigars and pipes is high in CO because of the nearly complete lack of ventilation through the cigar wrapper or pipe bowl (*21, 30*).

Reduction of Ciliatoxic Smoke Compounds

It is assumed that mucociliary clearance is essential for the maintenance of a normal pulmonary environment. Any interference with the lung clearance mechanism can result in an accumulation of toxic and tumorigenic agents and, consequently, in respiratory diseases. Studies of humans have shown that in certain smokers, lung clearance returns to normal after 3 months' cessation of smoking (*5*). These consider-

TABLE 22.—Effects of various forms of air dilution on carbon monoxide and carbon dioxide deliveries

Sample	Ventilation	CO(mg)	CO_2(mg)
Filter Cigarette A perforated tip	22%	10.6	35.1
Filter Cigarette A unperforated tip		13.6	43.5
% reduction		21	19
Cigarette B with tip open perforated	43%	8.7	30.7
Cigarette B unperforated tip		17.2	52.3
% reduction		49.4	41.2
Cigarette C with line perforated paper	52%	5.6	30.4
Cigarette C without line perforations		17.1	57.4
% reduction		67	48.7

SOURCE: Sloan, C.H. (*31*).

ations have led to efforts towards the identification and reduction of ciliatoxic components in cigarette smoke. Bioassays for the evaluation of the ciliatoxicity of cigarette smoke and of individual smoke components are carried out with isolated ciliated tissues, with organs, or with the intact animal (*1, 43*).

While the particulate matter of cigarette smoke inhibits mucociliary clearance to some extent, certain volatile smoke constituents show significant ciliatoxic potency. Table 23 lists gas phase components with relatively high ciliatoxicity as measured on isolated chicken trachea (*1*).

One or more successful methods for the specific reduction of ciliatoxic volatiles in cigarette smoke is charcoal filtration, a technique thoroughly explored over many years (*13, 18, 44*). The efficiency for removal of gas phase constituents of charcoal filter tips is listed in Table 24 (*12, 31*). An extensive study demonstrated that air dilution filters lowered delivery of gaseous aldehydes, CO, HCN, etc. (*12*).

The design of cigarettes can also significantly influence the ciliatoxicity of the mainstream smoke. This is important since modification of the design characteristics of cigarettes is primarily aimed at lowering tar and nicotine content of smoke and may not concurrently consider ciliatoxicity of the smoke. Studies on the mainstream smoke of cigarettes made from certain reconstituted tobacco sheets or tobacco substitutes and on mainstream smoke of filter cigarettes with air dilution have shown a reduction in ciliatoxici-

TABLE 23.—Vapor phase constituents with high ciliatoxic potency—in vitro

Compound	Potency	Amount in smoke (μg/puff) Typical (Range)
Hydrogen Cyanide	+ + +	38(16–63)
Formaldehyde	+ + +	5(25–11)
Acrolein	+ + +	10(5.6–10.4)
Sulfur Dioxide	+ + +	<1
Crotonaldehyde	+ +	1.6
2,3-Butanedione	+ +	12
Ammonia	+ +	1
Nitrogen Dioxide	+ +	<10
Methacrolein	+	1
Vinyl Acetate	+	0.5
Nitric Oxide	+	60(12–75)

Score — ED_{50}(8 puffs) (μg/puff)
+ + + High = <50
+ + Moderate = 50–100
+ Low = 100–500
SOURCE: Battista, S.P. (*1*).

ty as well as lower levels of hydrogen cyanide, formaldehyde, and tar (*24–26*).

Volatile Phenols and Catechols

In the experimental setting, volatile phenols were considered to contribute to the tumor-promoting activity of cigarette smoke. Several studies have demonstrated that various types of cellulose acetate filter tips selectively removed volatile phenols from cigarette mainstream smoke (*10, 31, 44*). However, in bioassays on mouse skin with cigarette tar and in inhalation studies with diluted whole smoke on Syrian golden hamsters, a selective reduction of volatile phenols was not paralleled by a selective reduction of tumorigenicity (*8, 24–26*).

Catechols, which are known co-carcinogens in the experimental setting, are not selectively reduced by filtration from cigarette smoke (*3, 22*). Cigarette fillers low in wax layer components, either by use of tobacco stems, reconstituted tobacco sheet, or tobacco extracted with a hexane-ethanol mixture, delivered smoke significantly reduced in catechols (*6*). Although it has not been directly established that a selective reduction in catechol leads to a significant reduction of the tumorigenic potential of cigarette smoke, it is of interest that all those tars or whole smokes of cigarettes which are low in catechol also have a significantly lower tumorigenic activity (*7, 8, 24–26*).

TABLE 24.—Removal of some gas-phase components of cigarette smoke by an activated carbon filter*

Compound	Removal %
Methane	0
Acetylene	0
Ethane	0
Propene	26.2
Chloromethane	25.9
Propane	17
Methanol	51.9
Acetaldehyde	55.4
Butene	59.5
Ethanol	58.7
Acetonitrile	68.3
Acrolein	91
Acetone	78.9
Acrylonitrile	44.4
Isoprene	76.9
Pentadiene	96.5
2-Butanone	97.8
Hexane	73.9
Benzene	55
Dimethylfuran	95.4
Pyridine	92.5
Toluene	60

* 100 Mg activated carbon; Sample No. M-S-4.
SOURCE: Kensler, C.J. (*18*).

Volatile N-Nitrosamines

As discussed earlier, N-nitrosamine formation in tobacco smoke is determined by the nitrate content of the tobacco. Lowering of the nitrate content leads to a reduction of volatile nitrosamines, as has been demonstrated for the smoke of Burley tobaccos grown at varying rates of N-fertilization (*15*). Certain other agricultural practices can also lead to a reduction of volatile nitrosamines in the smoke of tobaccos (*38*). More importantly, however, selective removal (70 to 80 percent) of volatile nitrosamines from the smoke can be achieved by cellulose filters (*4, 38*). At present, it has not been demonstrated that a significant reduction of volatile N-nitrosamines will lead to a significant reduction of the tumorigenic potential of cigarette smoke. The detection of differences in the tumorigenic potential of the smoke of cigarettes which vary greatly in N-nitrosamine content (*23*) is likely to be difficult because of the low sensitivity of the experimental models presently available.

Particulate Phase

Tar

In the experimental setting, a dose response has been established between tar application or smoke inhaled and tumor yield (*2, 8*). These data support epidemiological findings relating the amount of cigarette smoke inhaled and the likelihood of cancer of the oral cavity, cancer of the lung, cardiovascular disease, and respiratory disease in humans (*14, 41, 45*). Thus, as long as warnings of health hazards from smoking are disregarded and as long as cigarettes are consumed, efforts towards a reduction of tar and smoke components which may contribute to these health hazards should be continued.

Several approaches affect tar reduction in the smoke by modification of the cigarette filler (*11, 44*), and many of these have, in fact, been applied to cigarettes manufactured in the United States and other countries (Figure 15). The most widely used techniques are summarized in Table 25. The application of a combination of these techniques has led to low tar cigarettes; air dilution of smoke is a prominent feature of many of the recently introduced low-tar brands (<10 mg). Homogenized leaf curing (*37*) and reduction of tobacco proteins (*34*) are currently being thoroughly investigated as additional methods for reduction of tar, nicotine, and other harmful smoke components.

Nicotine

Nicotine and the minor tobacco alkaloids are largely responsible for tobacco habituation, smoke flavor, and smoke toxicity and are the precursors for the tobacco specific N-nitrosamines. Since 1926, research programs have been directed toward the reduction of the tobacco alkaloids (*19*); a combination of methods has, in fact, led to a drastic lowering of nicotine in the smoke of U.S. cigarettes (Figure 16). The methods summarized in Table 25 for the reduction of tar in cigarette smoke apply also to the reduction of nicotine in the smoke. Selective reduction of tobacco alkaloids has been achieved by breeding specific varieties and by close spacing of tobacco plants. After harvesting the tobacco, leaf nicotine can also be selectively reduced by oxidation with bacterial enzymes, special curing conditions, reaction with alkylating agents, extraction with water and ammonia, and by steam distillation. Since cigarettes in the United States and in most foreign countries are made of flue-cured tobacco, are blends with flue-cured tobacco as a major ingredient or, in a few cases, are blends with Turkish tobacco, the pH of the resulting mainstream smoke is below 6.5 and thus essentially contains only protonated nicotine. Nicotine salts, however, are a part of the particulate matter and are, therefore, not amenable to significant selective filtration.

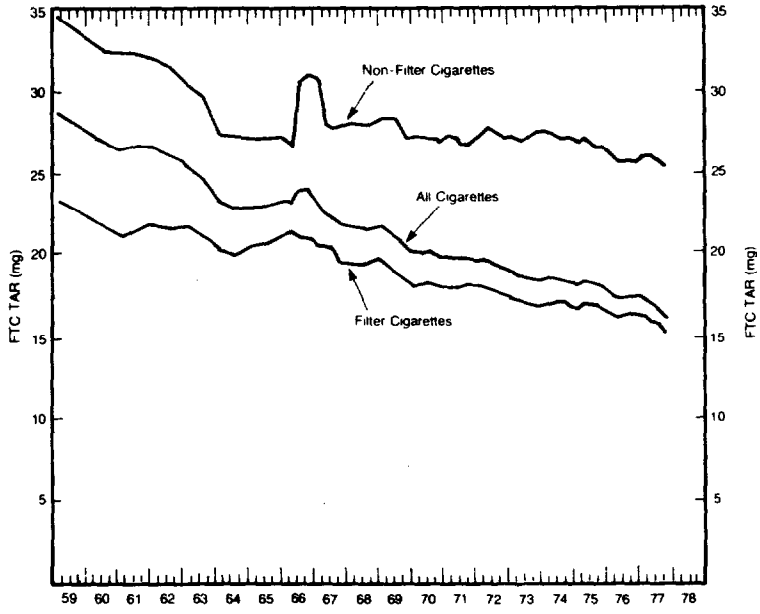


FIGURE 15.—Sales-weighted average "tar" deliveries of U.S. cigarettes from 1957 to the the present.

SOURCE: Wakeham, H. (*59*).

Polynuclear Aromatic Hydrocarbons

As early as 1957, it was demonstrated that polynuclear aromatic hydrocarbons (PAH) play an important role in tobacco carcinogenesis (*46*). When the PAH-containing neutral subfraction is removed from the tar, the carcinogenic activity of the PAH-free tar on mouse skin is reduced by more than 50 percent (*9, 17*). Detailed studies have shown that the PAH are the major tumor initiators in the smoke; a significant reduction of the polycyclic hydrocarbons leads to a concomitant reduction of the tumorigenic activity of the tar on mouse skin and of the whole smoke on the larynx of Syrian golden hamsters (*7, 12, 16, 20, 24, 25, 44*).

As discussed earlier, PAH are primarily pyrosynthesized from C,H-radicals. Therefore, their formation in smoke can be inhibited by radical scavengers. Thus, when nitrate levels in tobacco are increased, the nitrogen oxides formed in the burning cone serve as C,H-radical scavengers and inhibit PAH-formation (*28*). Since the mechanism of the pyrosynthesis of PAH from C,H-radicals is valid for most of the PAH in tobacco smoke, benzo(*a*)pyrene is often used generally as an indicator of PAH levels and specifically as an indicator of the carcinogenic potential of the smoke as measured in animal experiments. However, this "indicator" concept can be applied only to smoke

TABLE 25.—Some measures for "tar" reduction in cigarette smoke

1. *Agricultural Techniques*
   a. Genetics and breeding
   b. Planting density (plants/acre)
   c. Nitrate fertilization
   d. Application of agricultural chemicals
   e. Stage of topping
2. *Selection of Raw Tobacco*
   a. Tobacco type
   b. Stalk position
   c. Nitrate content
   d. Selection by specific tobacco constituent (e.g. protein, carbohydrates, resins)
3. *Treatment of Tobacco*
   a. Curling
   b. Homogenized leaf curing
   c. Grading
   d. Fermentation
   e. Extraction
   f. Tobacco expansion (freeze-drying)
4. *Tobacco Additives*
5. *Blending*
6. *Amount of:*
   a. Tobacco
   b. Stems
   c. Reconstituted tobacco
   d. Expanded tobacco
7. *Tobacco Cut*
8. *Smoke Dilution*
   a. Porous cigarette paper
   b. Perforated cigarette paper
   c. Perforated filter tips
9. *Smoke Filtration*

SOURCE: Tso, T.C. (*35*).

deriving from cigarettes primarily made up of the same precursor material, i.e., tobacco leaves. The "indicator" concept was applied in measuring BαP formation in many attempts to achieve PAH reduction in smoke. The PAH yield in smoke can be reduced selectively by

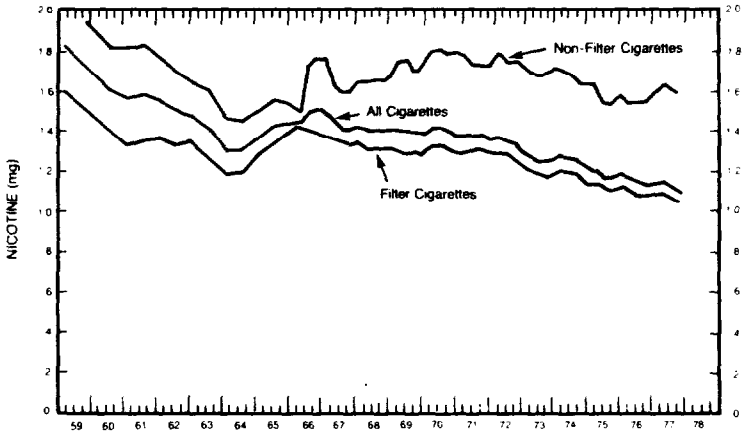


FIGURE 16.—Sales-weighted average nicotine deliveries of U.S. cigarettes from 1957 to present.

SOURCE: Wakeham, H. (*59*).

increasing combustibility of the cigarette filler, by reducing the wax content of the tobacco lamina, and by adding compounds to tobacco which provide radical-scavengers during burning of the cigarette, thus utilizing the concept of inhibiting PAH-pyrosynthesis as discussed above. Since PAH have low volatility, they are a part of the condensed smoke matter (tar) and cannot be selectively removed by filtration.

Increased combustilibity can be achieved by air dilution, by increasing the filling power of the tobacco blend, and by selection of tobaccos rich in nitrates or low in wax content. Combustion is also improved by addition of reconstituted tobacco sheet (RTS), expanded (freeze-dried) tobaccos, and tobacco substitutes with special physical characteristics. The reduction of the wax layer in the blend is often achieved by tobacco selection and by using diluents such as RTS, expanded tobacco, and tobacco ribs and stems.

A number of efforts have been directed toward the addition of chemicals to the blend, a process which gives rise to agents capable of inhibiting pyroformation of PAH. These studies have often been successful; however, they are primarily of academic interest since the addition of chemicals can give rise to new toxic agents.

As discussed before, many of the laboratory methods for the reduction of the toxicity of cigarette smoke have found application in the commercial cigarette. Today most U.S. cigarette blends contain tobacco stems, RTS (>10 percent), and expanded tobacco.

As a consequence of the use of different tobacco blends, the nitrate content during the last 15 years has risen from about 0.5 percent to more than 1 percent. It has not been determined if an increase in

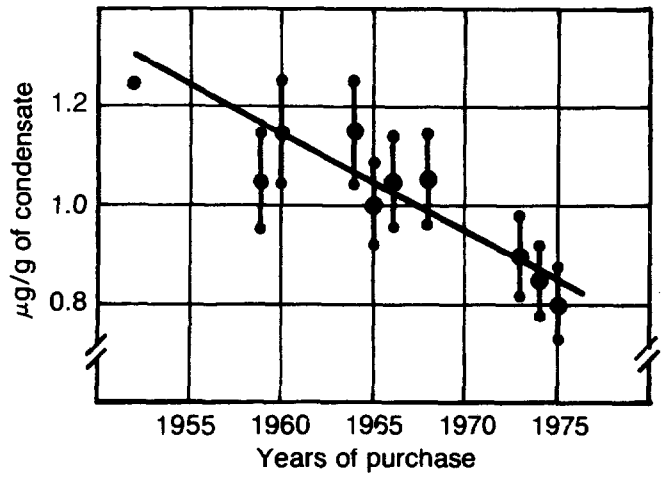


FIGURE 17.—Benzo(a) pyrene in the smoke condensate of a leading U.S. nonfilter cigarette.
SOURCE: Weber, K.H. (*41*).

nitrosamines has accompanied the increase in nitrate content. The result is that the content of PAH in the smoke of commercial cigarettes has significantly decreased during the last 25 years, as shown by the decrease of BαP in the smoke of a leading U.S. nonfilter cigarette in that period (Figure 17). Accordingly, the carcinogenicity of the tar of the same cigarette on mouse skin has significantly decreased over the years.

Nonvolatile N-Nitrosamines

As discussed earlier, about half of the tobacco-specific N-nitrosamines, NNN, NNK, and NAtB (Figure 3), in the smoke of U.S. cigarettes transfers directly from the tobacco into the smoke. In the leaf these carcinogenic nitrosamines are formed during curing and fermentation. It appears possible that they can be reduced in processed tobacco by specific bacteria, i.e., by pathways similar to those affecting nicotine reduction by bacteria (*19*). The reduction of the tobacco-specific nitrosamines in the smoke by selective filtration is not feasible and other methods for their reduction have not been reported thus far.

In the case of the carcinogenic N-nitrosodiethanolamine, the replacement of the precursor (diethanolamine) by another solubilizing agent for maleic hydrazide, the sucker growth inhibitor, is strongly suggested. For example, the potassium salt of maleic hydrazide would be more desirable.

Polonium-210

During smoking, Po^{210} is partially transferred from the tobacco into the mainstream smoke (*20*). Since a major portion of Po^{210} in U.S. tobaccos originates from the phosphate fertilizer (*36*), efforts should be continued to eliminate the use of fertilizers containing Po^{210}. A more effective way to reduce or remove Po^{210} and Pb^{210} is through the homogenized leaf-curing extraction process after harvesting. A gradual reduction of Po^{210} in tobacco is also expected to occur during the next decade with the decrease of airborne Po^{210}. Smoke filtration also removes radioactive particulates.

Summary

A number of methods have led to reduction of tar and of toxic and tumorigenic agents in the smoke of cigarettes. Table 26 lists the approaches that have led to the reduction of the ciliatoxicity and to selective reduction of the carcinogenicity and tumor-promoting activity of the smoke of experimental cigarettes. As mentioned repeatedly, many of these methods have already been incorporated in the modified blended U.S. cigarette of today.

TABLE 26.—Reduction of biological activity of cigarette smoke*

Method	CO	Cilia Toxicity	"Tar"	Nicotine	BaP	Selective Biological Reduction		Remarks
						Carcino-genicity	Tumor Promoters	
Agricultural Aspects								
Tobacco Varieties (Bright-Burley)	±	±	+	+	+	+	+	
New Tobacco Cultivars	?	+	+	+	+	?	?	
Leaf Position	+	+	+	+	+	?	?	Lowest stalk position; highest reduction
Selection by NO_3	+	±	+	+	+	+	?	
Tobacco Processing								
Extraction:								
Organic Solvents	±	±	+	+	+	+	?	Only of academic interest
Cut	±	±	±	±	±	±?	?	
Stems		+	+	+	-	++	++	
Reconstituted Tobacco Sheets (RTS)**	±	+	+	+	+	+	±	Some RTS give high CO
Reconstituted Tobacco Sheets (Paper Process)	±	+	++	+	+	++	?	
Expanded Tobacco	+	+?	++	++	++	±?	±	
Cigarette Production								
Porosity of Paper	++	+	+	+	+	±	?	
Perforated Filters	++	+	+	+	+	±	?	
Cellulose Acetate Filters	±	±	+	+	+	±	±	
Charcoal Filter***	±	++	+	+	+	+	±	
Additives: NO_3	±	-	+	+	+	+	±	Only of academic interest
Tobacco Substitutes	±	+	++	++	+	++	+	

*Reductions: ++ ≥50%, + significant; ± insignificant; ±? questionable; - increase; ? unknown.
**Data given for reconstituted tobacco sheets relate to those not made by the paper process.
***Reductions of "tar," nicotine, and BaP are in general greater with cellulose acetate filters than with charcoal filters.
SOURCE: Wynder, E.L. (42)

Reductions of the Toxic Activity of Cigarette Smoke: References

(*1*) BATTISTA, S.P. Cilia toxic components of cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 517-534.

(*2*) BOCK, F.G. Dose response: Experimental carcinogenesis. Toward a Less Harmful Cigarette. National Cancer Institute Monograph No. 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, 1968, pp. 57-63.

(*3*) BRUNNEMANN, K.D., LEE, H.-C., HOFFMANN, D. Chemical studies on tobacco smoke. XLVII. On the quantitative analysis of catechols and their reduction. Analytical Letters 9(10): 939-955, 1976.

(*4*) BRUNNEMANN, K.D., YU, L., HOFFMANN, D. Assessment of carcinogenic volatile N-nitrosamines in tobacco and in mainstream and sidestream smoke from cigarettes. Cancer Research 37(9): 3218-3222, September 1977.

(*5*) CAMNER, P., PHILIPSON, K., ARVIDSSON, T. Withdrawal of cigarette smoking. A study on tracheobronchial clearance. Archives of Environmental Health 26(2): 90-92, February 1973.

(*6*) CARTER, W.L., HASEGAWA, I. Fixation of tobacco smoke aerosols for size distribution studies. Journal of Colloid and Interface Science 53(1): 134-141, October 1975.

(*7*) DONTENWILL, W.P. Tumorigenic effect of chronic cigarette smoke inhalation on Syrian golden hamsters. In: Karbe, E., Park, J.F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. New York, Springer-Verlag, 1974, pp. 331-359.

(*8*) DONTENWILL, W., CHEVALIER, H.-J., HARKE, H.-P., LAFRENZ, U., RECKZEH, G., SCHNEIDER, B. Investigations on the effects of chronic cigarette-smoke inhalation in Syrian golden hamsters. Journal of the National Cancer Institute 51(6): 1781-1832, December 1973.

(*9*) DONTENWILL, W., ELMENHORST, H., HARKE, H.-P., RECKZEH, G., WEBER, K. H., MISFELD, J., TIMM, J. Experimentelle untersuchungen ueber die tumorerzeugende wirkung von zigarettenrauch-kondensaten an der maeusehaut (Experimental studies on tumorigenic activity of cigarette smoke condensate in mouse skin). Parts 1, 2, and 3. Zeitschrift fuer Krebsforschung und Klinische Onkologie 73: 265-314, 1970.

(*10*) GEORGE, T.W., KEITH, C.H. The selective filtration of tobacco smoke. In: Wynder, E.L., Hoffmann, D. (Editors). Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, pp. 577-622.

(*11*) GORI, G.B. Approaches to the reduction of total particulate matter (TPM) in cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 451-461.

(*12*) GORI, G.B., BATTISTA, S.P., THAYER, P.S., GUERIN, M.R., LYNCH, C.J. Chemistry and in vitro bioassay of smoke from experimental filter cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 76-1076, 1976, 42 pp.

(*13*) HAAG, H.B., LARSON, P.S., FINNEGAN, J.K. Effect of filtration on the chemical and irritating properties of cigarette smoke. American Medical Association Archives of Otolaryngology 69: 261-265, March 1959.

(*14*) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. Some recent findings concerning cigarette smoking. In: Hiatt, H.H., Watson, J.D., Winsten, J.A. (Editors). Origins of Human Cancer. Book A: Incidence of Cancer in Humans. New York, Cold Spring Harbor Laboratory, 1977, pp. 101-112.

(*15*) HECHT, S.S., TSO, T.C., HOFFMANN, D. Selective reduction of tumorigenicity of tobacco smoke. IV. Approaches to the reduction of nitrosamines and aromatic amines. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 535-545.

(*16*) HOFFMANN, D., WYNDER, E.L. Selective reduction of the tumorigenicity of tobacco smoke. III. The reduction of polynuclear aromatic hydrocarbons in cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 495-504.

(*17*) HOFFMANN, D., WYNDER, E.L. A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. Cancer 27(4): 848-864, April 1971.

(*18*) KENSLER, C.J., BATTISTA, S.P. Components of cigarette smoke with ciliary-depressant activity. Their selective removal by filters containing activated charcoal granules. New England Journal of Medicine 269(22): 1161-1166, 1963.

(*19*) KUHN, K., KLUS, H. Possibilities for the reduction of nicotine in cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 463-494.

(*20*) MARTELL, E.A. Radioactivity of tobacco trichomes and insoluble cigarette smoke particles. Nature 249: 215-217, May 17, 1974.

(*20a*) MCKENNIS, H., JR. The excretion and metabolism of nicotine. Annals of the New York Academy of Sciences 90: 36-42, 1960.

(*20b*) MCKENNIS, H., JR., TURNBULL, L.B., BOWMAN, E.R. γ-(3-pyridyl)-γ-methylaminobutyric acid as a urinary metabolite of nicotine. Journal of the American Chemical Society 79: 6342-6343, 1957.

(*20c*) MCKENNIS, H., JR., TURNBULL, L.B., BOWMAN, E.R., WADA, E. Demethylation of continine *in vivo*, Journal of the American Chemical Society 81: 3951-3954, 1959.

(*20d*) MCKENNIS, H., JR., TURNBULL, L.B., SCHWARTZ, S.L., TAMAKI, E., BOWMAN, E.R. Demethylation in the metabolism of (-)-nicotine. Journal of Biological Chemistry 237: 541-546, 1962.

(*21*) MILLER, J.E. Determination of the components of pipe tobacco and cigar smoke by means of a new smoking machine. Proceedings of the Third World Tobacco Scientific Congress, Salisbury, Southern Rhodesia, 1963, pp. 584-595.

(*22*) MOLD, J.D., PEYTON, M.P., MEANS, R.E., WALKER T.B. Determination of catechol in cigarette smoke. Analyst 91: 189-194, March 1966.

(23) MORIE, G.P., SLOAN, C.H. Determination of N-nitrosodimethylamine in the smoke of high-nitrate tobacco cigarettes. Beitraege zur Tabakforschung 7(2): 61-66, June 1973.

(24) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 1. Toward Less Hazardous Cigarettes. The First Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-905, 1976, 148 pp.

(25) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 2. Toward Less Hazardous Cigarettes. The Second Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1111, 1976, 153 pp.

(26) NATIONAL CANCER INSTITUTE, SMOKING AND HEALTH PROGRAM. Report No. 3. Toward Less Hazardous Cigarettes. The Third Set of Experimental Cigarettes. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1280, 1977, 152 pp.

(27) NORMAN, V. The effect of perforated tipping paper on the yield of various smoke components. Beitraege zur Tabakforschung 7(5): 282-287, September 1974.

(28) RATHKAMP, G., HOFFMANN, D. Chemical studies on tobacco smoke. XIII. Inhibition of the pyrosynthesis of several selected smoke constituents. Beitraege zur Tabakforschung 5(6): 302-306, December 1970.

(29) RICKARDS, J.C., OWENS, W.F., JR. Effect of porous cigarette papers on the yield of the major vapor phase and certain particulate phase components of cigarette smoke. Presented at the 20th Tobacco Chemists' Research Conference, Winston-Salem, North Carolina, November 1-3, 1966, p. 25. (Abstract)

(30) SCHMELTZ, I., BRUNNEMANN, K.D., HOFFMANN, D., CORNELL, A. On the chemistry of cigar smoke: Comparisons between experimental little and large cigars. Beitraege zur Tabakforschung 8(6): 367-377, June 1976.

(31) SLOAN, C.H., LEWIS, J.S., MORIE, G.P. Computerization of the gas-phase analysis of cigarette smoke. Tobacco Science 21: 57, 1977.

(32) SPEARS, A.W. Factors affecting smoke delivery of nicotine and carbon monoxide. In: Tobacco and Health Research Institute and the Kentucky Tobacco Research Board; Proceedings of 1975 Symposium—Nicotine and Carbon Monoxide. Lexington, University of Kentucky, November 17, 18, 1975, pp. 12-18.

(33) TIGGELBECK, D. Vapor phase modification—An under-utilized technology. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 507-514.

(34) TSO, T.C., GORI, G.B. A novel approach in tobacco production as a food source and smoke material—year 1976 and year 2000. Proceedings of the Sixth International Tobacco Scientific Congress, Tokyo, Japan, November 14–20, 1976. Tokyo, Coresta and the Japan Tobacco and Salt Corporation, pp. 81-86.

(35) TSO, T.C., GORI, G.B., HOFFMANN, D. Reduction of nicotine and tar in tobacco and in cigarettes through agricultural techniques. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 35-48.

(36) TSO, T.C., HARLEY, N., ALEXANDER, L.T. Source of lead-210 and polonium-210 in tobacco. Science 153(3738): 880-882, August 19, 1966.

(37) TSO, T.C., LOWE, R., DEJONG, D.W. Homogenized leaf curing. I. Theoretical basis and some preliminary results. Beitraege zur Tabakforschung 8(1): 44-51, January 1975.

(38) TSO, T.C., SIMS, J.L., JOHNSON, D.E. Some agronomic factors affecting N-dimethylnitrosamine content in cigarette smoke. Beitraege zur Tabakforschung 8(1): 34-38, January 1975.

(39) WAKEHAM, H. Sales weighted average "tar" and nicotine deliveries of U. S. cigarettes from 1957 to present. In: Wynder, E.L., Hecht, S.S. (Editors). Lung Cancer. UICC Technical Report Series—Volume 25, Geneva, International Union Against Cancer, 1976, pp. 151–152.

(40) WALD, N.J., HOWARD, S., EVANS, J. Smoking tables for carbon monoxide? British Medical Journal 1(6007): 434-435, February 21, 1976.

(41) WEBER, K.H. Recent changes in tobacco products and their acceptance by the consumer. Proceedings of the Sixth International Tobacco Scientific Congress, Tokyo, Japan, November 14–20, 1976. Tokyo, Coresta and the Japan Tobacco and Salt Corporation, pp. 47–63.

(42) WYNDER, E.L., HECHT, S. (Editors). Lung Cancer. UICC Technical Report Series—Volume 25, Geneva, International Union Against Cancer, 1976, p. 138.

(43) WYNDER, E.L., HOFFMANN, D. Experimental tobacco carcinogenesis. Science 162: 862-871, November 22, 1968.

(44) WYNDER, E.L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967, 730 pp.

(45) WYNDER, E.L., STELLMAN, S.D. Comparative epidemiology of tobacco-related cancers. Cancer Research 37: 4608-4622, December 1977.

(46) WYNDER, E.L., WRIGHT, G. A study of tobacco carcinogenesis I. The primary fractions. Cancer 10(2): 255-271, March/April 1957.

Future Considerations

Research as described in the previous sections of this chapter has led to extensive scientific knowledge of the hazardous constituents of tobacco smoke and the association between tobacco usage and disease incidence. Additional research in several areas is warranted, however, to expand and refine this knowledge and to address challenging new problems that have been identified during previous research efforts.

In particular, of the more than 2,000 chemicals that have already been identified in tobacco smoke, relatively little is known about their metabolism and deposition within the human smoker. In addition to the effects of such chemicals individually, their synergistic effects must also be investigated. Furthermore, it is premature to infer that all carcinogens, co-carcinogens, and promotors in tobacco smoke have been identified.

Further research is also required for a better understanding of the role of smoke components and their metabolites on specific organ systems and in order to define more clearly the association between tobacco usage and disease incidence. Related to this type of inquiry is the investigation of how behavioral aspects of tobacco usage (particularly the frequency and depth of inhalation) influence the biochemical and physiological effects of pyrolyzed tobacco products on the human smoker. In conjunction with a better understanding of these issues, insights into the physiological alterations effected by smoke components such as nicotine, flavor additives, and other pyrolysis products may lead to further efforts to identify feasible pharmacologic intervention techniques to facilitate smoking cessation.

Concomitant with developing the kinds of information referred to above is the need for further identification of the precursors of pyrolized smoke components in the tobacco leaf itself. This, in turn, will guide agronomists and processors in controlling the levels of selected precursors in tobacco products. With the addition of selected physical characteristics, such as the type and porosity of wrappers and the materials used for filters, tobacco products can be produced that yield less toxic smoke.

The evidence is overwhelming that tobacco smoke is hazardous to the user; there is no scientific basis for asserting that non-toxic tobacco smoke is feasible. However, the potential for reducing the toxicity of tobacco smoke is indeed feasible, particularly within the research areas discussed above.

15. BIOLOGICAL INFLUENCES ON CIGARETTE SMOKING.

National Institute on Drug Abuse

PART II

THE BEHAVIORAL ASPECTS OF SMOKING

CONTENTS

LIST OF TABLES

Introduction

The present chapter reviews current knowledge concerning the biological, biochemical, and physiological correlates of the smoking habit over the three stages of its development. These are respectively: establishment, maintenance, and cessation of the behavior. While there is overlap in each of these stages, one can conceptually divide the process and evaluate from a biological perspective the metabolism and fate of the major constituents of tobacco, the role of nicotine, dependence liability and tolerance associated with the smoking habit, and its physiological correlates. Recommendations for new research initiatives are included where appropriate throughout the text.

Chemistry and Biochemistry of Tobacco Smoke

Cigarette smoke contains a number of compounds that may act as pharmacological reinforcers and facilitate establishment of the smoking habit. Although it is difficult for a psychopharmacologist to ignore the possibility, indeed the probability or certainty, that the chemical composition of cigarette smoke is of vital importance in explaining smoking behavior, there are behavioral scientists who totally ignore chemistry. They focus instead upon the fact that smoking is initiated by peer pressure, and some have expressed the view that oral and manual satisfaction is all that is necessary to maintain the habit. Although it may be inappropriate to go to the opposite extreme and deny the importance of psychological factors in the establishment of the smoking habit, there is much direct evidence that cigarette smoking necessarily involves tobacco and probably nicotine. Cigarettes made of nontobacco materials such as lettuce or cubebs are not popular. The evidence that nicotine is a vital ingredient is somewhat more circumstantial.

A pack-a-day smoker takes more than 50,000 puffs per year and each puff delivers a rich assortment of chemicals into the lungs and bloodstream. Each puff stamps in the habit a little more and augments the establishment of secondary reinforcers, such as the sight and smell of cigarettes, the lighting procedure, and the milieu and context of a meal with a cup of coffee or a cocktail. It would be surprising if chemical factors were not involved in these pleasurable experiences. It is not surprising that such an overlearned habit surrounded by secondary reinforcers is difficult to extinguish.

The possible candidates for reinforcing pharmacological agents in the establishment of the smoking habit are shown in Tables 1 and 2 (*118*). Although nicotine is the most popular suspect for the reinforcing agent in tobacco, there are other possibilities. Tar and carbon monoxide are the two most likely contenders.

TABLE 1.—Cigarette smoke: gas phase components (μg/cigarette*)

Carbon monoxide	13,400
Carbon dioxide	50,600
Ammonia	80
Hydrogen cyanide (hydrocyanic acid)**	240
Isoprene (2-Me-1,3 butadiene)	582
Acetaldehyde	770
Acrolein (2-propenal)	84
Toluene	108
N-Nitrosodimethylamine	0.08
N-Nitrosomethylethylamine	0.03
Hydrazine	0.03
Nitromethane	0.5
Nitroethane	1.1
Nitrobenzene	25
Acetone	578
Benzene	67

* 85 mm non-filter, blended cigarette (U.S.)
** Gas phase portion only (74 μg/cig. in particulate phase)
SOURCE: Schmeltz, I. (*118*).

TABLE 2.—Cigarette smoke: particulate phase components (μg/cigarette)

TPM* wet	31,500
dry	27,900
FTC**	26,100
Nicotine	1,800
Phenol	86.4
o-Cresol	20.4
m- and *p*-Cresol	49.5
2,4 Dimethylphenol	9.0
p-Ethylphenol	18.2
β-Naphthylamine	0.028
N-Nitrosonornicotine	0.14
Carbazole	1.0
N-Methylcarbazole	0.23
Indole	14
N-Methylindole	0.42
Benz(*a*)anthracene	0.044
Benzo(*a*)pyrene	0.025
Fluorene	0.42
Fluoranthene	0.26
Chrysene	0.04
DDD	1.75
DDT	0.77
4,4′-Dichlorostilbene	1.73

* U.S. cigarette, 85 mm, without filter tip, 1968
** TPM-FTC = TPM-H_2O-nicotine
SOURCE: Schmeltz, I. (*118*).

Carbon Monoxide

After nicotine, the substance in cigarette smoke with the most

pronounced acute pharmacological action is carbon monoxide (CO). Cigarette smoke contains 1 to 5 percent CO, or 10,000 to 50,000 parts per million (ppm). Carbon monoxide impairs the oxygen-carrying capacity of the blood and may impair functioning of the nervous system. It appears to pose a threat, both acutely and chronically, to the functioning of those with cardiovascular disease. Indeed, it is thought by some (*128*) that the carbon monoxide in cigarette smoke is partially responsible for the increased risk of myocardial infarction and stroke in cigarette smokers. The combination of nicotine, with its catecholamine releasing properties, and carbon monoxide in the blood of smokers may enhance cardiovascular risk.

Little evidence exists to support the hypothesis that carbon monoxide is the reinforcing agent in establishing the smoking habit, although it may interact with nicotine. Quite possibly carbon monoxide may deter a few smokers from establishing the smoking habit because it may induce headaches which would deter further smoking. Other forms of tobacco (snuff and chewing tobacco) that have been used through the ages do not produce carbon monoxide.

Tar

Tar, the particulate phase of cigarette smoke, is also of importance in the establishment of the smoking habit. The possibility that tar may be reinforcing is not so easily disproved because the tar and nicotine content of cigarettes tend to co-vary. One study in which the tar and nicotine were dissociated and varied (*38*) showed that the number of cigarettes smoked was related to the nicotine content but not to the tar. There were indications that there may be an interaction between tar and nicotine. For example, nicotine strongly influenced strength ratings in the expected direction, while high tar cigarettes were actually perceived as milder than low tar. The results are consistent with the hypothesis that people smoke to obtain nicotine, but it would be important to extend and confirm these findings with a wider range of tar and nicotine content.

Nicotine

Nicotine has been proposed as the primary incentive in smoking (*63*) and may be instrumental in the establishment of the smoking habit. Whether or not it is the only reinforcing agent, it is still the most powerful pharmacological agent in cigarette smoke. Nicotine is rapidly extracted, enters the pulmonary circulation, is pumped to the aorta where it stimulates the aortic and carotid chemoreceptors, and may produce reflex stimulation of the respiratory and cardiovascular centers in the brain stem.

Within one circulation period, one fourth of the inhaled nicotine passes through the brain capillaries and, since it is highly permeable to the blood brain barrier (*99*), passes promptly into the brain. Once in the

brain, nicotine stimulates nicotine receptors. It also releases various biogenic amines, including the catecholamines and possibly 5-hydroxytryptamine. It may also stimulate some as yet unidentified receptors. It stimulates the emetic chemoreceptor trigger zone in the medulla and, in novices or in large doses, it causes nausea and vomiting. A variety of hypothalamic and pituitary hormones are stimulated by nicotine (*143*). The effects of nicotine on associative centers in the brain are still unexplored but may be of extreme importance in explaining its use and desirability during initiation of the smoking habit. Studies from a number of laboratories indicate that nicotine can have a facilitating effect upon learning and memory in animals (*84*), and possibly in humans (*2*).

The other three-fourths of the inhaled nicotine is delivered to the rest of the body and acts wherever there are nicotinic sites. Thus it stimulates autonomic ganglia with, for example, activation of the gastrointestinal tract. By the same mechanism, it releases epinephrine from the adrenal gland with all the "fight or flight" reactions that this hormone can produce, including mydriasis, tachycardia, vasoconstriction, bronchiolar dilitation, decrease in gastrointestinal motility (though this is generally successfully overcome by nicotinic ganglionic stimulation), and glycogenolysis. It also produces a rise in free fatty acids in the blood, and it can release catecholamines such as norepinephrine from nerve endings and chromaffin cells through the body. These diffuse physiological changes may contribute to increased arousal and thus be important corollaries in the establishment of the smoking habit.

Much of the evidence for the role of nicotine as the primary reinforcer in cigarette smoke is circumstantial. Smokers prefer cigarettes with nicotine than without (*40*), though they will smoke nicotine-free cigarettes.

Cigarettes with a nicotine content of less than 0.3 mg/cig do not do well on the market but recently have been increasing in popularity. Generally, these are smoked by individuals who are trying to cut down or somehow diminish the harmful effects of smoking. Tobacco-free cigarettes are doomed to oblivion almost from the start. Lettuce cigarettes had a brief vogue in the United States, but the two companies producing the two different brands on the market went bankrupt.

It is important to note that low or no-nicotine cigarettes allow their smokers to go through all the motions of smoking. Lighting, handling, and puffing can be the same as with usual cigarettes, so the opportunity for visual, olfactory, and oral gratification is present. It is the rare smoker, however, who continues to smoke cigarettes lacking nicotine for any length of time when the more popular high nicotine cigarettes are available. The most likely explanation for this preference is that nicotine is reinforcing.

Metabolism and Fate of Tobacco in the Body

There is little data relating metabolism and fate of tobacco to the establishment of the smoking habit in adolescence. Differences, however, have been found in the metabolism of tobacco in adult nonsmokers and smokers. Beckett and Triggs (*8*) administered nicotine to smokers and nonsmokers and measured urinary nicotine content. The nicotine content in urine from smokers (55 to 70 percent) was consistently higher than from nonsmokers (25 to 50 percent). It would be useful to do enzyme studies in a large sample of adolescent and preadolescent subjects to determine whether chemical profiles might help predict who will take up smoking and who will not. Also, if there are biological deterrents to smoking, it would be useful to find them.

Predisposing Factors

Genetic

Relatively little is known about biological factors in the initiation of the smoking habit. Many studies that have implicated biological factors in the initiation of smoking behavior attribute the behavior to a genetic predisposition. Initial twin studies by R. A. Fisher (*33*) led him to hypothesize that genotype was a significant variable in smoking behavior. In his survey of twins from Germany and England, he reported that monozygotic twins were more concordant in their smoking behavior than dizygotic twins.

Eysenck (*30*) has measured personality variables and has concluded that smoking behavior is related to the extroversion-introversion dimensions of personality. Eysenck's theory assumes that differences in these dimensions of personality are for the most part determined by hereditary factors. He presents evidence indicating that monozygotic twins are more alike on these dimensions than dizygotic twins, and that cigarette smoking is associated with the extroversion dimension of personality. These data have in part formed the basis for the common genotype hypothesis. This hypothesis states that tobacco smoking and lung cancer (and in the theory of Eysenck, personality factors) are due to a common genetic mechanism (*76*). Subsequent analysis of twin studies have supported (*18, 119*) and denied (*113, 139*) a significant genetic influence on smoking behavior. However, Cederlof, et al. (*19*) recently published an extensive review of the data from the Swedish twin registry and concluded that "the constitutional hypothesis as advanced by Fisher and still supported by a few, has here been tested in twin studies. The results from the Swedish monozygotic twin series speak strongly against this constitutional hypothesis." The Chapter on Mortality in this report contains a more complete discussion of this topic.

In general, studies from which inferences about genetic mechanisms and smoking have been made are subject to many of the pitfalls

associated with survey-type research. Studies of twins are among the most popular means of assessing genetic factors (*14*). Unfortunately, the small number of subjects used in twin studies (particularly monozygotic) has limited the inferences that can be made about genetic mechanisms. An additional confounder not controlled in twin studies is the prenatal environment. The prenatal environment for monozygotic twins is likely to be more similar (i.e., twin positions, common circulatory factors, etc.) than for dizygotic twins (*88*). Further progress in this area will depend on more exhaustive and sophisticated methods of analysis.

Endocrinological

The importance of endocrine factors in the establishment of the smoking habit has not been explored. There is abundant evidence that hormonal changes in puberty occur at about the same time that individuals start smoking. Retrospective studies indicate that teenage smokers are more outgoing, self-confident, and rebellious toward established authority than their nonsmoking counterparts.

The acute endocrine changes associated with cigarette smoking are difficult to interpret because of non-specific stress factors which may accompany smoking. Winternitz and Quillen (*149*) measured ACTH and growth hormone levels in nonsmokers after smoking two cigarettes. There was a rapid increase in the plasma levels of both hormones, but the authors were unable to determine if the effect was due to the tobacco smoke or to the stress created by smoking. The subjects developed nausea, became pale, and started sweating. In chronic smokers a sharp rise in plasma cortisol was observed after two cigarettes and was maintained for several hours. Growth hormone levels peaked at 1 hour and fell back to control levels during the second hour of measurement. No significant changes were found in LH, FSH, TRH, and testosterone levels.

One of the most frequently demonstrated endocrine effects of nicotine is the stimulation of vasopressin release from the supraoptic nucleus (*5, 46, 110*). Robinson and his colleagues have shown in humans that nicotine stimulates the release of a neurophysin associated with vasopressin secretion. A second estrogen-stimulated neurophysin was not affected by nicotine treatment.

In a similar study, Hayward and Pavasuthipaisit (*46*) measured plasma vasopressin levels in adult female monkeys after intravenous infusion of nicotine (100 μg/lkg/min). A significant increase in circulating vaspressin levels was measured that could, in part, be abolished by pre-treatment with promethazine and diphenhydramine. The association between endocrinological responses and smoking is not clear, however. That smoking *causes* such responses has been established, but it would be important to determine whether these responses in turn reinforce further smoking.

Acute Effects of Tobacco and Its Constituents Upon Establishment of Smoking

Central Nervous System

It is clear that tobacco has reinforcing properties that motivate its users to continue smoking even when they are aware of the possible health consequences. Nicotine appears to be the chemical in tobacco that is most likely responsible for these effects (*63*). When the nicotine and tar content are varied independently, it is the nicotine content that is correlated with ratings of strength and satisfaction (*39*). Numerous investigators have shown that nicotine will release norepinephrine from postganglionic sympathetic sites, acetylcholine from postganglionic parasympathetic sites, and epinephrine from the adrenal medulla. However, the primary sites of reinforcement appear to be in the central nervous system. Oldendorf (*99*) has demonstrated that nicotine readily crosses the blood-brain barrier. Stolerman, et al. (*127*) administered mecamylamine, a central nicotine antagonist, to smokers and observed an increase in cigarette consumption. This change was presumably an attempt to overcome the blockade. Further, when the peripheral antagonist, pentolinium, was administered, no change in cigarette consumption was noted. These data are supported by animal studies indicating that rats trained to discriminate nicotine from saline do not generalize the response to similar drugs (*116*). In a related study, Hirschhorn and Rosecrans (*51*) reported that mecamylamine abolished an established nicotine discriminative response.

An important central nervous system effect of nicotine is its ability to modulate arousal levels. The cortical EEG has been used by many investigators as an index of changes in arousal processes (*58, 66, 135*). When smokers are deprived of tobacco for short periods of time, there is an increase in lower-frequency and high-amplitude waveforms in their EEG, thus indicating a possible state of "hypoarousal." Interpretation of these studies has proved difficult because adequate control groups were not employed. It is possible that the process of inhaling in a manner that simulates smoking will elicit the same EEG changes as smoking a cigarette.

The study of Kales, et al. (*66*) in some ways tempers this criticism in that it demonstrated differences in sleep patterns between nondeprived and deprived smoking conditions. During deprivation, smokers spent more time in REM sleep than during nondeprived states. This result could also be due to nonspecific stress.

Research has shown that animals may self-administer nicotine. For example, Pradhan and Bowling (*106*) studied the effects of intraperitoneal administration of nicotine on self-stimulation in rats. The baseline rate of self-stimulation varied as a function of electrode placement, current intensities, and time spent lever-pressing. At high baseline levels of self-stimulation, nicotine enhanced the rate of stimulation.

These data are consistent with other studies that demonstrate that drug effects are largely dependent upon baseline levels of self-stimulation. In a somewhat different approach, Yanagita (*153*) has studied the reinforcing properties of nicotine by demonstrating that monkeys will self-administer nicotine on a regular basis when given the opportunity. An earlier study by Deneau and Inoki (*23*) presented similar results.

There are very few studies in which nicotine alone has been administered to man in an attempt to produce reinforcement (*64, 65, 80*). Johnston injected himself and other volunteers with nicotine and obtained clear evidence of reinforcement. These unique studies were uncontrolled for suggestion, however. There were three studies in which nicotine was given either by ingestion or intravenously, and in all three, it was incapable of completely suppressing smoking, though it usually had some suppressant effect. Indeed, in the experiment by Kumar, et al. (*75*), there was no discernible effect of a rapid intravenous infusion of 1.17 mg of nicotine. Subjects went on puffing their cigarettes just as they did with an equivalent injection of placebo, and there was no delay in latency to the first puff.

The results are disturbing to proponents of the nicotine hypothesis of smoking. It is clear that the intravenous infusions had no effect on the subsequent puffing of cigarettes, whereas the cigarettes smoked immediately preceding the test session had a marked effect both on latency to the first puff and on the rate and volume of puffing. Perhaps the nicotine delivered to the blood and brain were not equivalent in the two conditions. Perhaps the intravenous dose should have been higher; it might have been swamped by the fact that *ad lib* smoking was allowed during the intravenous administration of nicotine. Clearly more research is needed to clarify these results.

If it could be established that central nervous system effects of smoking were reinforcing, it would be important to study these actions in novices.

Cardiovascular System

Before he takes his first cigarette, the novice is not likely to be aware of his cardiovascular system. The first cigarette, however, may have a very profound effect upon the heart and blood vessels of a nonsmoker. The tachycardia may be perceived either as a pleasant or unpleasant sensation. The cardiovascular changes associated with tobacco intake resemble the effects elicited by nicotine alone. Both sympathetic and parasympathetic ganglia are stimulated by low concentrations of nicotine, and nicotine can have sympathomimetic effects by releasing epinephrine and norepinephrine from chromaffin cells in the adrenal medulla, heart, blood vessels, and skin (*139*,. Increases in heart rate (10 to 25 beats per minute), blood pressure (10 to 20 mm Hg systolic, 5 to 15 mm Hg diastolic) and cardiac output (0.5 $l/min/m^2$) typically occur in

both nonsmokers and smokers after smoking one or two cigarettes. In addition, digital blood flow and finger and toe temperature fall (*139, 151*).

The acute cardiovascular responses to tobacco and nicotine have been summarized in the Surgeon General's reports on the health consequences of smoking (*136, 138*). These reports list the following acute changes from smoking: increased (1) heart rate, (2) blood pressure, (3) cardiac output, (4) stroke volume, (5) velocity of contraction of the heart, (6) myocardial contractile force, (7) coronary blood flow, (8) myocardial oxygen consumption, (9) arrhythmia induction, and (10) electrocardiographic changes. These effects are assumed to be due to catecholamine release from the adrenal medulla, chromaffin tissue, or sympathetic nerve endings, and are similar to those obtained by sympathetic stimulation. They are to a considerable extent mediated by sympathetic excitation (*139*). These diverse cardiovascular changes may be a significant component in shifting the arousal continuum toward an optimum level for smokers. However, there are no controlled experiments that definitely rule them in or out as contributors to the reinforcing properties of cigarettes.

Maintenance of the Smoking Habit

The biological factors which can be implicated in the maintenance of smoking have, by no means, been thoroughly investigated. A great deal is known about the *harmful* biological consequences of smoking, but very little about the *beneficial* effects. It is evident that some component or components in tobacco and tobacco smoke must be reinforcing, but these have not been unequivocally identified. As noted earlier, the possible candidates for reinforcing agents can be seen in the two tables (Tables 1 and 2) from Schmeltz and Hoffman (*118*). The leading contender is nicotine because it is clearly a powerful pharmacological substance and is administered in ways consistent with its action as a reinforcer. There are, however, some inconsistencies in the literature. Yanagita (*153*) has reported low levels of nicotine self-administration in monkeys and rats respectively, while Russell, et al. (*111*) report a lack of evidence for self-administration in man, as well as in other animals. The present discussion focuses upon tolerance to tobacco and its constituents, the metabolism and fate of the constituents, and their physiological effects as they relate to the maintenance of the smoking habit.

Tolerance

By definition, tolerance is manifested by a decreasing response to repeated administration of the same dose of a drug, or by the requirement for increasing doses in order to elicit the same response. Martin (*81*), Jaffe and Sharpless (*61*), and others have proposed models

which imply that dependence and tolerance are based upon identical mechanisms. It is difficult to think of an example of a drug to which dependence occurs that does not also involve tolerance. On the other hand, tolerance may occur without dependence (e.g., phenothiazine, antihistamines).

Three kinds of tolerance are apt to occur with tobacco use as with other types of drug use: drug dispositional or metabolic tolerance, tissue or pharmacodynamic tolerance, and behavioral tolerance. The first refers to methods that the body uses to eliminate or to deactivate the drug. For most chemicals derived from tobacco, the liver is the organ most heavily responsible for detoxifying or transforming them into inactive and eliminable forms. The kidney is also important, especially for alkaloids whose water solubility varies with the pH of the solution. The second kind of tolerance refers to changes in the ability of receptors to be activated by the drug at its final site of action. The third type refers to the way in which the subject using the drug changes his behavior to adapt to the effects which the drug repeatedly produces.

Of the compounds contained in tobacco and tobacco smoke (*118*), three are of primary biological importance: tar, carbon monoxide, and nicotine. There is evidence that tolerance can develop to the effects of each of these, although their interaction has scarcely been studied. While there is evidence that tolerance may develop to other components such as acetone and phenol, it is unclear how much they contribute to the pharmacological actions of cigarettes.

Nicotine

Stolerman, et al. (*126*) examined the interaction between pairs of injections of nicotine which varied both in dose and in interval. Two measures of spontaneous locomotor activity of rats in a T-maze were taken: rears and entries. After a single treatment with nicotine, acute tolerance developed as indicated by a shift of the dose-response curve. The dose of nicotine required to produce a given decrement in activity was multiplied by a factor of about 2.4 when a delay of 2 hours was taken between the two injections. When the initial dose was varied, it was found that there was an optimal level for producing tolerance. Higher doses were less effective. An explanation for the relative ineffectiveness of the higher doses in producing tolerance is not available. A general debilitating effect of pretreatment with large doses does not seem to explain it, as rats given a saline challenge exhibited normal motor activity. Perhaps the debilitating effects of a large pretreatment dose and a challenge somehow summate.

Carbon Monoxide

Levels of carbon monoxide achieved in the human body following cigarette smoking increase levels of carboxyhemoglobin. These chronically high levels of carboxyhemoglobin found in smokers can induce polycythemia by increasing hemoglobin levels. These compensatory changes enable the smoker to tolerate increased carbon monoxide levels and to cope with the oxygen deficit produced by cigarettes.

Tar

Tar is defined as the total particulate matter (TPM) collected by a Cambridge filter after subtracting moisture and nicotine. The polycyclic aromatic hydrocarbons are generally blamed for a substantial portion of the carcinogenic activity of tar. They are also powerful enzyme inducers and are undoubtedly responsible for much of the tolerance to themselves and a variety of other compounds produced by smoking. The tar content of cigarette smoke for all brands is determined yearly by the Federal Trade Commission which publishes a listing, along with nicotine content. Tar and nicotine tend to co-vary and thus their effects may be confounded. Obviously, tar is obtained in the smoke from pipes and cigars but not from chewing tobacco and snuff. The latter do not deliver pyrolysis products, such as carbon monoxide, and may thus be somewhat safer. Because the hepatic microsomal enzyme formation is induced by a number of carcinogens in the tar fraction of cigarette smoke, including benzopyrene (*96*), smokers are rendered tolerant to both the therapeutic and toxic effects of a wide variety of drugs (*129*). Even the enzymes in platelets are activated (*53*).

The phenomenon of tolerance to the effects of tobacco products has been clearly demonstrated in both humans and animals. As might be expected, most of the emphasis has focused upon nicotine, but carbon monoxide and tar components also play an important role. As with all other drugs, tolerance varies with subjects and functions. Certain invertebrate forms which feed on the tobacco plant have a high genetically determined tolerance. It is reasonable to assume that even in humans some of the variance in response to tobacco is innately determined and may account for some of the high concordance in smoking behavior seen in identical twins. Other forms of tolerance are clearly the result of experience and develop after exposure to tobacco products. Much more research needs to be done to determine the degree of tolerance which develops in different physiological and psychological functions after tobacco use. For example, it is evident that even in heavy smokers of long duration the heart rate speeds up after each cigarette. On the other hand, nausea and vomiting diminish and disappear with continuing moderate use of cigarettes. It would be very informative indeed to know what changes take place at the

putative sites of action of nicotine with chronic use. Do nicotinic synapses at ganglia change in the same way as nicotinic synapses in the brain? Do carbon monoxide and tar constituents have any action on these components or on enzyme systems elsewhere in the body? Answers to these questions will enable us to understand better the physiological basis of the smoking habit.

Tolerance to the effects of cigarette smoke was noted in dogs given cigarette smoke via tracheostomy (*44*). At the beginning of the study the smoke was aversive, but with the passage of time, animals exhibited tail wagging and improved cooperation. In a careful study, Stolerman, et al. (*127*) showed the development of both acute and chronic tolerance in rats. Nicotine administered intraperitoneally to experimentally naive rats depressed activity in a Y-shaped runway in a dose-related manner. After a single intraperitoneal dose of nicotine, acute tolerance to the depressant action of a second dose developed with a definite time course. This became maximal after 2 hours and wore off after about 8 hours. Repeated intraperitoneal doses of nicotine (three times daily for 8 days) elicited chronic tolerance which persisted for at least 90 days after the end of regular treatment with the drug. Tolerance was also produced when nicotine was administered in rats' drinking water and through reservoirs implanted subcutaneously. It appears, then, that tolerance to nicotine in rats can develop quickly, may be easily measured, and persists for prolonged periods after withdrawal. In these experiments, rapid withdrawal of nicotine did not produce the signs of illness which morphine withdrawal regularly produced. The existence of prolonged tolerance to nicotine in rats suggests that the same phenomenon might exist in man. If tolerance to the unpleasant effects of nicotine, such as nausea, developed more rapidly and persisted longer, it might facilitate relapse to tobacco use.

Metabolism

Nicotine

Tne metabolic fate of 1 mg of nicotine base injected intravenously in humans (actually as nicotine hydrogen tartrate) was intensively investigated by Beckett, et al (*7*). They found that smokers excrete nicotine significantly faster than nonsmokers. None of the smokers reported any nausea from the nicotine injections, but this was reported in varying degrees by all nonsmokers. Haines, et al. (*42*) reported that the plasma concentrations of nicotine were actually higher in smokers than in nonsmokers 1 minute after smoking, but these results were confounded by the fact that nonsmokers were instructed to smoke cigarettes. Obviously smokers were able to inhale more effectively than nonsmokers, in part because they had acquired tolerance to the aversive effects of cigarette smoke on the respiratory passages. Indeed, some of the tolerance that smokers show to cigarette smoke

may be correlated with diminished function of the respiratory epithelium and possible depression of taste and smell (*70*). The proposition that heavy smokers adjust their plasma nicotine levels is compatible with the observation that regular smokers commonly consume about 20 to 30 cigarettes during the smoking day (approximately one every 30 to 40 minutes) and that the biological half life of nicotine in humans is approximately 20 to 30 minutes (*57, 111*). While studies with intravenous nicotine (*80*) show changes in smoking rate apparently due to nicotine concentration in the blood, studies using nicotine gum (*73*) did not show the same effects as intravenous nicotine. It is postulated that the nicotine derived from the gum is absorbed in the intestine and sent to the liver directly via the portal and is there metabolized; therefore less nicotine enters the systemic circulation. Most investigations of smoking rates indicate that much more than plasma nicotine level regulation is involved.

Carbon Moroxide

The metabolism of carbon monoxide involves both the exhalation of the substance from the lungs and a compensatory increased hematocrit to increase oxygen capacity. The former is slowed by the high affinity of carbon monoxide for hemoglobin, and the latter's rate is limited by the process of hematopoiesis. Carboxyhemoglobin has a half life in the body of at least 3 to 4 hours (*137*). It is not known whether the metabolism of carbon monoxide plays a physiological role in the maintenance of the smoking habit.

Tar

Some examples of the effects of induction of microsomal enzymes are cited by Hunter and Chasseaud (*54*). Aryl hydrocarbon hydroxylase is regularly induced by smoking. Benzopyrene hydroxylase and aminozao dye N-methylase were higher in the placentae of pregnant smoking women than in those of nonsmokers. Since tar induces the enzymes of its own metabolism, the smokers might be expected to continue to smoke so as to maintain the levels of tar in the blood, thereby maintaining the action of tar on the metabolism of toxic substances, as discussed above. Metabolism of benzodiazepines, propoxyphene, pentazocine and phenacetin is increased in smokers. Xanthines such as theophylline are also metabolized more quickly in smokers (*105*) and, by inference, so should caffeine be metabolized more quickly. Perhaps this is why heavy smokers drink more coffee than nonsmokers (*9*).

Dependence

Dependence may play an extremely important biological role in the maintenance of the smoking habit (*147*). The characterization of tobacco use as a dependence process raises the issue of tobacco

withdrawal. Thus, the subject of dependence is deferred to the section on cessation of the smoking habit to be discussed in conjunction with the acute effects of cessation and the abstinence syndrome.

Physiological Effects of Tobacco and Its Constituents in the Maintenance of Smoking

Although a great deal has been written in previous editions of the Surgeon General's Report on the untoward effects of smoking, very little has been said about the factors that might be responsible for the establishment and maintenance of the habit. In the past 15 years the public has been exposed to ample warnings about the dangers of smoking; nonetheless the incidence of smoking remains high. Therefore, it is important to consider both the evidence and hypotheses about why smoking is such a tenacious habit. The actions of cigarette smoke and its components upon the central nervous system, cardiovascular system, and endocrine system might give us a clue to the strength and persistence of the habit.

Central Nervous System

In their study of smokers, deprived smokers, and nonsmokers, Knott and Venables (*72*) showed that the deprived smoker is characterized by a "state of cortical hypo-excitation and that tobacco smoking increased cortical excitation to the level of the nonsmoker." Citing the findings that tobacco smoking improves efficiency, prevents deterioration of reaction time (*35*), and improves learning (*1*, *3*, *17*), they suggest "that individuals smoke to achieve this specific psychological state of increased vigilance and attention associated with alpha frequency."

Nelsen, et al. (*95*) studied the effects of nicotine administered (100 μg/kg) subcutaneously to rats. The rats had electrodes placed in the reticular formation which, when stimulated, blocked visual learning tasks. The nicotine attenuated the electrical stimulation and increased learning. The suggestion is made that the nicotine-induced limbic system activation antagonized the behavioral disruption.

In Carruthers' attempt to isolate the "rewarding centers" (*16*), he used a β-blocker, oxprenolol, to decrease epinephrine and norepinephrine associated with anxiety and smoking. The secondary effects of increased heart rate, blood pressure, and free fatty acids were blocked along with the systemic increase in catecholamines, and yet the satisfaction subjectively evaluated was unchanged. His conclusion was that there may be a hypothalamic norepinephrine release leading to pleasure. It is not clear whether the oxprenolol crosses the blood-brain barrier. The more conservative conclusion would be that heart rate, blood pressure, and free fatty acid increases might not be involved in the pleasure associated with smoking.

In addition to the learning studies mentioned above, recent studies add the following data. Stevens (*124*) studied 115 males on four learning tasks. His conclusion was that those who smoked more than 12 cigarettes per day did significantly less well than the nonsmokers and light smokers. Andersson and Hockey (*2*) showed that, in two groups of 24 female students who were habitual smokers, the group in a control, no-smoking condition showed immediate serial recall equivalent to that of the group allowed to smoke one cigarette. The group not smoking did perform better in incidental memory, such as remembering in which corner the words were presented. This suggested that the cigarette increased attentional selectivity during increased arousal. Elgerot (*28*) used three complex and two simple tests to determine differences between a 15-hour abstaining group and the same group after smoking freely. In the nonsmoking condition, they improved on complex tests but were unchanged with respect to simple tests. The interpretation is based on the performance-arousal curve: "According to the Yerkes-Dodson law, the optimal level for arousal is lower for complex than for simpler tests." The conclusion is that the combination of the task and the cigarette led to an arousal level too great for the complex tests. An alternative hypothesis is that the smokers were under-aroused and that the abstainers were anxious enough, but not too anxious. The second explanation would account for the finding, but it is not consistent with other authors. Elgerot (*28*) cites the following effects in habitual smokers: (1) decreased hand-steadiness (*36*), (2) improved simple and choice reaction times (*93*), (3) improved driving tasks demanding sustained performance (*48*), and (4) impaired short-term memory but favorable effects on consolidation (*1*). Some of these changes in arousal levels and functioning capacities may be of benefit to the smoker and may reinforce maintenance of the smoking habit.

Other effects of smoking on the nervous system may be positively reinforcing. Decreased acetylcholine axonal transport and synthesis in neurons (*49*) may lead to decreased GI motility and augment the sympathetic response in calming digestion. Other investigators have shown no basic differences in the basic taste sensations between smokers and nonsmokers (*83*).

Cardiovascular System

The most commonly reported acute changes in the cardiovascular system are the following: increase in plasma catecholamines (*4, 78*), increased heart rate (*4, 5, 78*), increased blood pressure (*4, 5*), vasoconstriction (*43, 94*), and increased carboxyhemoglobin (*4, 98*). It is conceivable that cardiovascular changes are associated with pleasant emotional experiences, although Carruther's (*16*) β-blocking experiment would not support this possibility. Possibly decreased peripheral blood flow (*43*) is a heat-conserving mechanism which may drive

individuals to smoke. The increased viscosity of the blood due to increased hematocrit (*140*) is of unknown benefit on a chronic basis.

Endocrinological System

Although there has been much recent research on endocrine effects of smoking, the role these play in the smoking habit has scarcely been examined. With the development of more refined and more economical techniques for measuring hormones and their actions, we can expect an acceleration of research in this area.

Hayward and Pavasuthipaisit (*46*) administered IV nicotine to monkeys, causing an increase of arginine vasopressin (AVP) without changes in plasma osmolarity. Husain, et al. (*55*) and Robinson (*109*) also demonstrated the release of AVP plus neurophysins in humans.

Cryer, et al. (*22*) demonstrated that growth hormones and cortisol are released by smoking and are unaffected by β-blockers. Both are involved in protein and carbohydrate metabolism. Perhaps their effect on plasma glucose helps reinforce the smoking habit. Similar results were found by others (*100, 141, 149*).

Perhaps a factor involved in maintenance of smoking is the increased lipolysis due to release of catecholamines and glucocorticoids. A common reason given for returning to smoking is weight gain (*150*).

Other endocrinological effects of nicotine include increased gastric HCl secretion (*24, 89*), decreased pancreatic bicarbonates and water secretion secondary to inhibition of secretin (*11, 12, 13, 25*), changes in placental hormones (*21, 122*), alteration in prostaglandin formation (*144*), and delayed LH surge in female rats (*85*). Also, it is known that in smokers there is decreased sperm quality and distribution (*117*). Smokers and nonsmokers do not seem to vary in LH, TSH, T4, and FSH (*149*), however.

Cessation of the Smoking Habit

Early Effects of Cessation

Cessation of smoking is associated with alterations in CNS, cardiovascular, and other physiological functions. Whether these are true "withdrawal" phenomena characterized by a rebound or merely a return to normal levels still remains to be determined. It is evident, however, that significant changes do occur.

A number of physiological changes have been observed on withdrawal from tobacco. Decreases in heart rate and diastolic blood pressure are observed as early as 6 hours after withdrawal (*91*). These changes persist for at least 3 days (*71*), (*146*) and perhaps for 30 (*37*). Decreased excretion of both adrenaline and norepinephrine (*92*) and various metabolic changes have also been observed (*37*).

These metabolic and peripheral effects, which are often associated with decreased arousal, have been supported by EEG studies showing increases in low-frequency activity (*135*) and alterations in cortical alpha frequencies (*72*). Ulett and Itil (*135*) recorded cortical EEG from heavy smokers (one pack of cigarettes per day) in an attempt to detect EEG changes associated with acute withdrawal. Baseline EEG measurements were obtained while the smokers engaged in their normal smoking pattern and were compared with data from the same individuals after they were deprived of tobacco for 24 hours. It was found that there was a significant increase in the low-frequency EEG bands (3-5-7 cycles/sec) during deprivation. This effect was readily reversed after the subjects smoked two cigarettes within a 5-minute period.

In a similar study, Knott and Venables (*72*) did a computer analysis of cortical alpha activity in male nonsmokers, smokers asked to abstain for a 13- to 15-hour period, and smokers who continued their normal pattern of smoking. Analysis of variance of pre-smoking alpha activity indicated the mean alpha frequency of the subjects in the deprived group was significantly lower (9.3 Hz) than in the nonsmoking group (10 Hz) and nondeprived group (9.9 Hz). When the deprived group smoked two cigarettes, the alpha frequency increased to the levels of the nonsmoker and smoker control groups. Thus, there is evidence for a rebound effect and a true withdrawal reaction. The data are interpreted as indicating that deprived smokers are in a state of cortical "hypo-excitation," and that smoking has the effect of increasing excitability to levels comparable to those found in non-smoking and nondeprived groups. Since all groups were equal on measures of extroversion, the authors hypothesize that they have described a true "smoking factor" rather than a difference due to personality. Alternatively, one could conclude from the same data that the results obtained are due to the removal of an arousal-producing drug from a group of people who are ordinarily hypo-aroused.

Numerous other physiological changes have been noted to occur after cessation of smoking. Ejrup (*27*) reports that weight gain is a common sequela to cessation. Although not generally observed, he reported that, in a number of patients, blisters in the mouth occurred along with constipation upon cessation of smoking. If the patients resumed smoking, the blisters disappeared.

Krumholz, et al. (*74*) have measured changes in cardiopulmonary function at rest and during exercise 3 and 6 weeks after cessation of smoking. All subjects had smoked more than one pack of cigarettes a day for at least 5 years. Changes during exercise were measured on the standard bicycle-ergometer test. Following 3 weeks of abstinence, heart rate, oxygen debt, and ratio of oxygen debt to total increase in oxygen uptake during exercise were significantly reduced. In addition, expiratory peak flow and D_L were significantly increased. Pulmonary

compliance increased after 3 weeks and continued to do so at 6 weeks. At 6 weeks, maximum voluntary ventilation and inspiratory reserve volume were increased and functional residual capacity was decreased.

Glauser and colleagues (*37, 38*) studied seven subjects before and 1 month after cessation of smoking. The following measures were found to have changed significantly: (1) body weight increased from a mean of 188 to 195 pounds, (2) body surface area increased from 2.03 to 2.05 m, (3) heart rate decreased from 60 to 57 beats per minute, (4) sugar levels (30 seconds after eating) fell from 137 to 123 mg percent, (5) protein-bound iodine decreased from 5.1 to 4.6 μg percent, (6) serum calcium decreased from 10.2 to 9.7 mg percent, and (7) oxygen consumption decreased from 283 to 260 ml of oxygen/min. The authors concluded that the metabolic change that follows cessation of smoking may be one important variable that causes an increase in weight.

Myrsten, et al. (*93*) have studied chronic smokers who smoked for 5 days, abstained for 5 days, and smoked for 5 additional days. Results from this group were compared with those from a nonabstaining group of smokers. A number of physiological differences were noted during the abstinence period. Adrenaline and noradrenaline excretion levels decreased, skin temperature increased, heart rate decreased, and hand steadiness improved.

Accompanying these objective changes in physiology and performance are subjectively reported changes in physical symptoms, arousal, and mood. These have been reported in studies of smokers sampled while actually undergoing withdrawal (*34, 41, 146*), as well as in retrospective studies of ex-smokers up to 14 years after cessation (*15, 34, 82, 103, 112, 131, 152*). Although the specific symptoms reported in each study differ, as does the percentage of abstinent smokers reporting each symptom, a consistent pattern of symptoms can still be discerned. Common among the physical symptoms reported are nausea, headache, constipation, diarrhea, and increased appetite (*41, 92, 146*). Also reported are disturbances of arousal, including drowsiness and fatigue, as well as insomnia and other sleep disturbances (*92, 152*). Inability to concentrate is a common complaint and is consistent with objective assessments of the concentration of smokers in abstinence (*46*). Thus, the objective changes reviewed above appear to be reflected in the subjective experience and self-reports of deprived smokers.

Long Term Effects of Cessation

Once a smoker gets past the initial 3- to 14-day withdrawal effects (*45, 59, 120*), what biological factors tend to encourage the now ex-smoker to continue abstinence? The factors opposing most ex-smokers' attempts to refrain seem to win out, since relapse is so frequent. In all cessation methods described, about two-thirds are able to attain some degree of abstinence for a short duration, but about half of these return to smoking in 1 to 2 years (*20, 68*). Is it the methodology of

cessation or the post-cessation factors which determine continuation of abstinence? Kasl (*69*) claims "there is evidence that smokers who stop spontaneously have a lower rate of relapse than those who seek help and participate in some sort of program." The effects of cessation on the central nervous system, cardiovascular system, and endocrine system which might encourage continued abstinence will be discussed along with some of the psychobehavioral components.

Cardiovascular System

When a smoker terminates his intake of tobacco, he reduces his risk in a number of cardiovascular diseases: coronary heart disease (*29, 50, 67, 123*), cerebrovascular accidents (*50*), recurrence of myocardial infarction (*29*), sudden death from CHD (*67, 123*), myocardial infarction (*123*), and complications of atherosclerosis (*101*). These reduced risks are measurable on populations, but what cardiovascular benefits of cessation exist to individuals? One report says that the subendothelial edema of small arterioles and vasa vasorum is secondary to the carbon monoxide of cigarettes and that this, including coronary arteries (*5*), tends to return to normal after 5 to 10 years of cessation. This might reinforce cessation, especially in ex-smokers with angina pectoris or other ischemic heart disease. Janzon (*62*), using venous occlusion plethysmography on the calf, found that after 8 to 9 weeks of cessation peripheral blood flow increased measurably, whereas the control group of continuing smokers actually decreased their peripheral blood flow. It is likely that this improvement of circulation would be accompanied by a sense of well-being and reinforce abstinence as time progressed. The decrease in heart rate and blood pressure (*52*), along with decreased catecholamines, may be a factor in continuing abstinence. Related to the cardiovascular benefits of cessation, it was found that peak-expiratory flow rates of 57 liters/min resulted (*90*), an increase which would be positively reinforcing, especially in active ex-smokers.

Endocrinological System

If the metabolic rate declines (*52*), the major effect would be increased weight, as has been noted by many (*34, 37, 82, 148*). This would tend to reinforce smoking in most people. But there may be some unseen benefit of decreased metabolism in those who are either able to maintain their weight or who are not self-conscious of weight gain.

In Pearson's study of theophylline metabolism (*102*), he found that smokers' half-life of theophylline was 4.2 hours while nonsmokers' was 7.1. Upon cessation, the normalization (toward 7.1) took 3 months to 2 years, implying that there may be induced enzymes in the smoker which do not readily normalize. This may be indicative of other metabolite-clearing processes and, because the normalization effect is gradual, may keep the ex-smoker in a "smoking" state so that he does

not "miss" this aspect of smoking. Is it possible that this kind of normalization is responsible for so many returning to smoking after 1 to 2 years (*20, 68*)? Another possible influence may be in sex hormonal levels. After 3 months there is improved quality of sperm motility and density as well as fertility (*117*).

Other Effects

Pederson and Lefcoe (*103*) used the Jackson Personality Inventory and a modification of the Reid-Ware Internal-External Control Scale and found no difference between smokers and successful ex-smokers. They point out that ex-smokers have usually tried to stop at least once and failed, have stopped for health reasons, have experienced cravings and discomfort, and have used substitutes. The fact that spontaneous quitters are more successful than those who get help (*69*) implies that they are either more strong-willed and independent, primed to give up the habit because of other negative factors, or less dependent upon cigarettes. West's description (*145*) of ex-smokers is that they are more likely to be male, older, have smoked less before cessation, started smoking at a later age, have a milieu that is supportive of their stopping, and have fewer indices of neurosis and few psychosomatic symptoms. Lebowitz and Burrows (*77*) discuss the finding that ex-smokers have higher incidence of diagnosed disease and less incidence of symptoms when compared to smokers, suggesting that when it "becomes official" that smoking caused an illness, the smoker will quit more readily than if his symptoms are unattached to etiology or specific pathology.

Another possible effect of cessation may be decreased "chest pain" in those having gastroesophageal reflex, as discussed by Bennett (*10*).

By far the the most common, and clinically the most important, symptom to appear following withdrawal from tobacco is craving for tobacco. The best estimates indicate that 90 percent of all smokers in withdrawal will verbalize their need for cigarettes (*41*). Moreover, among smokers who have been abstinent for 5 to 9 years, one out of five report that they continue to have at least an occasional craving for tobacco (*34*). The importance of craving lies not in its universality or persistence, but in its relation to the clinical goal of modifying smoking behavior. Indeed, the importance of the tobacco withdrawal syndrome in its entirety is based on its provocative role in causing relapse among abstinent smokers.

Dependence

As stated earlier, characterizing tobacco use as a dependence process necessarily raises the issue of tobacco withdrawal. Some authorities believe an abstinence syndrome is crucial to the definition of drug dependence. Indeed, some of the initial reluctance to label tobacco as a

dependence-producing substance rested on doubts concerning the existence of a tobacco withdrawal syndrome. This was the position taken by the Surgeon General in 1964, when first alerting the country to the dangers of tobacco. Since then, there has been an accumulation of studies which suggest that withdrawal from tobacco does produce a variety of signs and symptoms which can be characterized as a *tobacco withdrawal syndrome*. Although the syndrome is variable and is only roughly described and understood, its existence is no longer a matter of great controversy. It is characteristic of withdrawal syndromes that their severity is dose-dependent (*60*). Therefore, it is expected that heavy smokers would report more severe withdrawal symptoms than light smokers.

The inconsistency of the effect of deprivation is reflected in the literature. Studies by Myrsten, et al. (*92*) and Mausner (*83*) report no differences in this regard between light and heavy smokers. In contrast, Burns (*15*) reports that subjects who suffered withdrawal symptoms had smoked an average of 6.9 cigarettes/day more than asymptomatic subjects ($p<.01$). Wynder, et al. (*152*) report that the proportion of abstinent smokers reporting more than one withdrawal symptom increases with baseline consumption.

Another possible confounding factor is that, because smokers can vary their smoking consumption in other ways—depth of inhalation, number of puffs, etc.—cigarette consumption may actually be a very poor measure of dose. Also, differences in nicotine metabolism introduce variability in dose even among those who consume similar amounts of nicotine. Thus, estimating a smoker's dose may require measuring serum levels of nicotine or its metabolites. In the one study which has approached this problem, Zeidenberg, et al. (*154*) found among men a higher and significant correlation between serum cotinine levels before treatment and self-reported "degree of difficulty" in smoking cessation. There is some indication that the severity of the abstinence syndrome is dose-dependent, but much ambiguity remains. Because dose dependency is so characteristic of withdrawal syndromes from other substances, establishing this effect for tobacco would be an important step toward an understanding of tobacco dependency. Further research into the relationship should probably proceed along the lines followed by Zeidenberg, et al., using serum cotinine levels rather than cigarette consumption as the independent variable. Dependent measures should include more refined instruments than Zeidenberg and his coworkers' estimates of "difficulty" and should explore both the number of withdrawal symptoms and their severity.

Two studies have focused upon the diurnal variations in withdrawal symptoms (*79, 87*). Data from a study by Meade and Wald (*87*) show that craving in abstinent smokers and in "ad lib" smoking have the same diurnal pattern; that is, the lowest peak occurs when the subject

wakes up, gradually rising to a peak in the evening, then falling again at bedtime. Thus, there is a consistent function which describes three different stages of the habit and its control (unrestricted smoking, abstinence, and relapse). The meaning of the underlying function has not been determined. Two different types of explanation are plausible. One focuses on diurnal variation in the internal environment of the smoker, suggesting the influence of some metabolic factor with diurnal variation. The other explanation focuses on the diurnal variation in the social environment, e.g., the timing of work, meals, social contact, recreation, and so on, which affects craving for tobacco. Research which accurately measures craving and relates it to environmental stimulus events and circadian variations in the internal environment could help to decide between these explanations. A more comprehensive understanding of how craving varies with stimulus events and with time of day might prove helpful in designing interventions which help prepare smokers to cope with their craving.

Time Course and Duration

While the time course of the abstinence syndrome following abrupt withdrawal from other dependence-producing substances has been systematically studied (*60*), assessment of the course of the tobacco withdrawal syndrome is made difficult by the subtlety and variability of the symptoms (*139*).

The onset of the syndrome appears to be rapid. Changes in mood (*115*) and performance (*93*) are evident. Early effects are not easily distinguishable from the absence of nicotine effects or the effects of simple frustration. Another study reports data suggesting a decrease in symptoms over time (*41*).

After a marked decline in the first week, the tobacco withdrawal syndrome becomes increasingly less yielding. Estimates of the tobacco withdrawal syndrome's duration have been made in retrospective studies which ask ex-smokers to recall how long their discomfort or "difficulty" lasted. However, these studies produce contradictory findings. Burns (*15*) reports a range from 1 to 12 weeks, and Wynder, et al. (*152*) report that most symptoms were gone after 4 weeks. In contrast, Mausner (*83*) reports that, of the ex-smokers who ventured an estimate, fully two-thirds stated that their difficulty had lasted between 1 month and 5 years. In another retrospective study, 21 percent of the sample of ex-smokers reported at least intermittent craving for cigarettes 5 to 9 years after cessation (*34*). Thus, the duration of the tobacco withdrawal syndrome appears to be extremely variable, and no definitive estimate is yet available.

Degree of Deprivation

Even with continued use, reduction in the dose of a dependence-producing substance typically results in the emergence of a withdrawal syndrome (*60*). It has been shown that smokers who changed to low-nicotine cigarettes often report the gamut of acute withdrawal symptoms described above (*32, 114*). Abrupt and total withdrawal from tobacco, however, is associated with a withdrawal syndrome that subsides more quickly and is no worse than that seen in partial abstinence.

Gradual Reduction and Chronic Withdrawal

Despite the usefulness of gradual withdrawal in other dependency disorders, and despite the congruence of this method with sound behavioral principles, there is considerable evidence suggesting that gradual withdrawal from tobacco is associated with treatment failure (*26, 41, 82, 138*). This discrepancy may be explained by the observation that partial abstinence from smoking leads to *more*, rather than less, discomfort in withdrawal. The result is that a partially abstinent smoker is in a chronic state of withdrawal. Typically, this chronic state of withdrawal leads to relapse and a return to baseline rates of smoking (*26*).

Although this explanation is plausible and fits the data available, it must be treated with caution pending further research. Since all of the research relies on smokers who have chosen whether to quit "cold turkey" or by gradual reduction, there is still the possibility that smokers in some way predisposed to experience a protracted withdrawal syndrome disproportionately choose the gradual reduction method. What is needed is experimental research in which smokers are randomly assigned to "cold turkey" or gradual reduction groups and in which the effects on the course of the abstinence syndrome are evaluated.

Another direction for new research might be to determine the threshold for the onset of the abstinence syndrome in gradual reduction. Perhaps there is some rate or degree of reduction which would not precipitate withdrawal, so that a smoker *could* be weaned from tobacco. In addition to a "rate of reduction" parameter, the onset of severe withdrawal may also be controlled by the absolute dose as well. The relationship between degree of tobacco deprivation and the emergence of withdrawal symptoms deserves further study.

Other Factors Possibly Affecting the Abstinence Syndrome

In addition to the factors already cited, the tobacco withdrawal syndrome may be affected by a number of other variables whose influence remains to be determined. One could speculate, for example, about differences between types of smokers in the severity, pattern,

and course of abstinence. A study by Ikard and Tomkins (*56*) suggests that "addictive smokers" experience more severe craving. The smokers in this study were deprived of tobacco only for three hours, however, so that the effects of this typology on the clinical abstinence syndrome are still essentially unknown and deserving of study. Other individual difference variables also deserve study. For example, smoking history, especially such variables as previous attempts to quit and the reason for failure, may affect the withdrawal syndrome. Since the symptoms of withdrawal are relatively ill-defined, the smoker's expectations and set are probably related to his experience of abstinence, as is his motivation to quit (*6*).

Another major factor whose relationship is potentially important, but unexpected, is sex. There is fragmentary evidence suggesting that the abstinence syndrome is more severe in women than in men. Unfortunately, relevant data are too seldom analyzed for this sex difference. For example, Guilford (*41*) reports data separately by sex, but does not submit it to statistical analysis of the sex difference. Yet, of 18 major symptoms reported by her subjects in the first 4 days of abstinence, 15 show some sex difference. Among these 15 symptoms, 13 are more frequently reported by women. The difference is statistically significant (sign test, $N = 15$, $r \leq 2$, $p < .005$). Data reported in a number of other studies line up in the same direction, though the effect fails to reach significance in the individual studies (*104*, *131*, *152*).

It seems likely, then, that women report more abstinence symptoms than men. The importance of this finding lies in its possible relation to another sex difference in smoking cessation: it is well established that women are more likely to fail in smoking cessation efforts. Guilford (*41*), for example, has presented data suggesting that the relationship between withdrawal symptoms and failure in smoking cessation is stronger for women than for men. Thus, women experience more discomfort in withdrawal and are more affected by it in their attempts to quit smoking. It seems likely that this is at least partly responsible for their lower rates of successful cessation.

Nor are organismic variables the only variables relevant here. The method used to achieve cessation may well have an effect on the subsequent withdrawal syndrome. Environmental factors, such as the smoker's social environment, are potentially powerful determinants of the smoker's experience of withdrawal. These and other events, such as social drinking, may produce conditioned craving and are to be considered high risk situations for relapse (*79*). Thus, in addition to the few factors whose influence on the tobacco withdrawal syndrome is known, there are many other potentially important variables whose effects remain to be determined.

Techniques for Measuring Tobacco Usage

The question of how to measure the use of cigarettes is an important one when evaluating the various methods of cessation and the benefits of cessation versus the risks of continuance, and when determining the validity of the reports of study subjects' compliance. (It may also be important in "quantifying" risk factors for disease in current smokers, such as type of cigarette, inhaling pattern, and so forth.) There are five potential sources of information to determine whether or not a person has smoked: urine, blood, breath, saliva, and verbal.

Urine

In the urine, one can assay for the constituents of the cigarette smoke itself or for excretion products that are associated with the physiological effects. Using the Goldbaun and Womanski method, Prado and associates (*107*) measured nicotine excretion in smokers averaging 20 cigarettes/day and found nicotine in the urine in concentrations varying directly with number of cigarettes and inversely with pH of the urine. When deprived of cigarettes for 12 hours, there was no nicotine found in the urine. Trojnar (*133*) compared the urine quantities of adrenaline, norepinephrine, vanilinomandelic acid (a derivative of epinephrine and norepinephrine via monoamine oxidase and catecholamine-o-methyl transferase), and 5-hydrosyindolacetic acid in nonsmokers and those who had quit for at least 6 months. The nonsmokers' and quitters' levels were indistinguishable until the ex-smokers smoked an average of 14 cigarettes. Urine metabolite levels, with the exception of norepinephrine, rose when measured on the second day, (EPI 2.04 g/day, VMA 1.31 g/day, SHIAA 2.4 g/day). In a second study, Trojnar (*132*) found that all four values were increased in smokers over nonsmokers without any discontinuance.

A potential problem in measuring the physiological metabolites associated with smoking is in false positives. This can occur when a subject may have experienced severe anxiety, with increased catecholamines, but did not smoke. The urine nicotine level would seem to be more specific, but both methods would have to be used every 12 hours or less to be accurate.

Blood

One constituent found in blood is carbon monoxide, combined to form carboxyhemoglobin (COHb). Sillett, et al. (*121*) describe the simplicity of using the I.L. 182 CO-Oximeter and the potential for giving subjects quick feedback on their performance. They also say it is possible to detect when those who switch from cigarettes to cigars continue to inhale. Turner (*134*) points out that the average nonsmoker's blood in London has 1.3 percent COHb and that 2 percent is used as a suggestion that smoking has resumed. As cities vary in CO in the air,

standards would have to be set depending on locale. When Ohlin, et al. (*97*) confronted 32 patients at an antismoking clinic with their elevated COHb levels, 13 immediately changed their report, admitting recidivism. When considering COHb, one must take environmental and occupation sources of CO into account. Although COHb increases proportionally with number of cigarettes (*125*) and varies with nicotine content (*111*), discretion is necessary in using data.

Serum cotinine levels may be a reliable tool in determining cessation, according to Zeidenberg, et al. (*154*). With a half-life of 30 hours, as opposed to nicotine's 30 minutes, and the relative constancy of the cotinine levels in regular smokers, it is possible in this way to evaluate long-range abstinence.

Breath

The determination of mean alveolar CO partial pressure described by Rawbone, et al. (*108*) makes it possible to determine the carboxyhemoglobin levels of the blood with a correlation of $r = .96$. Also, by subtracting expired CO from inspired, it is possible to determine if a smoker is an inhaler. Vogt, et al. (*142*) used expired CO and serum thiocyanate to assess exposure to cigarettes. Smokers had higher levels of both (CO 8 ppm, SCN-100 μmol/l)—three times greater in those smoking more than a pack a day than in nonsmokers. The correlation between smoking and each variable separately was less than the two combined (CO = .476; SCN = .479; both = .571). The researchers were 99 percent accurate in separating "typical" smoking habits from nonsmokers' habits and hypothesized the possibility of grading intermediate levels for exposure to smoke. No mention was made of environmental or occupational sources of CO or CN.

Saliva

The presence of nicotine in saliva can be determined by gas chromatography and an alkali flame ionization detector (i.e., nitrogen detector) (*31*), but it is difficult to distinguish a pattern of smoking. Nonsmokers separated from smokers can be distinguished from nonsmokers who smoke passively. While this is a sensitive method of measurement, the presence of nicotine in saliva does not prove direct use of tobacco. Using this method, it may be possible to determine a maximal level attainable by passive smoking and use that value as a cut-off in determining probable usage.

Tenovuo and Maekinen (*130*) measured thiocyanate and ionizable iodine in saliva with the following results:

	Thiocyanate (mg/liter)	
	Males	Females
Smokers	210±75	124±46

Nonsmokers	91±44	62±32

	Ionizable Iodine	
	Males	Females
Smokers	7.2±.9	10.1±3.6
Nonsmokers	13.4±9.7	13.9±8.0

Although controls using the same subjects, both smoking and abstaining, were not employed, this technique can adequately separate the values of smokers' and nonsmokers' thiocyanate, especially for males. It should be noted, however, that the overlap between smokers and nonsmokers is considerable and that Vogt found no correlation between the tar content of cigarettes and the thiocyanate levels in saliva.

Verbal

Although there are several biological assays measuring use of cigarettes, McMahan, et al. (*86*) propose using the verbal report of the subject, confirmed by an appropriate associate of the subject. They point out that the correlation between reports of the subject and the associate about the subject's smoking behavior is $r = .86$. While the correlation indicating that the subject and associate agree is encouraging, that may be all this study says. A smoker who does not want the researcher to know his smoking habit accurately will probably either not allow the associate to see him in his true habit or will encourage the associate to "interpret" his smoking pattern along the lines he wishes to portray. Other methods may be used, such as a lie detector, but unfortunately they are beatable.

The only "fool-proof" method of determining use is to observe the subject at all times. Even here the degree of inhalation cannot be accurately determined. Since this approach is highly impractical, biological tests must be employed, and understanding of the potential source of inaccuracy must be considered before drawing firm conclusions. Based on the above descriptions, it would seem that the most practical method would be measurement of nicotine, cotinine, and thiocyanate in the urine. If none of these is found in the urine, the conclusion is that the subject has not smoked (or has borrowed urine). If some nicotine is found in the urine, could it have been from passive smoking? One should note, too, that quantitative analysis of nicotine in body fluids will take on increasing significance, since tar and nicotine levels are being decreased in cigarettes, and researchers will need to know not only whether a subject smoked, but how much.

Biological Influences on Cigarette Smoking: References

(1) ANDERSSON, K. Effects of cigarette smoking on learning and retention. Psychopharmacologia 41(1): 1-5, 1975.

(2) ANDERSSON, K., HOCKEY, G.R.J. Effects of cigarette smoking on incidental memory. Psychopharmacologia 52(3): 223-226, 1977.

(3) ANDERSSON, K., POST, B. Effects of cigarette smoking on verbal rote learning and physiological arousal. Scandinavian Journal of Psychology 15: 263-267, 1974.

(4) ANSCHUETZ, F. Rauchen und periphere arterielle verschlusskrankheit (Smoking and peripheral arterial occlusive disease). Fortschritte der Medizin 93(10): 504-507, April 3, 1975.

(5) BAILEY, W.M. Cigarette smoking and premature cardiovascular disease. Journal of the Medical Association of Georgia 64(10): 397-398, October 1975.

(6) BAREFOOT, J.C., GIRODO, M. The misattribution of smoking cessation symptoms. Canadian Journal of Behavioral Science/Revue Canadienne de Sciences du Comportement 4(4): 358-363, 1972.

(7) BECKETT, A.H., GORROD, J.W., JENNER, P. The effect of smoking on nicotine metabolism *in vivo* in man. Journal of Pharmacy and Pharmacology 23 (Supplement): 62S-67S, December 1971.

(8) BECKETT, A.H., TRIGGS, E.J. Enzyme induction in man caused by smoking. Nature 216: 587, November 11, 1967.

(9) BENNETT, A.E., DOLL, R., HOWELL, R.W. Sugar consumption and cigarette smoking. Lancet 1(7655): 1011-1014, May 16, 1970.

(10) BENNETT, J.R. Cigarette smoking and chest pain. British Medical Journal 1(6001): 97, January 10, 1976. (Letter)

(11) BODEN, G., SHORE, L.S., ESSA-KOUMAR, N., LANDOR, J.H. Effect of nicotine on serum secretin and exocrine pancreatic secretion. American Journal of Digestive Diseases 21(11): 974-977, November 1976.

(12) BRANDBORG, L.L. Peptic ulcer disease. Primary Care 2(1): 109-119, March 1975.

(13) BROWN, P. The influence of smoking on pancreatic function in man. Medical Journal of Australia 2(8): 290, 292-293, August 21, 1976.

(14) BURCH, P.R.J. Coronary heart disease. Tests of etiological hypotheses. American Heart Journal 93(6): 805-806, June 1977.

(15) BURNS, B.H. Chronic chest disease, personality, and success in stopping cigarette smoking. British Journal of Preventive and Social Medicine 23(1): 23-27, February 1969.

(16) CARRUTHERS, M. Worrying about anxiety. Scottish Medical Journal 20(6): 289-290, November 1975.

(17) CARTER, G.L. Effects of cigarette smoking on learning. Perceptual and Motor Skills 39: 1344-1346, 1974.

(18) CEDERLOF, R., FLODERUS, B., FRIBERG, L. Cancer in MZ and DZ twins. Acta Geneticae Medicae et Gemellologiae 19(1-2): 69-74, January-April 1970.

(19) CEDERLOF, R., FRIBERG, L., LUNDMAN, T. The interactions of smoking, environment, and heredity and their implications for disease etiology. A report of epidemiological studies on the Swedish twin registries. Acta Medica Scandinavica Supplement 612: 7-128, September 1977.

(20) CHANGING TIMES. Those quit-smoking groups and how they work. Changing Times 31(2): 13-15, February 1977.

(21) CONNEY, A.H., JACOBSON, M.M., LEVIN, W. Effects of drugs on the metabolism of bilirubin and other normal body constituents. In: Bergsma, D., Blondheim, S.H. (Editors). Bilirubin Metabolism in the Newborn (II). The Second International Symposium, Maaleh Hahamishah (Jerusalem), April 1-5, 1974. Birth Defects: Original Article Series, Volume 12, No. 2, 1976, pp. 275-292.

(22) CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. New England Journal of Medicine 295(11): 573-577, September 9, 1976.

(23) DENEAU, G.A., INOKI, R. Nicotine self-administration in monkeys. Annals of the New York Academy of Sciences 142(1): 277-279, 1967.

(24) DINNO, M.A., ANDO, M., DINNO, F.H., HUANG, K.C., REHM, W.S. Effect of nicotine on gastric acid secretion: Evidence of electrogenic pump theory. American Journal of Physiology 232(3): E251-E257, March 1977.

(25) DZIENISZEWSKI, J. Fizjopatologia Zewnetrznego Wydzielania Trzustki (The physiopathology of the external pancreatic secretion). Przeglad Lekarski 33(2): 280-289, 1976.

(26) EISINGER, R.A. Nicotine and addiction to cigarettes. British Journal of Addiction 66: 150-156, 1971.

(27) EJRUP, B. The role of nicotine in smoking pleasure, nicotinism, treatment. In: von Euler, U.S. (Editor). Tobacco Alkaloids and Related Compounds. Proceedings of the Fourth International Symposium held at the Wenner-Gren Center, Stockholm, February 1964. Oxford, Pergamon Press, 1965, pp. 333-346.

(28) ELGEROT, A. Note on selective effects of short-term tobacco-abstinence on complex versus simple mental tasks. Perceptual and Motor Skills 42(2): 413-414, April 1976.

(29) ELMFELDT, D., TIBBLIN, G., VEDIN, A. WILHELMSEN, L., WILHELMSSON, C. Roekning och Hjaertinfarkt (Smoking and myocardial infarction). Laekartidningen 72(50): 4981-4984, 1975.

(30) EYSENCK, H.J. Personality and the maintenance of the smoking habit. In: Dunn, W. L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V. H. Winston and Sons, 1973, pp. 113-146.

(31) FEYERABEND, C., RUSSELL, M.A.H. Measurement of plasma nicotine by gas chromatography. Industrial and Scientific Synopsis Feature Service, Synopsis No. 468, June 1976, 17 pp.

(32) FINNEGAN, J.K., LARSON, P.S., HAAG, H.B. The role of nicotine in the cigarette habit. Science 102(2639): 94-96, July 27, 1945.

(33) FISHER, R.A. Cancer and smoking. Nature (London) 182: 596, August 30, 1958. (Letter)

(34) FLETCHER, C., DOLL, R. A survey of doctors' attitudes to smoking. British Journal of Preventive and Social Medicine 23(3): 145-153, August 1969.

(35) FRANKENHAEUSER, M., MYRSTEN, A.-L., POST, B., JOHANSSON, G. Behavioural and physiological effects of cigarette smoking in a monotonous situation. Psychopharmacologia 22(1): 1-7, 1971.

(36) FRANKENHAEUSER, M., MYRSTEN, A.-L., WASZAK, M., NERI, A., POST, B. Dosage and time effects of cigarette smoking. Psychopharmacologia 13: 311-319, 1968.

(37) GLAUSER, S.C., GLAUSER, E.M., REIDENBERG, M.M., RUSY, B.F., TALLARIDA, R.J. Metabolic changes associated with the cessation of cigarette smoking. Archives of Environmental Health 20(3): 377-381, March 1970.

(38) GLAUSER, S.C., GLAUSER, E.M., REIDENBERG, M.M., RUSY, B.F., TALLARIDA, R.J. Metabolic effect in man of the cessation of smoking. Pharmacologist 11(2): 283, 1969. (Abstract)

(39) GOLDFARB, T., GRITZ, E.R., JARVIK, M.E., STOLERMAN, I.P. Reactions to cigarettes as a function of nicotine and "tar". Clinical Pharmacology and Therapeutics 19(6): 767-772, June 1976.

(40) GOLDFARB, T.L., JARVIK, M.E., GLICK, S.D. Cigarette nicotine content as a determinant of human smoking behavior. Psychopharmacologia 17(1): 89-93, 1970.

(41) GUILFORD, J.S. Factors Related to Successful Abstinence from Smoking. Pittsburgh, American Institutes for Research, July 1966, 171 pp.

(42) HAINES, C.F., JR., MAHAJAN, D.K., MILJKOVIC, D., MILJKOVIC, M., VESELL, E.S. Radioimmunoassay of plasma nicotine in habituated and naive smokers. Clinical Pharmacology and Therapeutics 16(6): 1083-1089, December 1974.

(43) HALAWA, B., MAZUREK, W. Zachowanie sie przeplywu krwi przez tkanki obwodowe w czasie palenia papierosow (Blood flow in peripheral tissues during cigarette smoking). Polski Tygodnik Lekarski 30(52): 2165-2167, December 29, 1975.

(44) HAMMOND, E.C., AUERBACH, O., KIRMAN, D., GARFINKEL, L. Effects of cigarette smoking on dogs. I. Design of experiment, mortality, and findings in lung parenchyma. Archives of Environmental Health 21:740-753, December 1970.

(45) HARTELIUS, J., TIBBLING, L. Nicotine dependence and smoking cessation programs: A review. World Smoking and Health 2(1): 4-10, Summer 1977.

(46) HAYWARD, J.N., PAVASUTHIPAISIT, K. Vasopressin released by nicotine in the monkey. Neuroendocrinology 21(2): 120-129, 1976.

(47) HEIMSTRA, N.W. The effects of smoking on mood change. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 197-207.

(48) HEIMSTRA, N.W., BANCROFT, N.R., DEKOCK, A.R. Effects of smoking upon sustained performance in simulated driving task. Annals of the New York Academy of Sciences 142(1): 295-307, March 15, 1967.

(49) HEIWALL, P.-O., DAHLSTROM, A., LARSSON, P.-A. The effect of nicotine on intra-axonal transport in cholinergic motor neurons of the rat; influence of acutely administered, non-toxic doses. Acta Physiologica Scandinavica 97(3): 304-309, July 1976.

(50) HINMAN, A.R. Disease prevention in clinical practice. New York State Journal of Medicine 76(1): 50-53, January 1976.

(51) HIRSCHHORN, I.D., ROSECRANS, J.A. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine. Psychopharmacologia 40(2): 109-121, 1974.

(52) HJERMANN, I., HELGELAND, A., HOLME, I., LUND-LARSEN, P.G., LEREN, P. The intercorrelation of serum cholesterol, cigarette smoking, and body weight: The Oslo study. Acta Medica Scandinavica 200(6): 479-485, 1976.

(53) HORNS, D.J., GERRARD, J.M., RAO, G.H.R., KRIVIT, W., WHITE, J.G. Smoking and platelet labile aggregation stimulating substance (LASS) synthesizing activity. Thrombosis Research 9(6): 661-668, December 1976.

(54) HUNTER, J., CHASSEAUD, L.F. Clinical aspects of microsomal enzyme induction. In: Bridges, J.W., Chasseaud, L.F. (Editors). Progress in Drug Metabolism, Volume 1. New York, John Wiley and Sons, 1976, pp. 129-191.

(55) HUSAIN, M.K., FRANTZ, A.G., CIAROCHI, F., ROBINSON, A.G. Nicotine-stimulated release of neurophysin and vasopressin in humans. Journal of Clinical Endocrinology and Metabolism 41(6): 1113-1117, December 1975.

(56) IKARD, F.F., TOMKINS, S. The experience of affect as a determinant of smoking behavior: A series of validity studies. Journal of Abnormal Psychology 81(2): 172-181, April 1973.

(57) ISAAC, P.F., RAND, M.J. Cigarette smoking and plasma levels of nicotine. Nature (London) 236: 308-310, April 7, 1972.

(58) ITIL, T.M., ULETT, G.A., HSU, W., KLINGENBERG, H., ULETT, J.A. The effects of smoking withdrawal on quantitatively analyzed EEG. Clinical Electroencephalography 2(1): 44-51, 1971.

(59) JAFFE, J.H. Cigarette smoking as an addiction. American Lung Association Bulletin 62(5): 10-12, May 1976.

(60) JAFFE, J.H. Drug addiction and drug abuse. In: Goodman, L.S., Gilman, A. (Editors). The Pharmacological Basis of Therapeutics. Fourth Edition. New York, Macmillan, 1971, pp. 276-313.

(61) JAFFE, J.H., SHARPLESS, S.K. Pharmacological denervation supersensitivity in the central nervous system: A theory of physical dependence. In: Wikler, A. (Editor). The Addictive States. Volume 46. Proceedings of the Association for Research in Nervous and Mental Diseases, New York, December 2-3, 1966. Baltimore, Williams and Wilkins, 1968, pp. 226-246.

(62) JANZON, L. Smoking cessation and peripheral circulation. A population study in 59-year-old men with plethysmography and segmental measurements of systolic blood pressure. VASA; Zeitschrift fur Gefaesskrankheiten 4(3): 282-287, 1975.

(63) JARVIK, M.E. Further observations on nicotine as the reinforcing agent in smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V. H. Winston and Sons, 1973, pp. 33-49.

(64) JARVIK, M.E., GLICK, S.D., NAKAMURA, R.K. Inhibition of cigarette smoking by orally administered nicotine. Clinical Pharmacology and Therapeutics 11(4): 574-576, July/August 1970.

(65) JOHNSTON, L.M., GLASG, M.B. Tobacco smoking and nicotine. Lancet 2(6225): 742, December 19, 1942.

(66) KALES, J., ALLEN, C., PRESTON, T.A., TAN, T.L., KALES, A. Changes in REM sleep and dreaming with cigarette smoking and following withdrawal. Psychophysiology 7: 347-348, September 1970.

(67) KANNEL, W.B. Preventive cardiology: What should the clinician be doing about it? Postgraduate Medicine 61(1): 74-85, January 1977.

(68) KANZLER, M., JAFFE, J.H., ZEIDENBERG, P. Long- and short-term effectiveness of a large-scale proprietary smoking cessation program—a 4 year follow-up of Smokenders participants. Journal of Clinical Psychology 32(3): 661-669, July 1976.

(69) KASL, S.V. Social-psychological characteristics associated with behaviors which reduce cardiovascular risk. In: Enelow, A.J., Henderson, J.B. (Editors). Applying Behavioral Science to Cardiovascular Risk. Proceedings of a Conference, Seattle, Washington, June 17-19, 1974. American Heart Association, Inc., 1975, pp. 173-190.

(70) KITTEL, G. Moeglichkeiten der Olfaktometrie. Ermuedungsmessungen bei Rauchern (Possibilities in olfactometry. Measurements of fatigue in smokers). Zeitschrift fur Laryngologie Rhinologie und Otologie 49(6): 376-386, June 1970.

(71) KNAPP, P.H., BLISS, C.M., WELLS, H. Addictive aspects in heavy cigarette smoking. American Journal of Psychiatry 119: 966-972, April 1963.

(72) KNOTT, V.J., VENABLES, P.H. EEG alpha correlates of non-smokers, smokers, smoking, and smoking deprivation. Psychophysiology 14(2): 150-156, March 1977.

(73) KOZLOWSKI, L.T., JARVIK, M.E., GRITZ, E.R. Nicotine regulation and cigarette smoking. Clinical Pharmacology and Therapeutics 17(1): 93-97, January 1975.

(74) KRUMHOLZ, R.A., CHEVALIER, R.B., ROSS, J.C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. Annals of Internal Medicine 62(2): 197-207, February 1965.

(75) KUMAR, R., COOKE, E.C., LADER, M.H., RUSSELL, M.A.H. Is nicotine important in tobacco smoking? Clinical Pharmacology and Therapeutics 21(5): 520-529, May 1977.

(76) LARSON, P.S., SILVETTE, H. Tobacco: Experimental and Clinical Studies, Supplement 2. Baltimore, Williams and Wilkins, 1971, 563 pp.

(77) LEBOWITZ, M.D., BURROWS, B. The relationship of acute respiratory illness history to the prevalence and incidence of obstructive lung disorders. American Journal of Epidemiology 105(6): 544-554, June 1977.

(78) LEFKOWITZ, R.J. Smoking, catecholamines, and the heart. New England Journal of Medicine 295(11): 615-616, September 9, 1976.

(79) LEVINSON, B.L., SHAPIRO, D., SCHWARTZ, G.E., TURSKY B. Smoking elimination by gradual reduction. Behavior Therapy 2(4): 477-487, October 1971.

(80) LILIENFIELD, A.M. Problems and areas in genetic-epidemiological field studies. Annals of the New York Academy of Sciences 91(3): 797-805, June 7, 1961.

(81) MARTIN, W.R. A homeostatic and redundancy theory of tolerance to and dependence on narcotic analgesics. In: Wikler, A. (Editor). The Addictive States. Volume 46. Proceedings of the Association for Research in Nervous and Mental Disease, New York, December 2-3, 1966. Baltimore, Williams and Wilkins, 1968, pp. 206-225.

(82) MATARAZZO, J.D., SASLOW, G. Psychological and related characteristics of smokers and nonsmokers. Psychological Bulletin 57(6): 493-513, 1960.

(83) MAUSNER, J.S. Cigarette smoking among patients with respiratory disease. American Review of Respiratory Disease 102(5): 704-713, November 1970.

(84) MCBURNEY, D.H., MOSKAT, L.J. Taste thresholds in college-age smokers and nonsmokers. Perception and Psychophysics 18(2): 71-73, 1975.

(85) MCLEAN, B.K., RUBEL, A., NIKITOVITCH-WINER, M.B. The differential effects of exposure to tobacco smoke on the secretion of luteinizing hormone and prolactin in the proestrous rat. Endocrinology 100(6): 1566-1570, June 1977.

(86) MCMAHAN, C.A., RICHARDS, M.L., STRONG, J.P. Individual cigarette usage: Self-reported data as a function of respondent-reported data. Atherosclerosis 23(3): 477-488, May/June 1976.

(87) MEADE, T.W., WALD, N.J. Cigarette smoking patterns during the working day. British Journal of Preventive and Social Medicine 31(1):25-29, March 1977.

(88) MENDLEWICZ, J., RAINER, J.D. Genetic factors in affective disorders and schizophrenia and problems of genetic counseling. In: Usdin, E., Forrest, I.S. (Editors). Psychotherapeutic Drugs, Part I, Principles. New York, Marcel Dekker, Inc., 1976, pp. 329-357.

(89) MERTZ, D.P., THONGBHOUBESRA, T. Wirkung von nicotin auf die saeurebildung im menschlichen magen (Effect of nicotine on the production of gastric acid). Medizinische Klinik 71(4): 147-155, January 23, 1976.

(90) MURDOCK, R., EVA, J. Smoking clinics—whither? Community Health 6(3): 155-160, 1974.

(91) MURPHREE, H.B., SCHULTZ, R.E. Abstinence effects in smokers. Federation Proceedings 27: 220, 1968. (Abstract)

(92) MYRSTEN, A.-L., ELGEROT, A., EDGREN, B. Effects of abstinence from tobacco smoking on physiological and psychological arousal levels in habitual smokers. Psychosomatic Medicine 39(1): 25-38, January/February 1977.

(93) MYRSTEN, A.-L., POST, B., FRANKENHAEUSER, M., JOHANSSON, G. Changes in behavioral and physiological activation induced by cigarette smoking in habitual smokers. Psychopharmacologia 27(4): 305-312, 1972.

(94) NEDERGAARD, O.A., SCHROLD, J. The mechanism of action of nicotine on vascular adrenergic neuroeffector transmission. European Journal of Pharmacology 42: 315-329, 1977.

(95) NELSEN, J.M., PELLEY, K., GOLDSTEIN, L. Protection by nicotine from behavioral disruption caused by reticular formation stimulation in the rat. Pharmacology Biochemistry and Behavior 3(5): 749-754, September/October 1975.

(*96*) OATES, J.A., AZARNOFF, D.L., COHEN, S.N., MELMON, K.L. Medicinal misadventures. Emergency Medicine 7(7): 115-137, July 1975.

(*97*) OHLIN, P., LUNDH, B., WESTLING, H. Carbon monoxide blood levels and reported cessation of smoking. Psychopharmacology 49(3): 263-265, 1976.

(*98*) OKADA, Y., TYUMA, I., UEDA, Y., SUGIMOTO, T. Effect of carbon monoxide on equilibrium between oxygen and hemoglobin. American Journal of Physiology 230(2): 471-475, February 1976.

(*99*) OLDENDORF, W.H. Distribution of drugs to the brain. In: Jarvik, M.E. (Editor). Psychopharmacology in the Practice of Medicine. New York, Appleton-Century-Crofts, 1977, pp. 167-175.

(*100*) ORSETTI, A., AMARA, F., COLLARD, F., MIROUZE, J. Influence du tabac sur les hormones essentielles de la glycoregulation (The influence of tobacco on hormones essential to glycoregulation). Nouvelle Presse Medicale 4(21): 1571-1572, May 24, 1975.

(*101*) PARSONS, W.B., JR. Hyperlipidemia: To treat or not to treat. Arizona Medicine 32(4): 323-328, April 1975.

(*102*) PEARSON, R.E. Drug therapy problems. Arizona Medicine 33(11): 929-930, November 1976. (Letter)

(*103*) PEDERSON, L.L., LEFCOE, N.M. A psychological and behavioural comparison of ex-smokers and smokers. Journal of Chronic Diseases 29(7): 431-434, July 1976.

(*104*) PETERSON, D.I., LONERGAN, L.H., HARDINGE, M.G., TEEL, C.W. Results of a stop-smoking program. Archives of Environmental Health 16: 211-214, February 1968.

(*105*) POWELL, J.R., THIERCELIN, J.F., VOZEH, S., SANSOM, L., RIEGELMAN, S. The influence of cigarette smoking and sex on theophylline disposition. American Review of Respiratory Disease 116(1): 17-23, July 1977.

(*106*) PRADHAN, S.N., BOWLING, C. Effects of nicotine on self-stimulation in rats. Journal of Pharmacology and Experimental Therapeutics 176(1): 229-243, 1971.

(*107*) PRADO, A.B., DE CARVALHO, D., SILVA, H.C., GUIMARAES, L.F.L., CARDOSO, M.A.A. Identificacao e dosagem espectrofotometrica de nicotina em urina de fumantes. (Identification and spectrophotometric measurement of nicotine in the urine of smokers). Revista Brasileira de Medicina 31(9): 607-610, September 1974.

(*108*) RAWBONE, R.G., COPPIN, C.A., GUZ, A. Carbon monoxide in alveolar air as an index of exposure to cigarette smoke. Clinical Science and Molecular Medicine 51(5): 495-501, November 1976.

(*109*) ROBINSON, A.G. Isolation, assay, and secretion of individual human neurophysins. Journal of Clinical Investigation 55(2): 360-367, February 1975.

(*110*) ROBINSON, A.G., HALUSZCZAK, C., WILKINS, J.A., HUELLMANTEL, A.B., WATSON, C.G. Physiologic control of two neurophysins in humans. Journal of Clinical Endocrinology and Metabolism 44(2): 330-339, February 1977.

(*111*) RUSSELL, M.A.H., WILSON, C., PATEL, U.A., COLE, P.V., FEYERABEND, C. Comparison of effect on tobacco consumption and carbon monoxide absorption of changing to high and low nicotine cigarettes. In: Edwards, G., Russell, M.A.H., Hawks, D., MacCafferty, M. (Editors). Alcohol Dependence and Smoking Behaviour. London, Saxon House/Lexington Books, 1976, pp. 192-204.

(*112*) RYAN, F.J. Cold turkey in Greenfield, Iowa: A follow-up study. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 231-241.

(*113*) RYLE, A. Smoking and personality. British Medical Journal 1: 1652, May 28, 1960. (Letter)

(*114*) SCHACHTER, S. 1. Nicotine regulation in heavy and light smokers. Journal of Experimental Psychology: General 106(1): 5-12, March 1977.

(*115*) SCHECHTER, M.D., RAND, M. J. Effect of acute deprivation of smoking on aggression and hostility. Psychopharmacologia 35: 19-28, 1974.

(*116*) SCHECHTER, M.D., ROSECRANS, J.A. Nicotine as a discriminative cue in rats: Inability of related drugs to produce a nicotine-like cueing effect. Psychopharmacologia 27(4): 379-387, 1972.

(*117*) SCHIRREN, C. Der derzeitige stand andrologischer behandlungsmoeglichkeiten bei kinderloser ehe unter besonderer beruecksichtigung einer andrologischgynaekologischen kooperation (The present status of the treatment of male factors of infertility in barren couples with reference to cooperation between andrologists and gynaecologists). Geburtshilfe und Frauenheilkunde 35(5): 334-343, May 1975.

(*118*) SCHMELTZ, I., HOFFMANN, D. Chemical studies on tobacco smoke. 38. The physicochemical nature of cigarette smoke. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 13-34.

(*119*) SELTZER, C.C. Constitution and heredity in relation to tobacco smoking. Annals of the New York Academy of Sciences 142: 322-330, 1967.

(*120*) SHIFFMAN, S.M., JARVIK, M.E. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology 50(1): 35-39, 1976.

(*121*) SILLETT, R.W., TURNER, J.A.M., BALL, K.P. Monitoring of carboxyhemoglobin in a cardiovascular clinic. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. DHEW Publication No. (NIH) 76-1221, 1976, pp. 343-347.

(*122*) SPELLACY, W.N., BUHI, W.C., BIRK, S.A. The effect of smoking on serum human placental lactogen levels. American Journal of Obstetrics and Gynecology 127(3): 232-234, February 1, 1977.

(*123*) STAMLER, J. Primary prevention of sudden coronary death. Circulation 52 (6, Supplement III): III-258–III-279, December 1975.

(*124*) STEVENS, H.A. Evidence that suggests a negative association between cigarette smoking and learning performance. Journal of Clinical Psychology 32(4): 896-898, October 1976.

(*125*) STEWART, R.D., HAKE, C.L., WU, A., STEWART, T.A., KALBFLEISCH, J.H. Carboxyhemoglobin trend in Chicago blood donors, 1970-1974. Archives of Environmental Health 31(6): 280-286, November/December 1976.

(*126*) STOLERMAN, I.P., BUNKER, P., JARVIK, M.E. Nicotine tolerance in rats; role of dose and dose interval. Psychopharmacologia 34: 317-324, 1974.

(*127*) STOLERMAN, I.P., FINK, R., JARVIK, M.E. Acute and chronic tolerance to nicotine measured by activity in rats. Psychopharmacologia 30(4): 329-342, 1973.

(*128*) STRONG, J.P., RICHARDS, M.L., MCGILL, H.C., JR., EGGEN, D.A., MCMURRY, M.T. On the association of cigarette smoking with coronary and aortic atherosclerosis. Journal of Atherosclerosis Research 10: 303-317, 1969.

(*129*) SWETT, C., JR. Drowsiness due to chlorpromazine in relation to cigarette smoking. A report from the Boston Collaborative Drug Surveillance Program. Archives of General Psychiatry 31: 211-213, August 1974.

(*130*) TENOVUO, J., MAEKINEN, K.K. Concentration of thiocyanate and ionizable iodine in saliva of smokers and nonsmokers. Journal of Dental Research 55(4): 661-663, July/August 1976.

(*131*) TRAHAIR, R.C.S. Giving up cigarettes: 222 case studies. Medical Journal of Australia 1: 929-932, May 6, 1967.

(*132*) TROJNAR, R. Badania ukladu adrenergicznego i metabolizmu serotoniny u palaczy papierosow (Studies of adrenergic system and serotonin metabolism in cigarette smokers). Polski Tygodnik Lekarski 31(12): 473-476, March 22, 1976.

(*133*) TROJNAR, R. Wydalanie z moczem niektorych metabolitow katecholamin i serotoniny u bylych palaczy pod wplywem palenia papierosow (Urinary excretion of certain metabolities of serotonin and catecholamines after cigarette smoking in subjects who had stopped smoking). Polski Tygodnik Lekarski 31(13): 521-524, March 29, 1976.

(*134*) TURNER, J.A.M. Confirmation of abstinence from smoking. British Medical Journal 2(6038): 755, September 25, 1976. (Letter)

(*135*) ULETT, J.A., ITIL, T.M. Quantitative electroencephalogram in smoking and smoking deprivation. Science 164(3882): 969-970, May 23, 1969.

(*136*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report to the Surgeon General: 1971. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 71-7513, 1971, 458 pp.

(*137*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report to the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

(*138*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 77-8704, 1977, pp. 87-160.

(*139*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.

(*140*) VANUXEM, D., WEILLER, P.J., GRIMAUD, C., GABRIEL, B., MONGIN, M. Polyglobulie du fumeur (Polycythemia of the smoker). Nouvelle Presse Medicale 4(30): 2204, September 20, 1975.

(*141*) VERDY, M., ORSETTI, A., BALDET, L., PUECH-CATHALA, A.-M. Effet de la cigarette sur les taux seriques d'hormone de croissance et de TSH dans le diabete (The effect of cigarettes on serum levels of growth hormone and TSH in diabetics). L'Union Medicale du Canada 104(9): 1356-1359, September 1975.

(*142*) VOGT, T.M., SELVIN, S., WIDDOWSON, G., HULLEY, S.B. Expired air carbon monoxide and serum thiocyanate as objective measures of cigarette exposure. American Journal of Public Health 67(6): 545-549, June 1977.

(*143*) VOLLE, R.L., KOELLE, G.B. Ganglionic stimulating and blocking agents. In: Goodman, L.S., Gilman, A.G., Koelle, G.B. (Editors). The Pharmacological Basis of Therapeutics. Fifth Edition. New York, Macmillan, 1975, pp. 465-474.

(*144*) WENNMALM, A. Nicotine stimulates prostaglandin formation in the rabbit heart. British Journal of Pharmacology 59(1): 95-100, January 1977.

(*145*) WEST, D.W., GRAHAM, S., SWANSON, M., WILKINSON, G. Five-year follow-up of a smoking withdrawal clinic population. American Journal of Public Health 67(6): 536-544, June 1977.

(*146*) WEYBREW, B.B., STARK, J.E. Psychological and physiological changes associated with deprivation from smoking. U.S. Naval Submarine Medical Center, Submarine Medical Research Laboratory, Report No. 490, February 23, 1967, 19 pp.

(147) WIKLER, A. Characteristics of opioid addiction. In: Jarvik, M.E. (Editor). Psychopharmacology in the Practice of Medicine. New York, Appleton-Century-Crofts, 1977, pp. 419-432.

(148) WILHELMSEN, L. One year's experience in an anti-smoking clinic. Scandinavian Journal of Respiratory Diseases 49(4): 251-259, 1968.

(149) WINTERNITZ, W.W., QUILLEN, D. Acute hormonal response to cigarette smoking. Journal of Clinical Pharmacology 17(7): 389-397, July 1977.

(150) WOCIAL, B., CISWICKA-SZNAJDERMAN, M., JANUSZEWICZ, W. Wplyw palenia papierosow na zachowanie sie poziomu katecholamin, wolnych kwasow tluszczowych i kortyzolu w surowicy krwi (Effect of cigarette smoking on serum catecholamines, free fatty acids and cortisol). Kardiologia Polska 19(1): 59-65, 1976.

(151) WOOD, J.E. Effect of smoking on the peripheral circulation in relation to environmental temperature. Annals of the New York Academy of Sciences 90(1): 114-118, September 27, 1960.

(152) WYNDER, E.L., KAUFMAN, P.L., LESSER, R.L. A short-term follow-up study on ex-cigarette smokers, with special emphasis on persistent cough and weight gain. American Review of Respiratory Diseases 96(4): 645-655, October 1967.

(153) YANAGITA, T. Brief review on the use of self-administration techniques for predicting drug dependence potential. In: Thompson, T., Unna, K.R. (Editors). Predicting Dependence Liability of Stimulant and Depressant Drugs. Baltimore, University Park Press, 1976, pp. 231-242.

(154) ZEIDENBERG, P., JAFFE, J.H., KANZLER, M., LEVITT, M.D., LANGONE, J.J., VAN VUNAKIS, H. Nicotine: Cotinine levels in blood during cessation of smoking. Comprehensive Psychiatry 18(1): 93-101, January/February 1977.

16. BEHAVIORAL FACTORS IN THE ESTABLISHMENT, MAINTENANCE, AND CESSATION OF SMOKING.

National Institute on Drug Abuse

CONTENTS

Introduction

Smoking is a behavior—a highly complex act which is accompanied by certain cognitions and hedonic states and based on various biochemical and physiological processes. In that sense, research on smoking behavior is at the interface between psychosocial and biological investigations of smoking. While behavioral research has contributed greatly to the technology of smoking cessation, relatively few behavioral investigations have been carried out to elucidate the mechanisms underlying smoking. Because of this, the present chapter will focus on social learning theory and nicotine regulation as general considerations to provide a context for a behavioral analysis of smoking. An evaluation of the contributions from the experimental analysis of behavior to the treatment of cigarette smoking and recommendations for further research will be made. Behavioral research findings on the establishment, maintenance, and cessation of smoking will be summarized. Emphasis will be on those stages (*16*) of smoking which follow initiation and during which the processes that contribute to the tenacity of the habit and its resistance to change are set in motion.

The Social Learning Model

Social learning theory has functioned less as a formal explanatory model of smoking and more as a methodological approach with an associated intervention technology (*35*). The impetus for using behavior modification techniques has been provided by the belief that research procedures which operationalize definitions, emphasize well-controlled empirical research, and are derived from concepts from the experimental laboratory will provide valuable practical and theoretical knowledge—a belief justified by the previous contributions of the behavioral approach toward the understanding of other difficult problems in human behavior. Behavior modification is derived from basic research on animal learning by Pavlov and Skinner. It emphasizes the control of antecedent and consequent environmental events (stimuli) in determining behavior (*4*). Social learning theory represents an extension of behavior modification to situations which involve interpersonal activity, but it incorporates the added explanatory concept of modeling, based on imitation and social reinforcement.

In brief, a social learning explanation of smoking proceeds along the following general lines (*35*): The habit is acquired under conditions of social reinforcement, typically those of peer pressure. Initially the inhalation of smoke is aversive, but after sufficient practice, habituation (or tolerance) occurs, and the behavior begins to produce sufficient positive reinforcement in its own right to be sustained independently of social reinforcement. Smoking now generalizes to situations other than the one in which it was originally acquired. It is important to note

that, from the perspective of social learning theory, smoking is seen as a learned behavior from the onset.

The analysis continues as follows: Discriminations between situations in which smoking is punished socially and those in which it is either ignored or favorably received are formed, and various circumstances (both external and internal) begin to control smoking. Insofar as they are associated with smoking, some situations, such as an empty cigarette pack or an annoying telephone call, may serve as conditional stimuli (CS's) which elicit covert responses. These responses (i.e., physiological changes or discomfort, perceived as craving) increase the likelihood of smoking. In turn, they can serve as discriminative stimuli (SD's), setting the occasion for the reinforcement provided by smoking. Moreover, stimuli which are preparatory to the act of smoking, such as the sight of a cigarette, can function as secondary reinforcers for behaviors preceding them (for example, purchasing a full cigarette pack). These cues can also serve as discriminative stimuli for behaviors which follow them, such as lighting the cigarette, thus forming a linked chain of responses (a smoking ritual). For successful termination of the overt act of smoking to occur, the extinction of most or all of the conditional stimuli, secondary reinforcers, and discriminative stimuli which make up the habit is required. The way in which these ideas have been put to specific use in therapy will be discussed in some detail later in this chapter.

The number of emotional events which can influence smoking are potentially quite great. If smoking is seen, in part, as an avoidance/escape response to aversive withdrawal states, then, hypothetically, by a process of stimulus generalization, other dysphoric states (for example, anger, tension, boredom) might also serve as discriminative stimuli for smoking. Also, response generalization may occur. In this case, the smoking ritual serves as a temporary escape (coping response) from various aversive situations (that is, smoking as a response which provides relief). Smoking can be seen, therefore, as a generalized primary and secondary reinforcer providing both positive and negative reinforcement over a remarkably wide array of life situations.

From a social learning theory perspective, smoking is difficult to modify because of its ability to provide immediate reinforcement—nicotine from an inhaled cigarette reaches the brain in seven seconds (twice as fast as intravenous administration from the arm). Furthermore, the habit is tremendously overlearned: at ten puffs per cigarette, the pack-a-day smoker gets more than 70,000 nicotine "shots" in a year—a frequency which is unmatched by any other form of drug taking (*40*). While most smokers recognize that sustained smoking can lead to a variety of unpleasant events, ranging from bronchitis to lung cancer, the ultimate aversive consequences of smoking—though potentially of great magnitude—are delayed and therefore have less

influence over ongoing smoking behavior than immediate consequences. This is a situation common to a number of self-management problems (*37*). Unlike alcohol and many other drugs of dependence, there are few immediately noticeable negative consequences (*40*).

To a large extent, behavioral researchers have *assumed* relationships between environmental events and smoking. Treatment practices have been based on general theory rather than on research or a functional analysis of smoking behavior as such. Thus, though part of the promise of social learning theory has been fulfilled, and behavioral concepts may have generated new standards of effectiveness in the treatment of smoking, there has not been a comparable contribution to the understanding of smoking per se.

The Nicotine Addiction Model

A physiologically based model of smoking, emphasizing the key role of nicotine as a reinforcer, has evolved from the work of Schachter (*42, 43*) and others like Jarvik (*19*) and Russell (*40*). The main focus is on explaining the maintenance of the smoking habit following acquisition. Under this formulation, smoking is viewed as an escape/avoidance response to aversive stimulation provided by periodic nicotine withdrawal in the addicted smoker. An internal regulatory mechanism is implied which detects the level of nicotine and maintains it within characteristic upper and lower limits by regulating the frequency of smoking (and possibly other intake parameters).

Much of the evidence in support of smoking as negatively reinforced behavior comes from a series of innovative experiments conducted by Schachter and his associates over a 10-year span. In one study, Nesbitt (*30*) used the amount of shock a subject was willing to tolerate as a behavioral measure of anxiety. They found that heavy smokers tolerated a higher shock intensity (were less "anxious") when allowed to smoke than when not allowed to smoke; nonsmokers tolerated an intermediate shock intensity. The design did not allow a differentiation between the possibility that smokers tolerated higher shock intensity because of a "sedative" effect of smoking (positive reinforcement) or because smoking constituted escape from withdrawal symptoms perceived as "anxiety" (negative reinforcement). To test for this, Silverstein (*46*) varied the amount of nicotine in cigarettes given prior to shock presentation. He found that smokers given a high-nicotine cigarette tolerated more shock than smokers given low-nicotine cigarettes and that there was no significant difference between smokers given low-nicotine cigarettes and deprived smokers. He concluded that the sensory-motor and oral positive reinforcement provided by low-nicotine cigarettes played a negligible role in increasing shock tolerance compared with the negative reinforcement provided by escape from withdrawal symptoms using high-nicotine

cigarettes. Further support came from the observation that nonsmokers exhibited higher endurance thresholds (lower "anxiety") than deprived or low-nicotine smokers. This suggests that "smoking doesn't reduce anxiety or calm the nerves [but rather that] not smoking increases anxiety by throwing the smoker into withdrawal" (*54*). Thus, a nicotine deficit seems to exacerbate the distress induced by aversive shock. Heimstra, et al. (*15*) found the same effect for psychomotor performance on a simulated driving test.

The next problem was to account for why smokers smoke more when stressed. According to Schachter (*42*), the debilitating effects of no or low nicotine are the result of withdrawal, and the effect of stress is to put the smoker into withdrawal by depleting the available supply of nicotine. This hypothesis was strengthened and new leads were generated by biochemical studies showing that, while some nicotine is catabolized (mainly in the liver, at a constant rate determined in part by the duration of the habit), a fraction of the nicotine escapes detoxification and is eliminated directly in the urine. Furthermore, the rate of urinary excretion is rapid, increases linearly with dosage, and increases as the pH of the urine becomes more acid. The hypothesis was confirmed by direct manipulation of urinary acidity through the administration of mild acidifying agents like ascorbic acid or glutamic acid hydrochloride or alkalizers like sodium bicarbonate (*43*). In addition, stressful events associated with heavier smoking increased urinary acidity and nicotine excretion in the expected direction (*42*). To test whether stress or urinary pH or both were the independent variable, Schachter et al. (*43*) independently manipulated stress and pH and reported that smoking seemed to be under the control of urinary acidity rather than stress as such.

Schachter's model posits that nicotine is the primary reinforcer because of its role in reducing tension and distress associated with nicotine deprivation. If this is true, secondary reinforcers should be relatively unimportant. For example, smokers should not smoke nicotine-free cigarettes, and supplying alternative sources of nicotine should eliminate the desire to smoke. According to Jarvik (*19*), much of the evidence for the role of nicotine as the primary reinforcer in cigarette smoke is circumstantial. Smokers evidently prefer cigarettes with, rather than without, nicotine; but they will smoke nicotine-free cigarettes for a while if no others are available. The fact that smoking such cigarettes is not sustained despite the usual cues for smoking suggests that the other variables are secondary reinforcers that extinguish when nicotine—the primary reinforcer—is not present. Attempts to investigate the role of nicotine as the sufficient condition for smoking, however, have produced conflicting results. Preloading nicotine, by having subjects smoke or chew gum containing nicotine before testing, did reduce subsequent puffing (*20*, *21*, *25*). And administration of the drug mecamylamine, which functioned as a

nicotine "antagonist," increased the smoking rate (*52*). But Kumar, et al. (*21*) were unable to demonstrate a dose-response effect on subsequent smoking when nicotine preloading was administered intravenously. The fact that lettuce cigarettes reinforced with nicotine were as unacceptable as non-nicotine cigarettes also seems to undermine the nicotine-only hypothesis (*19*). Jarvik (*19*) concluded that nicotine may be a *necessary but not sufficient* condition for smoking behavior to occur and to be sustained and that more research is clearly needed to settle the issue of whether nicotine functions as the primary reinforcer or as a "reinforcing co-factor."

The nicotine addiction model suggests that the smoker regulates nicotine levels under widely varying conditions. It implies a mechanism which senses nicotine and provides the impetus for directed behavior—possibly a central "nicostat" or the integration of the various peripheral drug effects of nicotine. While the model is plausible and straightforward, critical tests have yet to be performed. Particularly, direct measurements of changes in nicotine titer and of the withdrawal state have not been attempted. Finally, among variables not adequately explained by the model are the role of environmental stimuli in the control of the habit, the nature of individual differences in smoking behavior (for example, light versus heavy smokers and occasional versus chronic smokers), and the mechanism(s) by which relapse occurs following withdrawal (*35*).

A Context for Behavioral Research on Smoking

Clearly, neither social learning theory nor the nicotine addiction model alone can provide a complete understanding of smoking at present. A recent model, the opponent process theory (*47, 48, 49, 53*) does attempt to link psychological and physiological factors involved in the maintenance of smoking in a more comprehensive fashion. The principal features of the opponent process model as it applies to smoking are as follows: (*1*) the reaction to cigarette smoke is biphasic, with a brief pleasurable component (*a* process) followed by a more sustained dysphoric component (*b* process); (*2*) the hedonic tone—pleasurable A state or dysphoric B state—is determined by the algebraic sum of the two opponent processes at a given point in time; and (*3*) stimuli associated with a given state can elicit this state as a conditioned response after repeated pairings.

The opponent process model assumes that cigarettes contain substances which provide pleasure (initiate the *a* process) during early use. While there may be some unpleasant effects on the first few occasions, these should be offset by the drug effect or by other reinforcers such as peer pressure; if not, the act of smoking will not continue. As cigarette smoking becomes established, the opponent

process grows in strength: the pleasurable A state weakens and the withdrawal B state intensifies correspondingly.

Because the *b* process is the opponent of the *a* process, the best way of attenuating the B state is to ingest the substance that produces the A state. As an operant behavior, smoking is both positively reinforced by a pleasurable consequence and negatively reinforced by terminating aversive withdrawal, thus setting up an addictive cycle. As the *b* process is further strengthened, still larger amounts of tobacco have to be smoked to produce a pleasurable A state, resulting in tolerance.

Stimuli associated with smoking (CS_A's), such as a pack of cigarettes or the sight of matches, should elicit a brief conditioned (pleasurable) A state at stimulus onset and a conditioned withdrawal (unpleasant) B state at stimulus offset. Furthermore, stimuli associated with the B state (CS_B's)—such as an empty cigarette pack, empty pockets, no stores, or "no smoking" signs—should elicit conditioned craving or withdrawal. The concept of conditioned A and B state elicitors leads to the important implication that, as the smoking habit becomes well established and the *b* process becomes stronger, CS_A's elicit a brief conditioned state which is pleasant but then is followed by a more extended conditioned craving which intensifies the pre-existing withdrawal B state. Similarly, CS_B's directly elicit conditioned craving, which also adds to the discomfort of the withdrawal state. An additional implication (derived from Pavlovian conditioning theory) is that as CS_B's become stronger, they may become more anticipatory, leading to shorter redosage and restimulation intervals until an asymptote is reached. If the smoker quits, the CS_B's and the *b* process should weaken eventually through disuse, but the CS_A's and the *a* process should intensify correspondingly. Thus, if a cigarette is smoked after a period of abstinence, the pleasurable component has increased to its original level and the resumption of the addictive cycle is facilitated. The smoker is clearly locked into the pattern of smoking and, in that sense, once established, the habit seems to be overdetermined.

The opponent process model has not been tested in formal research on cigarette smoking, though recent experiments in the area of opiate addiction do provide general support (*31, 44, 56*). The demonstration of conditionability, in particular, has important implications for the understanding of smoking recidivism. Wikler (*55*) has observed that environmental stimuli associated with withdrawal may precipitate conditioned craving (or withdrawal) even after an extended abstinence period has ended physical dependence in heroin addicts. The opponent process model predicts a biphasic response by smokers (A state followed by B state) to the presentation and removal of stimuli associated with cigarettes during acquisition. Later on in the addiction process, when tolerance is large, the dominant conditioned effects should be those of craving or withdrawal (B state predominates). The

implication for treatment is that unless conditioned craving is extinguished or modified as a part of therapy, the probability of relapse will remain high.

There are a number of different issues that need to be resolved among the current behavioral formulations of smoking before an adequate understanding is achieved. For example, the nicotine addiction model suggests that the day-to-day regulation of smoking is more under the control of pharmacological variables than of environmental stimuli, though their relative contribution remains to be determined. Moreover, the issue of whether smoking reduces anxiety is not settled. For example, Hutchinson and Emley (*18*) have suggested that nicotine can be classified as a tranquilizer since it decreases aggression as well as the conditioned emotional response (CER). They have speculated that difficulty in training animals to smoke under ordinary conditions may have been because a background of aversive stimulation is needed to provide motivation to use smoking to relieve anxiety. Also, as has been mentioned, the pharmacological primacy of nicotine implied by the nicotine addiction model has yet to be established unequivocally.

The opponent process model encounters similar problems. For example, Wikler (*55*) has argued that certain responses associated with chronic drug use, such as tolerance or conditioned withdrawal, are *counteradaptations*, serving to protect the organism by acting in a direction opposite to the normal drug effect. The opponent process model is stated in sufficiently general terms to incorporate these observations if certain (untested) assumptions are made: Wikler's observations emphasize the dominant drug-negative B state; in opponent process theory, the initial drug-positive *a* process (and thus the pleasurable A state) is still operative but may be so brief and attenuated that it goes undetected. Only closer examination of the time course for the response to drugs at different states of acquisition will settle this issue. An additional complication has been raised by Siegel (*45*), who has shown that the stimuli which constitute the ritual of (repeated) drug injection can elicit conditioned reactions which increase tolerance to the drug; extinction of these conditioned reactions, using a series of saline injections, results in decreased tolerance. Siegel proposes that tolerance is the result of compensatory *associative* processes and is not simply a pharmacological, nonassociative phenomenon. While opponent process theory can be modified to accommodate these findings, by defining them as the manifestations of stimuli which serve as conditioned B state elicitors, the relative contribution of associative and nonassociative factors cannot be specified at present. Furthermore, if tolerance is basically an associative process, the problem of explaining why certain substances, such as nicotine, produce tolerance while others do not will also have to be dealt with (*35*).

The remainder of the present discussion will re-examine some of the phenomena of acquisition, perpetuation, and termination of smoking from the point of view of the three models. Special attention will be given to implications for further research.

The Establishment of Smoking

The establishment of smoking can be seen as the result of initial experimentation with cigarettes repeated sufficiently often for acquisition of a habit and/or for addictive processes to take hold. Among the major variables contributing to initiation are social pressure and imitation of peers or family members who smoke (*1, 11*). The following variables influence the decision to smoke: peer pressure, best friends who are smokers, parents who smoke, adolescent rebellion, imitation of adult behavior, and misconceptions concerning the risks of smoking. A recommendation to conduct longitudinal comprehensive studies on the acquisition of smoking in the natural environment, and to determine the conditions under which smoking does or does not begin, would seem especially appropriate.

Once the smoking habit is acquired, the stage is set for addictive processes to contribute to the maintenance of the habit and to its overdetermination under the influence of the variables alluded to in the several smoking models. Additional physiological variables and explanatory variables from personality theory and typology studies (both types described elsewhere in the present report) are clearly relevant. These two sets of variables suggest a number of possible mechanisms by which acquisition might take place, although, as Leventhal and Cleary (*22*) point out, they are not necessarily the same mechanisms which contribute to onset. The need for careful, directed research in this area is evident to achieve a better understanding of onset and acquisition which may lead to more effective methods for prevention and treatment.

A promising approach to the investigation of physiological and behavioral, as well as psychosocial, factors in acquisition comes from animal research. Some studies have shown that nicotine facilitates conditioned-avoidance behavior as well as positively reinforced behavior in rats (*51*) and that it reduces social or pain-induced aggression in both animals and humans (*18*). Analogues of addiction might also be explored in the laboratory. While the laboratory approach might seem artificial to some, increasing experimental control by restricting extraneous variables has been useful in other difficult areas, such as alcoholism (e.g., Nathan and O'Brien (*29*)) and heroin addiction (e.g., O'Brien, et al. (*32*)). If such explorations are successful, subsequent research could be conducted under increasingly complex and more "natural" conditions. Finally, studies of different methods for deterring smoking in children (e.g., Evans (*7*) and Piper (*34*)) should

increase understanding of the conditions under which smoking begins and allow us to identify those environmental patterns which facilitate the movement from "experimental" smoking to addiction.

The Maintenance of Smoking

Once smoking is established as a habit, a number of factors contribute to its persistence and resistance to change. Each of the formulations described above devotes considerable attention to the phenomenon of maintenance, and a large body of research has been carried out from various points of view. In a sense, maintenance can be seen as a stage of smoking characterized by steady-state behavior. Pattern consistency is provided by environmental influences through stimulus control as well as by underlying physiological processes regulating consumption within characteristic limits. As an acquired motivation, smoking constitutes a behavioral pattern with powerful reinforcing value, overdetermined to a remarkable degree by its generating mechanisms. A better understanding of these processes is needed.

With a few exceptions, the determination of environmental influences on smoking has received relatively little direct attention experimentally, despite the fact that treatment techniques based on social learning theory have been used extensively. Among the better examples of a functional analysis of behavior is a study by Griffiths, et al. (*12*). Following detoxification, alcoholics in a residential laboratory were allowed to consume ethanol at certain times, and the amount of tobacco smoked was measured under various conditions. Cigarette smoking was shown to increase from 26 to 117 percent when the solutions consumed contained ethanol. The effect was robust, was observed in each of the five subjects, and was replicated 15 times employing a within-subject design. Control procedures indicated that the effect did not depend on: (1) the pattern of ethanol ingestion, (2) adjunctive maintenance through social interactions, (3) the pattern of days in which the ethanol or ethanol-free vehicle was scheduled, (4) alterations in the portion of cigarette smoked or the number of puffs taken, or (5) knowledge that a given drink did or did not contain ethanol. The study constitutes a good demonstration of the potential of the experimental analysis of smoking behavior, and the method should be extended to other problems of interest.

Smoking as an avoidance/escape response to withdrawal implies an internal regulatory mechanism by which the levels of nicotine (or other substances) are maintained within limits characteristic for each smoker. To get at these processes in research, measures should be taken of smoking behavior (specifying variables such as puff frequency and duration, depth of inhalation, amount of nicotine drawn from a standard cigarette), of major physiological variables (for example, cardiovascular changes, relevant biochemical activity including cholin-

ergic, catecholamine, and nicotine changes), and of cognitive variables (for example, hedonic states and the subjective desire to smoke at different points in time). As in investigations on the establishment of smoking, a laboratory approach may provide a good initial strategy, if supported by adequately controlled studies in the natural environment.

As a preliminary step, the variables involved in nicotine regulation should be explored directly in habitual smokers by studying the relationships between the act of smoking, subjective desire, and plasma nicotine levels. Also, nicotine excretion rates could be shifted using techniques identified by Schachter, such as drugs or psychological stress, to provide further modulation of physiological, behavioral, and subjective responses, thus replicating and extending previous work in this area. The demonstration of the contribution of nicotine by direct measurement might stimulate further explorations of the relationship between smoking behavior and other important biochemical variables such as catecholamines.

The Cessation of Smoking

Both initiation and cessation can be conceptualized as the result of decisions (evidenced by stated intention or other overt behavior) to start or to stop smoking. Thus, cognitive variables may play a major explanatory role, and the subjective utility of the change under consideration may provide important clues for predicting its outcome or success (*33*). (The cognitive aspects of initiation and quitting are extensively reviewed in a separate context elsewhere in this report.) Once the decision to start or stop smoking has been made, however, behavioral variables and the models described above come into play.

When habitual smokers stop smoking, they may experience a wide variety of unpleasant side effects, including craving for tobacco, irritability, restlessness, dullness, sleep disturbances, gastrointestinal disturbances, anxiety, and impairment of concentration, judgment, and psychomotor performance (*19*). The onset of symptoms may occur within hours or days after quitting and may persist from a few days to several months. Additional objective signs include a decrease in heart rate and blood pressure, increased rapid eye movement (REM) sleep, and slower rhythms in the EEG (*35*). Spontaneous jaw clenching (increased masseter potentials) lasting several weeks has been correlated with verbal reports of irritability (*18*).

After the ex-smoker successfully overcomes withdrawal symptoms, further problems may persist. In terms of the opponent process model, one can construct the following account: Subjectively, the pleasure of smoking in the addicted smoker is masked by the discomfort of craving from not smoking. After abstaining for a few weeks, however, craving decreases. If smoking is resumed, the first few cigarettes seem very strong and are highly pleasurable. Thus, the stage for re-addiction is

set. Moreover, various internal and external stimuli may serve as conditioned elicitors of craving or withdrawal. Particularly troublesome may be events too infrequent to extinguish quickly (e.g., attending a reunion where former classmates smoke) or emotional situations which resemble withdrawal (e.g., anticipation of an unpleasant or challenging social event).

A major contribution of the behavioral approach has been the development of new techniques in smoking cessation—procedures which seem to be more effective than those that preceded them. In most nonbehavioral clinics, fewer than half the smokers quit (e.g., Guilford (*13*)), and of those who quit only 25 to 30 percent are still abstinent 9 to 18 months later (*17*); the estimated long-term abstinence rate in nonbehavioral treatment is about 13 percent (*27*). The three main lines of behavioral treatment have involved punishment and aversive conditioning, stimulus control and contingency management, and controlled smoking procedures. While a thorough review of the modification of smoking is provided elsewhere in this report, the contribution of social learning to therapy is of sufficient importance to warrant a brief review here.

Aversive conditioning techniques are the oldest and most widely utilized behavioral procedures for smoking cessation. Among the aversive stimuli used have been electric shock (e.g., Best and Steffy (*3*)), covert or imagined aversive events, and cigarette smoke (e.g., Resnick (*39*)). The typical procedure has involved contingent punishment for overt smoking behavior in the laboratory or in the natural environment (e.g., Powell and Azrin (*38*)). Some investigators have attempted to punish motoric and cognitive components as well (e.g., Steffy, et al. (*50*)). With the exception of aversive smoking procedures, aversive conditioning techniques have not produced outstanding results (Bernstein and Glasgow (*2*)).

Aversive smoking combines the principles of extinction, negative practice, and aversive conditioning, using stimuli from the cigarettes themselves as the aversive component. The procedure assumes that the positive reinforcing aspects of a stimulus are reduced and become aversive if that stimulus is presented at an artificially elevated frequency or intensity. A further assumption is that aversion based on stimuli intrinsic to the maladaptive behavior is more salient and generalizable than that from artificial sources such as shock (Bernstein and Glasgow (*2*)). The most successful use of aversive smoking can be found in the recent work of Lichtenstein, et al. (*24*), using a technique called rapid smoking. The procedure calls for smoking cigarettes at a rapid rate (inhaling smoke about 6 seconds after each exhalation) until no more can be tolerated. Sessions are repeated on a daily basis until the smoker no longer reports a desire to smoke; booster sessions are provided if the desire returns. In a recent review of several studies using the procedure, the abstinence rate was 54 percent in short-term

follow-up and 36 percent in long-term follow-up (2 to 6 years after treatment). Though the method was a clear improvement over previous approaches, there are a number of problems which may make it less than the optimal procedure for the elimination of smoking. In particular, individuals with cardiopulmonary diseases—those who most need help—are the least likely to tolerate intense exposure to tobacco smoke without ill effect (*35*). Moreover, rapid smoking may be dangerous even to seemingly healthy people (*28*).

Another social learning approach to the modification of smoking behavior is represented by stimulus control tactics. The basic assumption is that smoking is associated with or controlled by environmental cues and that these cues (discriminative or conditional stimuli) contribute to the persistence of the habit (*2*). Treatment involves gradual elimination of smoking through programmed restriction of the range of stimuli that lead to smoking. Typically, self-monitoring is used to increase awareness of smoking along with designated daily quotas to provide targets for reduction (*36*). In general, stimulus control procedures have not been very effective in isolation (e.g., Levinson, et al. (*23*)). When used in combination with contingency contracting, in which deposited money is reimbursed for reaching specified goals (e.g., Elliott and Tighe (*6*)), and with other techniques, however, considerably better results are achieved (Bernstein and Glasgow (*2*)).

Recent research on multicomponent treatment procedures (employing techniques such as stimulus analysis, interference with situational control or environmental stimuli, social and monetary reinforcement of incompatible behavior, group support, and follow-up sessions, presented in an integrated sequence) has produced results as favorable as that reported for rapid smoking, with 61 percent of the first 100 participants quitting smoking after eight sessions of treatment and 32 percent not smoking a year after the onset of treatment (*36*). These data account for all smokers who entered treatment (including the 15 percent of the sample who could not be reached and were classified as smoking) and were based on self-reported smoking status corroborated by urinary nicotine analysis. The recidivism rate of 49 percent also compares favorably with the 70 to 75 percent recidivism reported for nonbehavioral clinics by Hunt and Bespalec (*17*). These positive findings are qualified somewhat by the observation that not all multicomponent treatment combinations are successful (e.g., Danaher (*5*)) and by a controlled multivariate study by Flaxman (*8*) indicating that the variables responsible for a successful outcome are poorly understood.

Smoking practices have changed considerably in recent years as smokers have attempted to reduce health risks on their own (Hammond, et al. (*14*)) by switching to filtered and low tar/nicotine cigarettes (Russell (*41*)). These natural trends provide a context for

recent research by Frederiksen and associates (*9*, *10*), demonstrating that behavioral technology can be used to control not only the rate and strength of cigarettes consumed but also to modify the topography of the habit. Additional impetus for the research comes from the fact that many smokers report difficulty reducing their smoking rate below 10 to 12 cigarettes per day (Levinson, et al. (*23*)). While it has been suggested that the reason for this is that the positive reinforcing value of each cigarette increases when fewer are smoked (Mausner (*26*)), according to opponent process theory there should be a corresponding lessening of the negative reinforcing effect resulting from withdrawal from nicotine over time. Clearly more research is needed to settle this issue. The technology developed by Fredericksen is still in the clinical development stage, and the long-term stability of the changes has yet to be determined. However, because some smokers are motivated to reduce their health risk even though they are unable to quit, controlled smoking technology may provide a useful alternative to the more traditional abstinence-oriented treatment and deserves further exploration.

While recent behavioral treatment seems more effective than previous approaches, 50 percent recidivism and 33 percent long-term abstinence leave considerable room for improvement. What is needed at present is outcome research directed at demonstrating the relative effectiveness of complete treatment packages in long-term randomized clinical trials. Subsequently, when a given procedure is shown to be superior in independent replications, components can be partitioned out and tested in order to produce clinical procedures that are both effective and efficient. Research designs should take into account the fact that recent improvements in outcome statistics for smoking-cessation clinics may reflect changing social attitudes toward smoking and higher levels of motivation rather than better treatment as such (*22*).

In an important sense, current treatment efforts—especially behavioral treatment—have been devoted primarily toward the modification of the overt act of smoking (an operant behavior). Less formal attention has been given to the cognitive and physiological respondents that constitute precursors of smoking (e.g., craving and withdrawal) and that are under the control of both environmental (exteroceptive) and emotional (interoceptive) stimuli. Moreover, the increased success of multicomponent programs may well be the result of more effective handling of these variables, using integrated sequences, than has been possible with unicomponent approaches. The fact that various previously neutral stimuli have been shown to elicit conditioned craving or withdrawal after being paired or associated with these states in various addictions has important implications for smoking treatment.

Treatment can be seen as extinguishing the act of smoking but not necessarily the concomitant conditioned cognitive or physiological respondents. As a result, the ex-smoker may continue to be exposed to various stimuli which have been associated with smoking, and the probability of relapse will remain great (for example, in the "negative affect" smoker (*36*)). Demonstrations that continued autonomic or cognitive reactivity persist after standard smoking-cessation therapy might lead to an entirely new approach to the old problem of relapse. Studies comparing a standard smoking-cessation treatment with "deconditioning" therapy, in which autonomic responses are extinguished in a simulated environment or modified directly using biofeedback, might lead to a demonstrably lower rate of recidivism for those smokers exposed to augmented therapy. The above suggests that basic research which leads to a better understanding of the mechanisms underlying smoking may result in the eventual development of a truly rational and more effective therapy for smoking.

Conclusions

The present chapter makes no claim to be exhaustive. Rather it has surveyed selectively what is known and not known concerning behavior in the establishment, maintenance, and cessation of smoking. The object has been to develop a context for directing research, for improving treatment, and for guiding social policy. In closing, a few specific recommendations seem appropriate.

While it is difficult to pinpoint accurately which of many research possibilities will be most fruitful on an *a priori* basis, certain themes seem particularly important for current behavioral research. They are the phenomenon of withdrawal, the reinforcing effects of nicotine, the role of nicotine antagonists or blockers, and the behavioral pharmacology of cigarette smoking.

1. Withdrawal symptoms of varying severity following cessation are among the principal reasons cited for relapse to smoking. Little scientific information is available on the sequelae to abstinence, however, and at present it is difficult to assess accurately their contribution to recidivism.

2. As discussed at some length, the problem of analyzing the reinforcing effects of nicotine is of great importance in understanding smoking. The role of nicotine as a positive and negative reinforcer should be examined in animals using various routes of administration as well as explored systematically in humans in laboratory and natural settings.

3. A related theme is derived from recent research suggesting that specific CNS receptor sites for nicotine can be blocked in a fashion analogous to the opiate antagonists. This phenomenon has implications

for understanding the effect of nicotine on the body as well as in helping smokers who have stopped to maintain abstinence.

4. The behavioral pharmacology of smoking deserves further emphasis. A more precise definition of smoking behaviors, involving psychometric analyses by puff volume, inter-puff interval, total amount smoked, and rate of smoking may have important implications for the understanding of stimulus control as well as of the relationship between blood nicotine levels and cigarette self-administration. Similarly, the development of objective criteria for validating dependent measures (such as self-reported smoking behavior using various biological assays) seems worthwhile.

In the treatment area, further improvement is clearly needed. Multicomponent procedures have provided sequences for handling different aspects of the smoking-cessation process; and components dealing specifically with problems in measuring baseline smoking, facilitating reduction, inducing abstinence, and managing side effects have been developed. Among the major current deficits for all approaches and programs, however, is maintenance of nonsmoking. Several suggestions have been made from a behavioral point of view. These include: (1) dealing promptly and effectively with the potential side effects of quitting (such as obesity and tension); (2) developing alternative activities to replace smoking (such as regular physical exercise or formal relaxation techniques); (3) providing a cognitive focus on mastery, self-help, and individual responsibility; and (4) adding "booster" sessions and continued interpersonal support in extended follow-up. Much more remains to be done—especially on the utilization of techniques derived from basic research, such as the extinction of conditioned craving described above.

Behavioral research may also make contributions to social policy. For example, the suggestion that nicotine plays a major or dominant role in the self-regulation of smoking raises the issue of the appropriateness of trying to persuade people to smoke low-tar, low-nicotine cigarettes. As Schachter (*42*) puts it, low-tar, high-nicotine cigarettes might be safer because fewer cigarettes would be smoked, thereby minimizing exposure to the products of incomplete combustion known to enhance the atherosclerotic process and to increase the risk of myocardial infarction (*19*). This problem could be investigated further, using a careful description of the number of cigarettes smoked and the number of puffs per cigarette (backed up with quantitative determinations of nicotine, carbon monoxide, tars, and other smoke products), to provide more exact information than is currently available from surveys of smoking in the natural environment. Finally, a greater understanding of the stimulus control of smoking and its limits may be very valuable. From a behavioral perspective, the current growing emphasis on the social unattractiveness of smoking (for example, the nonsmoker's rights movement) is helpful, because it provides a method which

administers more immediate social reinforcement for quitting and staying off cigarettes than has been possible when the focus was strictly on the health consequences of the habit. It should be noted that the effects of these social processes on the decision to quit smoking are still relatively underexplored.

Much work remains to be done in the behavioral research area. Sufficient progress has been made, however, to indicate that the development of a rational therapy for smoking based on a scientific understanding of smoking behavior and its underlying mechanisms constitutes a worthy objective.

Behavioral Factors in the Establishment, Maintenance, and Cessation of Smoking: References

(1) BERGEN, B.J., OLESEN, E. Some evidence for a peer group hypothesis about adolescent smoking. Health Education Journal 21: 113-119, 1963.

(2) BERNSTEIN, D.A., GLASGOW, R.E. The modification of smoking behavior. In: Pomerleau, O.F., Brady, J.P. (Editors). Behavioral Medicine: Theory and Practice. Baltimore, Williams and Wilkins, 1979, 50 pp. (in press)

(3) BEST, J.A., STEFFY, R.A. Smoking modification procedures for internal and external locus of control clients. Canadian Journal of Behavioral Science, 7(2): 155-165, 1975.

(4) BRADY, J.V. Learning and conditioning. In: Pomerleau, O.F. Brady, J.P. (Editors). Behavioral Medicine: Theory and Practice. Baltimore, Williams and Wilkins, 1979, 54 pp. (in press)

(5) DANAHER, B.G. Research on rapid smoking: Interim summary and recommendations. Addictive Behaviors 2(2): 151-156, 1977.

(6) ELLIOTT, R., TIGHE, T. Breaking the cigarette habit: Effects of a technique involving threatened loss of money. Psychological Record 18: 503-513, 1968.

(7) EVANS, R.I. Smoking in children: Developing a social psychological strategy of deterrence. Preventive Medicine 5: 122-127, 1976.

(8) FLAXMAN, J. Quitting smoking now or later: Gradual, abrupt, immediate, and delayed quitting. Behavior Therapy 9(2): 260-270, 1978.

(9) FREDERIKSEN, L.W., MILLER, P.M., PETERSON, G.L. Topographical components of smoking behavior. Addictive Behaviors 2(1): 55-61, 1977.

(10) FREDERIKSEN, L.W., PETERSON, G.L., MURPHY, W.D. Controlled smoking: Development and maintenance. Addictive Behaviors 1(3): 193-196, 1976.

(11) GORSUCH, R.L., BUTLER, M.C. Initial drug abuse: A review of predisposing social psychological factors. Psychological Bulletin 83(1): 120-137, 1976.

(12) GRIFFITHS, R.R., BIGELOW, G.E., LIEBSON, I. Facilitation of human tobacco self-administration by ethanol: A behavior analysis. Journal of the Experimental Analysis of Behavior 25(3): 279-292, 1976.

(13) GUILFORD, J.S. Group Treatment versus individual initiative in the cessation of smoking. Journal of Applied Psychology 56(2): 162-167, 1972.

(14) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. Environmental Research 12(3): 263-274, December 1976.

(15) HEIMSTRA, N.W., BANCROFT, N.P., DEKOCK, A.R. Effects of smoking upon sustained performance in a simulated driving task. Annals of the New York Academy of Sciences 142(Article 1): 295-307, March 15, 1967.

(16) HORN, D. A model for the study of personal choice health behavior. International Journal of Health Education 19(2): 3-12, April-June 1976.

(17) HUNT, W.A., BESPALEC, D.A. An evaluation of current methods of modifying smoking behavior. Journal of Clinical Psychology 30: 431-438, 1974.

(18) HUTCHINSON, R.R., EMLEY, G.S. Effects of nicotine on avoidance, conditioned suppression and aggression response measures in animals and man. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 171-196.

(19) JARVIK, M.E. Biological factors underlying the smoking habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph No. 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 122-148.

(20) KOZLOWSKI, L.T., JARVIK, M.E., GRITZ, E.R. Nicotine regulation and cigarette smoking. Clinical Pharmacology and Therapeutics 17(1): 93-97, 1975.

(21) KUMAR, R., COOKE, E.C., LADER, M.H., RUSSELL, M.A.H. Is nicotine important in tobacco smoking? Clinical Pharmacology and Therapeutics 21(5): 520-529, 1977.

(22) LEVENTHAL, H., CLEARY, P.D. The Smoking Problem: A Review of the Research, Theory and Research Policies in Behavioral Risk Modification. Research and Analytic Report Series. University of Wisconsin, Madison, 1977, 102 pp.

(23) LEVINSON, B.L., SHAPIRO, D., SCHWARTZ, G.E., TURSKY, B. Smoking elimination by gradual reduction. Behavior Therapy 2(4): 477-487, October 1971.

(24) LICHTENSTEIN, E., PENNER, M.R. Long-term effects of rapid smoking treatment for dependent cigarette smokers. Addictive Behaviors 2: 1-12, 1977.

(25) LUCCHESI, B.R., SCHUSTER, C.R., EMLEY, G.S. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clinical Pharmacology and Therapeutics 8(6): 789-796, 1967.

(26) MAUSNER, B. Some comments on the failure of behavior therapy as a technique for modifying cigarette smoking. Journal of Consulting and Clinical Psychology 36(2): 167-170, April 1971.

(27) MCFALL, R.M., HAMMEN, C.L. Motivation, structure, and self monitoring: role of nonspecific factors in smoking reduction. Journal of Consulting and Clinical Psychology 37(1): 80-86, 1971.

(28) MILLER, L.C., SCHILLING, A.F., LOGAN, D.L., JOHNSON, R.L. Potential hazards of rapid smoking as a technic for the modification of smoking behavior. New England Journal of Medicine 297(11): 590-592, September 15, 1977.

(29) NATHAN, P.E., O'BRIEN, J.S. An experimental analysis of the behavior of alcoholics and nonalcoholics during prolonged experimental drinking: A necessary precursor of behavior therapy? Behavior Therapy 2: 455-476, 1971.

(30) NESBITT, P.D. Smoking, physiological arousal and emotional response. Journal of Personality and Social Psychology 25(1): 137-144, 1973.

(31) O'BRIEN, C.P., TESTA, T.J., O'BRIEN, T.J. GREENSTEIN, R. Conditioning in human opiate addicts. The Pavlovian Journal of Biological Science 11(4): 195-202, October-December 1976.

(32) O'BRIEN, C.P., TESTA, T., O'BRIEN, T.J., BRADY, J.P., WELLS, B. Conditioned narcotic withdrawal in humans. Science 195: 1000-1002, 1977.

(33) PECHACEK, T.F., DANAHER, B.C. How and why people quit smoking: Cognitive-behavioral implications. In: Kendall, P.C., Hollan, S.D. (Editors). Cognitive-Behavioral Interventions: Theory, Research and Procedures. New York, Academic Press, c 1979. (in press)

(34) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study: Results of the first year. Canadian Journal of Public Health 62: 432-441, September/October 1971.

(35) POMERLEAU, O.F. Why people smoke: Current psychobiological models. In: Davidson, P. (Editor). Behavioral Medicine: Changing Health Life Styles. New York, Brunner-Mazel, 1979, 38 pp. (in press)

(36) POMERLEAU, O., ADKINS, D., PERTSCHUK, M. Predictors of outcome and recidivism in smoking-cessation treatment. Addictive Behaviors 3: 65-70, 1978.

(37) POMERLEAU, O., BASS, F., CROWN, V. Role of behavior modification in preventive medicine. New England Journal of Medicine 292: 1277-1282, June 12, 1975.

(38) POWELL, J., AZRIN, N. The effects of shock as a punisher for cigarette smoking. Journal of Applied Behavior Analysis 1(1): 63-71, 1968.

(39) RESNICK, J.H. The control of smoking behavior by stimulus satiation. Behavior Research and Therapy 6: 113-114, 1968.

(40) RUSSELL, M.A.H. Smoking problems: An overview. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on smoking behavior. NIDA Research Monograph No. 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 13-33.

(41) RUSSELL, M.A.H. Tar, nicotine, and CO yields of cigarettes. British Medical Journal 3(5982): 540, August 30, 1975.

(42) SCHACHTER, S. Pharmacological and psychological determinants of smoking. Annals of Internal Medicine 88(1): 104-114, January 1978.

(43) SCHACHTER, S., SILVERSTEIN, B., KOZLOWSKI, L.T., PERLICK, D., HERMAN, C.P., LIEBLING, B. Studies of the interaction of psychological and pharmacological determinants of smoking. Journal of Experimental Psychology: General 106(1): 3-40, 1977.

(44) SCHUSTER, C.R., THOMPSON, T. Self-administration of and behavioral dependence on drugs. Annual Review of Pharmacology 9: 483-502, 1969.

(45) SIEGEL, S. Morphine tolerance acquisition as an associative process. Journal of Experimental Psychology: Animal Behavior Processes 3(1): 1-13, January 1977.

(46) SILVERSTEIN, B. An addiction explanation of cigarette-induced relaxation. Unpublished doctoral dissertation, Columbia University, 1976, 68 pp.

(47) SOLOMON, R.L. An opponent-process theory of acquired motivation: IV. The affective dynamics of addiction. In: Maser, J.D., Seligman, M.E.P. (Editors). Psychopathology: Experimental Models. San Francisco, W.H. Freeman, 1977, pp 66-103.

(48) SOLOMON, R.L. CORBIT, J.D. An opponent-process theory of motivation: I. Temporal dynamics of affect. Psychological Review 81(2): 119-145, 1974.

(49) SOLOMON, R.L. CORBIT, J.D. An opponent-process theory of motivation: II. Cigarette addiction. Journal of Abnormal Psychology 81(2): 158-171, 1973.

(50) STEFFY, R.A., MEICHENBAUM, D., BEST, J.A. Aversive and cognitive factors in the modification of smoking behavior. Behavior Research and Therapy 8: 115-125, 1970.

(51) STEPHENS, R.M. Psychophysiological variables in cigarette smoking and reinforcing effects of nicotine. Addictive Behaviors 2: 1-7, 1977.

(52) STOLERMAN, I.P., GOLDFARB, T., FINK, R., JARVIK, M.E. Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia 28: 247-259, 1973.

(53) TERNES, J.W. An opponent-process theory of habitual behavior with special reference to smoking. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Monograph No. 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 157-185.

(54) TIME MAGAZINE. The chemistry of smoking. Time Magazine, February 21, 1977, p. 48.

(55) WIKLER, A. Dynamics of drug dependence. Archives of General Psychiatry 28: 611-616, May 1973.

(56) WIKLER, A., PESCOR, F.T. Classical conditioning of a morphine abstinence phenomenon, reinforcement of opioid-drinking behavior and "relapse" in morphine-addicted rats. Psychopharmacologia 10: 255-284, 1967.

17. SMOKING IN CHILDREN AND ADOLESCENTS: PSYCHOSOCIAL DETERMINANTS AND PREVENTION STRATEGIES.

National Institute of Child Health and Human Development

CONTENTS

Introduction

In spite of a decrease in adult smoking since the dissemination of the 1964 U.S. Surgeon General's Report on Smoking and Health, there is discouraging evidence that smoking among teenage boys is remaining virtually constant and among teenage girls it is actually increasing. It is apparent that more knowledge is needed concerning the way in which the psychosocial factors that may contribute to the initiation of smoking can be applied to the development of effective strategies to deter the onset of smoking.

It is possible that prevention programs directed at children and adolescents have generally placed too much confidence in merely communicating knowledge about the dangers of smoking. Developers of these programs may assume that such fear arousal will in itself be sufficient to thwart smoking. In fact, as will be amplified later in this chapter, by the time children reach junior high school, almost all of them believe smoking is dangerous. It appears that communications concerning the dangers of smoking whether delivered from schools, churches, voluntary agencies, mass media, the family, peers, governmental agencies, industrial organizations, consumer organizations, or labor unions (individually or collectively) have, indeed, been effective in persuading children and adolescents that smoking is dangerous. However, it is also evident that fear of the consequences of smoking may in itself not be sufficient to discourage a substantial number of children from beginning to smoke when they approach adolescence.

Some investigators in this field have contended that at an earlier level of the child's development, perhaps between the ages of 4 to 9 or 10, the child takes quite literally the dangers of smoking. In fact, it is often observed at this level of development that children may be especially worried if they observe a parent or older sibling smoking. They will admonish them to stop smoking because it "can cause cancer or a heart attack." Yet as they approach adolescence, many of these same children will begin smoking.

Responses from the teenagers themselves suggest that peer pressure to smoke may be one of the major influences. There is also some evidence that the smoking parent becomes a model for the child. If both parents smoke there is a greater likelihood that the child will begin smoking than if only one parent smokes or if neither parent smokes. But even if one parent smokes, this may influence the child to smoke more than if neither parent smokes. Interestingly, if an older sibling and both parents smoke the child is about four times more likely to smoke than if there were no smokers in the family.

The influence of the mass media in the initiation of smoking is somewhat more difficult to establish. Smokers are depicted in films and television, as well as in cigarette advertising which tends to portray them in interesting and exciting environments, suggesting that attractive, desirable people tend to smoke. This would logically be

expected to influence children and teenagers much as the media and advertising affect the behavior of adults. Yet, the relationship between exposure to the mass media and the initiation of smoking is difficult to isolate from the other concurrent influences to which the child is exposed. In fact, a variety of psychosocial influences may interact to influence some children to begin smoking.

Some investigators examining the issue of why fear arousal may often have such a limited effect on health behavior suggest that much of the information communicated to children concerning smoking and its dangers may be too general and not sufficiently personalized. Also, the suggested harmful effects of smoking in many smoking control messages violate the concept of "time perspective." As children grow older they recognize that people around them who smoke do not die instantly and that heart attacks or cancer are not a certainty. They may need to be exposed to evidence that smoking has immediate physiological effects on the body. Younger adolescents particularly live in the present and are not preoccupied with the future. Emphasizing what might happen to them when they are much older may not be an effective way to persuade many of them to resist the pressures to begin smoking.

Becoming a smoker may have the immediate value to some teenagers of being accepted by their peers, feeling more mature because smoking is an adult behavior forbidden to the child, providing a level of physiological stimulation and pleasure, and might even serve the function of an act of defiance to authority figures. The prevention programs reviewed rarely incorporate such concepts. Rather, they focus primarily on information relating to the long-term dangers of smoking.

Furthermore, too few of the prevention programs are evaluated with sufficient rigor. As a result, in the same sense that there is insufficient basic behavioral research to link clearly many psychosocial factors to the initiation of smoking in children and adolescents, it is difficult to determine if many prevention programs significantly deter the onset of addictive smoking. Even if a program results in increased knowledge concerning the long-term dangers of smoking, in the absence of valid evidence of a direct impact on the incidence of smoking itself, it is possible that many widely disseminated prevention programs are, in the long-run, of only questionable value in actually deterring smoking. All of this suggests many avenues for future research and prevention programs.

To elaborate on the various points discussed above, the sections which follow deal with current smoking patterns and beliefs, relevant conceptual models in developmental and social psychology, typical psychosocial influences in the smoking decision, critical evaluations of some current prevention programs, and finally, some recommendations for future research and prevention programs.

Current Smoking Patterns and Beliefs

While cigarette smoking in the United States for adults over age 21 has declined, there has been a growth in the amount of smoking among the pre-adult population, primarily due to a dramatic increase in smoking among teenage girls (*61*). But care needs to be exercised when interpreting the findings of the studies reported since definitions of such terms as "regular smoker," "occasional smoker," "experimental smoker," and "nonsmoker," vary from one study to the next. For example, four national surveys conducted at 2-year intervals from 1968 through 1974 by the National Clearinghouse for Smoking and Health (*61, 86*) define a current regular smoker as one who smokes one or more cigarettes per week. On the other hand, an antismoking education study conducted at the University of Illinois (*18*) defines a current regular smoker as one who smokes cigarettes just about every day. Also contributing to the ambiguity of results is the way in which the categorization of frequency of smoking is dealt with in the analysis of results. For example, in the four national surveys previously cited, experimental smokers (those who have smoked at least a few puffs but less than one hundred cigarettes) were combined with nonsmokers in the analysis of the data. Experimental smokers are extremely important and should not be neglected in data analysis since experimental smoking is obviously the initial step toward confirmed smoking (*42*).

In the four surveys (*61*) conducted by the National Clearinghouse, approximately 16 percent of the teenage population, aged 12 to 18, were current regular smokers in 1974. The rate of regular smoking for the same age group in 1968 was approximately 12 percent. In the first survey, only about half as many girls as boys regularly smoked, but by 1974 this difference had virtually disappeared. In fact, regular smoking had slightly decreased for boys from 1970 to 1974, but this decrease was easily offset by the dramatic rise in smoking by girls.

Relevant to the problem of teenage smoking is the age of initiation of smoking. A significantly larger percentage of regular smokers aged 12 to 14 were reported among teenagers in 1974 (approximately 12 percent) than in 1968 (approximately 6 percent). This increase in regular smoking at younger ages suggests that the average age of the initiation of smoking is decreasing.

Further evidence concerning the age of initiation of smoking is available from retrospective data reflecting self-estimates of onset of smoking in the Current Population Surveys of 1955 and 1966 (*1*). No analysis of age trends in smoking initiation among males was reported since the number of male respondents was low, particularly in the 1966 survey. However, the responses from the female respondents, regardless of their current age, suggest a shift in the initiation of smoking to a younger age. For example, over twice as many females, aged 18 to

24, classified themselves as regular smokers by age 15 in 1966 than did the respondents of the same age group in 1955.

In the national surveys between 1968 and 1974 (*61*) the relationship between various factors related to socioeconomic status and smoking were examined. For example, teenagers who are employed outside the home are twice as likely to smoke as teenagers who are not employed. Also, educational and vocational aspirations are related to smoking. Students who plan to go to college are the least likely to smoke. A study conducted by Borland and Rudolph (*9*) determined that socioeconomic status bears some relationship to smoking in high school students (children in lower socioeconomic levels are more likely to smoke), but socioeconomic status correlates less with smoking than parental smoking or poor scholastic performance (although all three variables are themselves correlated).

The literature fails to address adequately the initiation of pre-adult smoking. Rather, the emphasis is on "regular" smokers. Nevertheless, inferences from such data may be helpful in suggesting factors that are related to the initiation of smoking.

As would be expected, beliefs of teenagers about smoking are related to whether or not they smoke. Of course, smokers generally hold more favorable attitudes toward smoking than do nonsmokers (*65*, *75*). Nevertheless, data (*59*) suggest that even teenage smokers seldom consider the decision to smoke a wise decision. For example, 77 percent of smokers believe that it is better not to start smoking than to have to quit. Over half of the teenage smokers believe that cigarette smoking becomes harmful after just 1 year of smoking. Eighty-four percent say it is habit forming, while 68 percent agree that it is a bad habit. Of all teenagers, 78 percent believe that cigarette smoking can cause lung cancer and heart disease. Eighty-seven percent of all teenagers and 77 percent of teenage smokers believe that smoking can harm their health. The vast majority of teenagers consider smoking as habit forming, but almost two-thirds do not feel that becoming addicted to smoking is an imminent threat to their health. Experimental smoking is considered safe.

Fishbein (*34*) cites evidence from a study conducted for the American Cancer Society in 1975 which suggests that teenage smoking is perceived by teenagers as more prevalent than it actually is. Eighty-three percent of the teenagers in this survey tend to think of other teenagers as being smokers rather than nonsmokers.

Finally, it should be pointed out that knowledge or beliefs about the dangers of smoking are often confused with attitudes toward smoking (*10*). Attitudes may be much more complex than simple beliefs about the harmful effects of smoking. Various factors influencing the complexity of attitudes toward smoking are discussed in the most recent report of the four national surveys mentioned earlier (*61*). These factors include the adverse effects of smoking on the individual's

health and on the environment (pollution), the psychological and sociological benefits of smoking (e.g., "makes you feel good"), rationalizations that allow smoking, perceptions of reasons for smoking and for smoking initiation, the negative stereotypes concerning smokers, attitudes toward authority, and control over one's destiny.

In essence, when considering both current smoking patterns and beliefs among children and adolescents, the factors related to smoking can be categorized in terms of perceived psychosocial benefits versus actual threats to health. Considering this dichotomy, the suggestion of the U.S. Public Health Service (*61*) should not be ignored:

> It is futile to continue to tell teenagers that smoking is harmful and that they shouldn't do it. They know that it is harmful. Most do not *want* to do it. The most effective thing that we can do is to help them to understand the benefits of smoking as compared with the costs and dangers so that they will have the facts that they need in order to make a thoughtful decision as to whether to smoke or not to smoke (p. 27).

Relevant Conceptual Models in Developmental and Social Psychology

Understanding the factors involved in the initiation of smoking among children and adolescents is a complex endeavor demanding the utilization of diverse conceptualizations. This section will consider four representative conceptual models in developmental and social psychology that would appear to be potentially useful in generating hypotheses to account for the initiation of smoking among the young and in providing conceptual bases for prevention programs. These conceptualizations are Piaget's Cognitive Development Theory, Erikson's Theory of Psychosocial Development, Bandura's Social Learning Theory and McGuire's Persuasive Communication Model.

The Cognitive Developmental Theory of Piaget (*26*, *69*), one of the most influential cognitive theories, is concerned with the nature and origin of knowledge. Piaget's view of the development of knowledge would appear to offer some applications to understanding the informational and decisional aspects of the initiation of smoking in the developing child.

Piaget views knowledge as developing out of the individual's adaptive interaction with the environment through the processes of assimilation (incorporation of concepts into existing cognitive structures) and accommodation (modification of cognitive structures). There are four major stages of intellectual development: (1) sensory-motor period (birth to 2 years), involving simple perceptual and motor adjustments to immediate environmental phenomena; (2) preoperational period (2 to 7 years), involving a preconceptual phase (the

emergence of linguistic skills and symbol construction abilities) and an intuitive phase (the emergence of more complex thoughts, images, and classification abilities based on perceptual similarity instead of logical considerations); (3) concrete operational period (7 to 11 years), involving reversible intellectual operational ability (utilizing a mental representation of a series of actions), conservational ability (realizing that quantity remains invariant despite perceptual transformations), a clearly defined concept of class inclusion, and the ability to take the viewpoint of another; and (4) formal operational period (11 to 15 years) involving the realization that reality is but one of a set of all possibilities. Thinking in this last stage is characterized by hypothetical-deductive reasoning, combinational analysis (consideration of multiple factors), propositional and rule-governed logic, and a futuristic perspective.

Piaget's ideas, especially those dealing with developing knowledge about the physical environment, have been extensively explored, although the investigation and application of his concepts involving adaptation to the social environment have only rarely been studied. The initiation of smoking, apparently an age-related behavior, appears most often to occur within the context of social interactions. Additionally, smoking involves an important decisional component requiring the utilization of cognitive or knowledge structures.

By the time they reach the seventh grade, the vast majority of children believe smoking is dangerous to one's health (*31*). Yet despite this knowledge, many adolescents, aged 12 to 14, experiment with smoking, and roughly 4 to 5 percent will smoke regularly (weekly) (*61*). This situation suggests that "social adaptation" may override "intellectual adaptation" or knowledge. Knowledge of the dangers of smoking often motivates a preadolescent to become a crusader against smoking, while the social pressures occurring during early adolescence may outweigh the effects of this concrete knowledge. So, the individual who had been at an earlier age an antismoking crusader may become a regular smoker or at least an experimental smoker as a teenager. This conflict between knowledge of the dangers of smoking and smoking suggests the possibility of observing the development of smoking within the Piagetian framework.

One contemporary psychoanalytic developmental model of consequence is Erikson's Theory of Psychosocial Development (*24, 25*) involving eight psychosocial crises. These crises are: (1) trust vs. mistrust (0 to 1 year), (2) autonomy vs. shame and doubt (2 to 3 years), (3) initiative vs. guilt (4 to 5 years), (4) industry vs. inferiority (6 to 11 years), (5) identity vs. role diffusion (12 to 18 years), (6) intimacy vs. isolation (young childhood), (7) generativity vs. stagnation (middle adulthood), and (8) ego integrity vs. despair (later adulthood). Of particular interest with reference to the initiation of smoking are Erikson's fourth and fifth psychosocial crises.

Both the struggle to overcome inferiority and the effort to establish a self identity have been cited in one form or another by numerous researchers interested in interpreting the initiation of smoking in adolescents. For example, Erikson's "identity-crisis" in adolescence (being torn between the roles of child and adult) might be an interesting basis for explaining the apparent influence of peer pressure in the initiation of smoking, particularly if this notion were explored in some depth empirically.

A third contribution which has greatly influenced developmental and social psychology is Bandura's Social Learning Theory (*6*). Bandura's theory, which is concerned with imitative or modeling processes, would also seem to be useful in understanding the processes involved in the initiation of smoking. Social learning theory emphasizes the roles played by vicarious, symbolic, and self-regulatory processes in the acquisition of behavior. Further, this theory suggests the importance of reciprocal determination or the continuous mutual interaction between self-generated and environmental determinants in exploring human behavior. Bandura sees social learning as governed by four component processes: attention, retention, motor reproduction, and motivation or incentive.

Smoking appears to be initiated as a result of social influences or, more particularly, the imitation of models such as peers, media stereotypes, and significant adults (e.g., parents and teachers) (*27*). Considering the nature of smoking, a behavior with possible delayed aversive consequences and often more immediate social reinforcing consequences (especially for children and adolescents), it would seem that investigating smoking within the social learning paradigm would generate many useful hypotheses concerning the initiation of smoking. For example, the impact on children of the models of smoking parents or the impact of smoking adult models depicted in the mass media could be further explored in the context of social learning.

Communications models which examine information processing hold some promise for understanding the factors underlying the initiation of smoking as well as for developing more effective prevention programs. McGuire's (*53*) Communication Persuasion Model, for example, analyzes the persuasive impact of communications according to five component processes: attention, comprehension, yielding, retention, and action.

If the communicator wants the message to be accepted and acted upon, it is important to remember that individuals exposed to the message must be paying attention if communication is even to begin. Comprehension of the contents of the message is equally important. Yielding to or agreeing with the conclusions advocated in the message is vital if the communication is to have effects in the desired direction. Retention, or the maintenance of the induced agreement, is particularly important if the beliefs are to be operative when the individual is

challenged by exposure to messages countering the accepted belief. By measuring the individual's response to such challenges, a useful evaluation of the impact of the communication on the subject, the degree of yield to the message, and the amount of resulting behavioral change or action resulting from the message may be obtained. McGuire's model would appear to be useful in both preparing and evaluating communications related to smoking prevention programs for children.

One of the most interesting aspects of McGuire's model is his "inoculation" approach to attitude change. McGuire suggests that existing attitudes may be strengthened by inoculating individuals against counter arguments to which they may be exposed. The application of this model to the pressures to initiate smoking would consist of "inoculating" adolescents against the social pressures to smoke which they may encounter at some future time. For example, Evans, et al. (*31*), using this approach in filmed messages, acquaint adolescents with the nature of the various social pressures to smoke. In a second film, they are inoculated against these pressures by being presented coping "strategies" based on information obtained from adolescents themselves. Further variations of such an inoculation approach would appear to be a promising means of relating a concept in social psychology to the deterrence of smoking in children and adolescents.

Typical Psychosocial Influences on the Smoking Decision

As mentioned earlier, despite extensive educational efforts, the onset of smoking in school-aged children continues relatively unabated, with age and grade level at which smoking begins reflecting a downward trend from high school and junior high school into the elementary grades (*61*). This trend has been reported consistently in the literature (*18*, *29*, *84*) and has grown at such an alarming rate that Kelson, et al. (*46*) refer to it as "the growing epidemic." It is generally agreed that the most effective way to attack the problem would be to influence children not to initiate smoking (*29*, *88*). Developing strategies of deterrence is dependent upon identifying those influences that lead children to begin smoking. While not all influences have been identified, many of them can be discerned in the literature related to children and smoking. Predictably, the influences most frequently cited include the role of the family, pressures from peer groups, formal education programs, and the effects of messages transmitted through the mass media. To a lesser extent, studies that explore the influences of individual differences and environmental factors have been reported.

Changing Sex Roles

As mentioned earlier, the disappearance of differences between the incidence of smoking of boys and girls is quite apparent (*61*). The reasons for these differences are not clearly established. Possible explanations, such as a differential impact of antismoking messages on the two sexes, have not yet been empirically demonstrated. Another possibility is that many social differences between the sexes are gradually disappearing in the light of the women's movement. A third possibility derives from the finding that smoking by teenage girls may have been perceived as more socially acceptable in 1974 than in 1968. This may have resulted in more honest self-reports of smoking; so instead of teenage girls actually smoking more, a more accurate indication of smoking by girls was being recorded.

Parental Smoking Habits

Parents who smoke clearly influence the smoking behavior of their children. In families where both parents smoke, 22.2 percent of the boys and 20.7 percent of the girls are also smokers, compared to 11.3 percent and 7.6 percent where neither parent smokes (*61*). These proportions have remained consistent over time. Merki (*55*) lists parental smoking habits as a major factor directly related to smoking by junior and senior high school students. Wohlford (*89*) uses identification theory to predict a direct relationship between parent and child smoking behavior. This relationship appears to be stronger for boys than for girls, a finding Wohlford attributes to stronger peer influences relative to smoking for girls. A recent American Cancer Society study (*58*) seems to confirm this notion. Borland and Rudolph (*9*) indicate that parental smoking is the second best predictor of smoking behavior in high school students. Palmer (*68*) reports similar findings for junior high school students. Edson (*23*) discusses both parental modeling and children's efforts to combat parental smoking as a result of the School Health Curriculum Project. Evans, et al. (*31*), in a smoking-deterrence investigation, incorporate a positive message for coping with parental smoking models, emphasizing that children can resist the pressure to imitate parents who smoke. Programs designed to educate parents who smoke on how they may be influencing their children to smoke should be considered important components of prevention programs. Also, research should be encouraged to examine the precise effects on the child of the smoking parent.

Parental Acceptance of Children's Smoking

While parental approval of smoking has been suggested as a contributing factor in influencing children to smoke, Allegrante, et al. (*3*) do not find parental approval to be a signficant factor, confirming Williams' (*88*) earlier conclusion that both smoking and nonsmoking

junior high students report that their parents disapprove or would disapprove of their smoking.

Siblings Who Smoke

Although Piper, et al. (*70*) report no significant relationship between older siblings and the smoking behavior of the subjects in their longitudinal study, two major surveys (*61, 88*) implicate the smoking behavior of older siblings as a possible influence on younger children. Twenty-eight to thirty percent of the boys and 25 to 26 percent of the girls who report regular smoking also have older siblings who smoke. If an older sibling and both parents smoke, the child is four times as likely to smoke as a child who has no smoking model in the family (*61*). Williams also reports the lowest incidence (4.2 percent) of smoking in those children who live in a household where neither parent smokes and where there are older siblings, none of whom smoke.

Rebellion Against Family Authority

While cigarette smoking as a form of rebellion against family and adult authority has not received much attention in the literature, a recent survey (*42*) indicates that smoking among teenage girls may reflect rebellious, anti-authority behavior.

Peer Pressures

Peer pressure is widely assumed to be a significant causal factor in the initiation of smoking. The strong influence of peer group pressures is generally evident in young adolescents (*38, 78*), but the precise relationship of such pressure to the initiation of smoking is more difficult to establish.

In an intensive participant-observation study of ninth-grade students with a follow-up 2 years later, Newman (*64*) reports that peer pressure and conformity to group status norms were perceived by subjects to be major factors in smoking. The relationship was not as strong when the subjects were in the 11th grade, but was significantly different at both grade levels (*63*). A survey by Palmer (*68*) of more than 3,000 junior high school students finds that the prevailing peer model to be the single most important variable contributing to the onset of smoking in this age group.

In a longitudinal study of Canadian school children, Matthews (*51*) finds that peer influence was a major factor in the initiation of smoking in the population surveyed. The influence of peers seems to come from "best friend" relationships, rather than from large or diversified group pressure. In a multivariate study of correlative factors in youthful cigarette smoking, Levitt and Edwards (*50*) report that having a best friend or group of friends who smoke appears to be the best predictor of smoking in children from the 5th through the 12th

grade. Bynner (*13*) finds the most important variable in explaining smoking behavior in English and Welsh schoolboys is the number of their friends who smoke. Williams (*88*) reviews a substantial number of studies which also conclude that pressures from peers and best friends are important influences to smoke.

In prevention programs, Newman (*63*) cautions against the utilization of nonsmoking student models whose general characteristics differ from those of the target population. The use of such models may alienate the target population against the antismoking message. Evans (*27, 31*) approaches the peer-pressure problem by presenting strategies for resisting peer pressure as filmed-sequence roles played by students selected from the target population.

School Environment

Specific school health education programs are addressed comprehensively in other chapters in this report. The dominant role of the school in the life of children and adolescents suggests the importance of the school environment in providing influences guiding the smoking decisions of children. Two important recommendations specified by the American Association for Health, Physical Education, and Recreation (*4*) are for schools to accept the responsibility for providing smoking education programs and for teachers and other school personnel to implement these programs.

The role of teachers, health professionals, and other adult role models as exemplars for the young is examined by a number of researchers (*16, 62, 80*). It may be important that such adult role models make positive statements related to their position on smoking. For example, teenagers perceive teachers as likely to be smokers (*42*). Sixty-eight percent of the girls and 67 percent of the boys judge most teachers to be smokers. A recent American Cancer Society survey (*5*) states that only 23 percent of female teachers and 18 percent of male teachers actually smoke. Such a difference in actual and perceived smoking behavior indicates a lack of communication in an area that could be critical in influencing the smoking decision in children and young adolescents.

Mass Media

In a Task Force Report on Respiratory Diseases, the National Institutes of Health (*60*) states that mass media have been used extensively in antismoking efforts, but exactly how they influence behavior is unclear. Ward (*87*) reports that, in a study designed to ascertain attitudes toward television commercials and to analyze the effects of television advertising on adolescents, the television medium appears to influence the formation of ideas and attitudes, yet does not "trigger" adolescents to buy a product. Ward's study indicates that cigarette ads are perceived by teenagers as hypocritical and are listed

as "least-liked" while antismoking ads are perceived as "straightforward" and are liked. The effects of messages in other media, such as billboards, magazines, and displays need to be more precisely studied. Mendelsohn (*54*) concludes that, in general, current mass media efforts to educate the public concerning health issues are disappointing. It is possible that because of cognitive and social differences in various development stages of children and adolescents, mass communications may not be the most appropriate means to reach children and adolescents with smoking-deterrence messages. More specifically, targeted communications might be better presented in selected target situations.

Individual Characteristics

The notion of being able to identify potential smokers has been an elusive goal for researchers. There are very few investigations relating personality variables to teenage smoking. Smith's (*79*) review of 35 personality and smoking studies found only four related to teenage smoking. After a search of the literature related to personality variables that may influence the initiation of smoking, Williams (*88*) concludes that "both the empirical results of previous studies and discussions of the state of the art of research into personality correlates suggest that personality will not provide the most fruitful approach to understanding why children do or do not take up cigarette smoking" (p. 15). There appears to be some agreement that personality is more related to the amount smoked than to who will begin to smoke (*17, 52, 85*).

Individual differences in smoking are related to variables such as age-in-grade, achievement in areas important to the young person, social involvement, and participation in organized activities. Creswell, et al. (*18*), and Laoye, et al. (*48*) find that student educational expectations are related to their smoking behavior. Creswell, et al. (*18*) also find some support for a relationship between above average modal age and smoking behavior. They find smoking to be perceived as a compensatory behavior for students who had not achieved success in more traditional roles. Hasenfus (*37*) postulates that children and young people may begin smoking out of a normal curiosity, but soon come to view smoking as a coping behavior similar to adult usage. Bergin and Wake (*7*) state that teenage smoking appears to be triggered by changes in living habits such as changes in residence, absence of a parent, or matriculation in a university. No conceptual framework or organized line of research has systematically guided the research related to individual characteristics in the initiation of smoking, and the literature reflects the patchwork quality of the existing knowledge.

Perceptions of Dangers of Smoking

A recent trend in smoking and health research involves an attempt to identify and modify perceptions on the part of children and adolescents of the dangers of smoking. Evans, et al. (*29*) suggest that fear-based smoking-deterrence messages to this age group, enumerating the future costs of smoking—heart disease, lung cancer, and other serious diseases or death—are often ineffective because most children and young adolescents are more present- than future-oriented. They find it difficult to perceive such future dangers as meaningful or even important. Studies designed to communicate the immediate physiological effects of cigarette smoking on healthy young people (*35, 77*) may help to make the health dangers more immediate and compelling. Filmed demonstrations comparing teenage smokers and nonsmokers by the nicotine in their saliva, the carbon monoxide in their breath, and their heart function are components of the 3-year longitudinal study by Evans, et al. (*31*).

Critical Evaluations of Some Current Prevention Programs

Several reviewers (*29, 34, 67*) point out the serious limitations that exist in evaluating research in this area. A lack of common definitions of smoking behavior, reliance on self-reporting and lack of objective measures of smoking, attrition rates in long-term studies, inappropriate statistical analyses, biased sampling errors inherent in using available volunteer populations, and lack of appropriate control groups are major limitations of the vast majority of the studies reviewed. The results of such studies must thus be viewed with caution.

Most smoking prevention programs have not been specifically directed at children and adolescents who logically should be the key target of such programs. Rather, they have been general public information campaigns conducted by private and governmental agencies, such as the American Heart Association, the American Cancer Society, and the U.S. Public Health Service. Various in-school educational programs incorporating information concerning the health hazards of smoking into course curricula and special programs with certain unique features have also been instituted.

Public Information Campaigns

Major criticisms are leveled at many public information smoking-prevention campaigns. Too often these programs fail to build in adequate evaluations. Also, they tend to be notional and atheoretical. Content and persuasive strategies in these campaigns are too often arbitrarily chosen, based on subjective judgment, rather than being systematically pretested. Bradshaw (*11*) reviews 14 public educational campaigns between 1960 and 1970 involving local communities, schools, and universities in both the United States and the United Kingdom. He

concludes that the effects of these campaigns on smoking behavior have been minimal at best with many producing no apparent effect. The failure to conduct adequate follow-up evaluations and to include comparison control groups in studies carried out are among other criticisms made of these campaigns. Recognizing the many limitations of these campaigns, Bradshaw calls for more systematically developed communications which can become the basis of widely disseminated programs to deter young people from acquiring the smoking habit.

Public information campaigns aimed at prevention can also be criticized for failing to evaluate the program's impact over extended periods of time. For example, Fishbein (*34*), in a recent report to the Federal Trade Commission, indicates that at the present time we do not have enough information about the beliefs, attitudes, and intentions already held by the public with respect to smoking decisions (i.e., to initiate, reduce, increase, or stop) or information regarding the degree to which these decisions are under attitudinal or normative control. Fishbein suggests that this information is necessary in order to develop communication materials of all kinds that would contain the most appropriate arguments for affecting a given smoking decision. Concluding his report, he states that "Although there is much that could be done immediately to inform the public, much more research is necessary if one wishes to maximize the likelihood that information will also influence a smoking decision" (p. vi).

Most critically, public information campaigns directed at prevention of smoking have been too broadly targeted. They have not reflected the beliefs, attitudes, and intentions held by what should be the prime target for prevention programs: children and adolescents. As mentioned earlier, such campaigns must take into consideration the specific developmental level of the child or adolescent. Evans, et al. (*31*), for example, find that older adolescents may respond to different smoking prevention messages than younger adolescents.

School Programs

The majority of school programs are preventive in intent, whether they are oriented toward exploring generic research issues or are merely single classroom demonstrations of so called "hands-on" programs designed to illustrate some specific aspect of smoking.

Unfortunately, the vast majority of such programs possess methodological shortcomings, particularly in evaluation designs. Many of the reports of these programs fail to present the documentation necessary for the most rudimentary evaluation by the reader. It should be noted, however, that much of the literature related to children and smoking is found in publications that may not require or encourage reports which are carefully detailed and which include rigorous evaluations.

Many of these reports are anecdotal or descriptive in nature or are offered merely as guidelines for curriculum planning and implementa-

tion. Such a morass of programs reported so loosely cannot be compared within any theoretical framework. This leads to frequent repetition of efforts. It appears that in school smoking-prevention programs, the "wheel" is regularly reinvented. Since a critical evaluation of most school programs is thus virtually impossible, at least some observations concerning current school programs will be presented and the implications of these observations for planning more rigorously evaluated programs will be discussed.

In a recent review, Thompson (*84*) expresses a general cynicism concerning the effectiveness of school programs. She further states that multimethod campaigns and youth-to-youth programs are generally ineffective. Terry and Woodward (*82*) report that relatively few teachers are trained as health educators, and Chen and Rakip (*15*) find serious problems in teacher implementation of programs on smoking and health. Teachers themselves often express a lack of confidence in their ability effectively to implement smoking education programs. This inability may be reflected in Levitt's (*49*) survey of 50,000 Indiana school children, in which less than 1 percent of the students indicate receiving information about smoking in school health classes. A comprehensive program for teacher training, at the preservice and inservice levels, in evaluating and implementing smoking and health programs is an area where effective action could be taken based on present knowledge and research.

One promising trend involves preplanned longitudinal, comprehensive studies in school settings carried out by large institutions (e.g., universities) with a strong commitment to evaluation. The pressure to produce immediate and specific effects on smoking is somewhat lessened because they are being carried out in the context of long-range evaluation. Thus the investigator has the opportunity to design conceptually sound projects based on sophisticated models. Such studies are also fruitful in producing spinoff studies that test specific hypotheses, pinpoint effects, and eliminate unworkable approaches. Stringent preplanned evaluation is an integral part of the best of these in-school programs. While such long range programs, implemented and evaluated over substantial periods of time, are both costly and difficult to manage scientifically and logistically, the data produced may have important implications for developing systematic theoretical concepts and in generating new research. Such studies may come closer to isolating the complex social, physiological, and psychological factors that underlie the smoking phenomenon. Generally, such programs are carried out so that the community continues to benefit from the program after its completion, since it provides pretested and evaluated materials for incorporation into school curricula.

One of the best known of the longitudinal, comprehensive studies is the National Clearinghouse for Smoking and Health's School Health Curriculum Project (based on the so-called Berkeley model) that has

been introduced into more than 200 school districts in 28 States. The curriculum is based on results of empirically tested concepts related to communicating health knowledge to children, including information about smoking. It is being implemented in programs from kindergarten through seventh grade at the present time. Evaluation components of the program are just now beginning to yield results. In the smoking area, a substantial relationship between enrollment and nonenrollment in the program and smoking knowledge and behavior has been claimed (*58*). However, a careful inspection of the quasi-experimental study on which that assertion is based reveals only small inconsistent differences (*56*). Detailed descriptions of the implementation of this program are given by Edson (*23*), Caramanica, et al. (*14*), and Albino and Davis (*2*). (The School Health Curriculum Project is discussed more fully in another chapter in this report.)

The University of Illinois Antismoking Education Study (*19, 20*) has been underway for more than a decade. It has produced several smoking-measurement instruments that have been used in a number of smoking studies. These instruments incorporate informational, attitudinal, and self-report behavioral components but have not been validated against more objective measures of actual smoking.

The Illinois Antismoking Education Study generated several kinds of studies which address themselves to evaluating various in-school approaches to control smoking. For example, in one study, Irwin, et al. (*41*) examine the relative impact of the regular classroom teacher as a smoking information communicator compared with teachers especially trained in health communication. Although they find that the classroom teacher was at least as effective as the specially trained teacher, more recent studies (*82*) do not necessarily support this conclusion. An intention-to-smoke measure was also developed as a result of the Illinois study. Using this measure, Laoye, et al. (*48*) find that a 2-year projection of smoking could be successfully demonstrated. Merki, et al. (*55*) explore smoking behavior of rural high school students and find that student smoking is related to parental smoking habits, participation in school group activities, and lower educational aspirations. From a 9-month participant-observation study, Newman (*63, 64*) concludes that both covert and overt smoking are low-status activities for ninth grade girls and overt smoking is a low-status activity for boys. (The Illinois study is also described more fully elsewhere in another chapter in this report.)

In Houston a 3-year longitudinal study reported by Evans, et al. (*31*) is being undertaken. It is designed to train junior high school students to resist the pressures to smoke from peers, the media, and models of smoking parents. Also involved in this study are interventions that monitor smoking and those that communicate immediate physiological effects of smoking. A nicotine-in-saliva measure is employed to increase the validity of self-reports of smoking. A major purpose of the

study is to explore the feasibility of incorporating into school health programs inoculations-against-social-pressures-to-smoke messages in lieu of the frequently used fear-arousal, impersonal, information-centered communications. Preliminary results indicate that such intervention strategies, based on the use of films whose content is derived from feedback from students themselves, may be effective with some students in deterring the onset of addicted smoking, although the final results await the completion of the final years of the investigation. Also, further replications of this general approach to thwarting smoking behavior in adolescents, using either films or more personalized interventions, are being undertaken at Stanford (Cheryl Perry), the University of Minnesota (C. A. Johnson), Tyler, Texas (Richard Evans), and elsewhere.

General Comments

Obviously, the psychosocial factors that influence the initiation of smoking are varied and complex. Aside from a few promising prevention programs, most of them fail to encompass psychosocial conceptual frameworks. Obviously, there is also a great need for such programs to be more carefully planned, controlled, and evaluated.

Fodor, et al. (*36*) propose that educational programs that deal with the totality of man as a complex being offer the most promise. "Smoking education must, in fact, become health education, taking into consideration the multiplicity of factors related to smoking and health—physical, mental, and social" (p. 94). Rabinowitz and Zimmerli (*72*) recognize the complex, long-range problem:

> What seems most crucial for future health education planning.....is that a 'one-size-fits-all' approach is contraindicated to student health teaching in terms of message content, structure, and perhaps, classroom delivery. To achieve comparable outcomes it may be essential that several distinct approaches to smoking education be explored for social subgroups with demonstrably different backgrounds of exposure, involvement, and maturation (p. 330).

The best efforts at present appear to possess at least some conceptual basis, are long-term, multiphasic studies attempting to establish good baseline data, develop and test specific hypotheses using carefully controlled methods of investigation, employ objective measures of smoking to validate self-reports, and include evaluations of the program through several years of implementation.

The ideal prevention program would follow the example of Sweden (*76*) where a 25-year effort has begun whose objective is to make those born in 1975 a nonsmoking generation. The program began in 1974 with expectant parents and is presently concentrating on withdrawal clinics and other measures to develop a nonsmoking environment for those children born in 1975. Educational efforts for adults and children

and increased governmental control over advertising and marketing of tobacco products are being implemented, and an all-out effort is being made to create a nonsmoking generation in a nonsmoking environment, supported by both governmental efforts and the general public.

Some Recommendations for Future Research and Prevention Programs

Although recommendations for future research and prevention programs logically emerged in several earlier sections of this chapter, some additional recommendations may be in order. Most of the current research concerning psychosocial determinants of smoking in children and adolescents tends to be correlational in nature. Because of the limited amount of variance accounted for, it is difficult to establish a precise linkage between any given psychosocial influence and the initiation of smoking. Just as Jessor and Jessor (*43*) have found with respect to the use of other drugs, it is likely that an array of social influences precipitates the onset of smoking. What may be needed now is the selection of some of these specific influences for particular attention. For example, the influence of the mass media on smoking initiation, which currently appears to be uncertain, might be better understood through a series of small, well-controlled basic investigations. The results of such investigations should be interpreted within the context of the broader impact of the mass media on the behavior of children and adolescents to avoid the criticisms leveled at how the research concerning violence and television was conducted. Additionally, just as the focus in the area of television or films and behavior has shifted from exploring how they precipitate antisocial behavior to how they may encourage prosocial behavior (*6*), some of these investigations should also examine how the mass media have perhaps inadvertently contributed to the child's decision *not* to begin smoking, or to quit before he or she has become a confirmed smoker. Perhaps the use of mass media to counter prosmoking influences should also be further explored. A similar approach might be used to explore more explicitly how to counteract the impact of social pressures in the initiation of smoking (*27, 31*).

Lacking in most of the investigations reviewed is an adequate conceptual base. As discussed earlier, certain types of major conceptual models in developmental and social psychology have gone virtually unexplored as a source of hypotheses for research in the area of smoking in children and adolescents. Many other current conceptual directions in psychology could well be explored as they relate to smoking. The theory of cognitive dissonance (*33*), Fishbein's belief-behavior concepts (*34*), Kohlberg's theory of moral development (*47*), impression formation (*81*), attribution theory (*44, 45*), decision-making in children (*12*), Jessor and Jessor's multi-determinant conceptual

structure of problem behavior (*43*), and the concept of risk-taking (*21*) are all examples of theoretical areas that might generate some testable hypotheses in this area of smoking.

Still another important area of research would be to explore the interrelationship of the initiation of smoking in children with other health behaviors. For example, some provocative studies (*8, 40*), though not confirmed by other studies such as O'Donnell's (*66*), suggest that smoking may be a "drug entrance ticket." Children who begin smoking are more likely to begin using alcohol and hard narcotics. Certainly, a careful examination of such types of health-behavioral interrelationships would be a crucial area of research. Likewise, how does smoking relate to the over-all lifestyle of the developing child? A look at the "natural development" of the smoker, perhaps even completing a few studies, such as those the Jessors (*43*) have done with drug usage, which examine very small samples of children over time, might generate a number of significant hypotheses.

However, as is being demonstrated in at least one current investigation (*31*), useful intervention programs might already be developed which may have a better chance of having a long-term impact on the smoking behavior of adolescents than the largely fear-arousal, impersonal, information-oriented approaches generally used. Virtually all investigations in this area report that adolescent smokers and nonsmokers alike really believe that smoking is potentially dangerous to one's health (*34*). Obviously, this fear does not appear to be enough to deter the onset of smoking or to be sufficiently successful in motivating smokers to stop (*31*). Therefore, other types of emphases in prevention programs should be developed. Such intervention programs should apply the method of successive approximation. At each step of the way, the target population of children or adolescents should provide input into the content of the intervention within the context of an appropriate psychosocial, conceptual framework. All intervention materials should be pretested on the children.

Whatever the content of the intervention program, great care should be taken to plan and utilize an adequate evaluation methodology. Failure to incorporate rigorous evaluation procedures emerges as a significant limitation of virtually all of the intervention programs reviewed. One particularly troublesome problem in evaluation methodology deals with the appropriate criterion for the impact of a program. Measures of information about smoking, attitudes towards smoking, or self-reports of smoking may not be adequate indicators of a program's impact. Serious questions are raised in contemporary social psychological literature (*30, 32*) concerning the relationship between information gain and attitude change and behavior. It would be most unfortunate to conclude that a demonstration of the presence of increased information about smoking dangers or an attitude change toward smoking has necessarily had a significant impact on smoking behavior.

Furthermore, as smoking among children and young adolescents is a taboo and socially unacceptable behavior in many social settings (e.g., in schools), self-reports of smoking may be inaccurate.

The majority of the investigations reviewed, whether they are examinations of psychosocial factors, surveys, smoking informational campaigns, or in-school educational programs, rely heavily upon self-report measures of smoking. Investigators (*73*) in the behavioral science literature describe the existence of an acquiescience or interpersonal expectation effect; that is, subjects report what they believe the experimenter expects whether or not it is a true reflection of their actual behavior. Dunn (*22*) questions how much credence can be given to the introspective reports of smokers. He states: "Factors such as the need for social approval of opinions and actions, the need to justify a preference commitment, order of presentation effects, brand imagery effects, halo effects, and the yea-saying tendency are collectively more determinative of a report of a smoke-induced sensory experience than is the sensory experience itself" (p. 98). Although this statement refers principally to self-reports of motivational factors in smoking, many of the same points can be applied to questioning the validity of self-reports of smoking itself.

Obviously, measures of smoking behavior that are more objective than self-reports of smoking are vital for a valid evaluation of programmed treatments. One such measure has been reported (*28, 31*). This involves the use of a procedure which appears to increase the validity of self-reports of smoking behavior. A mass spectrometric analysis of nicotine-in-saliva (*39*) is used to increase the validity of self-reports. Films depicting this analysis procedure are shown to students before they have produced a saliva specimen and before they are requested to record self-reports of their smoking behavior. This results in significantly more reports of smoking. Other investigators (*74*) are exploring the use of chemical indicators of smoking. However, using only direct chemical indicators as the major dependent measures may be too costly or may only be recording recent smoking. For example, nicotine, because of its "half-life" when measured in the blood, records smoking for only a very brief period (*28*). Developing improved techniques for more direct measurement of smoking is clearly an important area for future investigations.

Finally, future research and prevention programs should address themselves to the problem of establishing a truly long-term impact. Many smoking prevention programs often report optimistic success rates. The reporting of such success rates should be qualified by the possibility of the individual beginning to smoke at some later time. Inferences about the evolution of smoking suggest that by the end of the ninth grade very few adolescents are confirmed smokers. The critical level of the onset of confirmed smoking appears to be in high school (*88*). Therefore, the true impact of any deterrence-of-smoking

program with adolescents may not even be measurable until after the adolescent has entered high school. This problem is not unlike the backsliding or recidivism encountered in virtually all smoking cessation programs (*71, 83*).

Thus, in recommendations for future research and in the development and implementation of prevention programs with children and adolescents, the range of possibilities appears vast. Perhaps with a focus on the initiation of smoking, much critical new knowledge of the developing life style of children and adolescents will also emerge. Surely, smoking must be regarded within the total context of the individual's development. Perhaps the real question to be answered is: why do we knowingly choose to engage in self-destructive behavior when so much of our energy is directed toward preserving our lives?

Smoking in Children and Adolescents: Psychosocial Determinants and Prevention Strategies: References

(1) AHMED, P.I., GLEESON, G.A. Changes in Cigarette Smoking Habits Between 1955 and 1966. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, PHS Publication No. 1000, Series 10, No. 59, April 1970, 33 pp.

(2) ALBINO, J., DAVIS, R. A health education program that works. Phi Delta Kappan 57(4): 256-259, 1975.

(3) ALLEGRANTE, J.P., O'ROURKE, T.W., TUNCALP, S. A multivariate analysis of selected psychosocial variables on the development of subsequent youth smoking behavior. Journal of Drug Education 7(3): 237-248, 1977-1978.

(4) AMERICAN ASSOCIATION OF HEALTH, PHYSICAL EDUCATION, AND RECREATION. Smoking education: The school's responsibility. Journal of School Health 41: 444-445, October 1971.

(5) AMERICAN CANCER SOCIETY. A Study of Public Schools Teachers' Cigarette Smoking Attitudes and Habits. American Cancer Society, August 1976, 77 pp.

(6) BANDURA, A. Social Learning Theory. Englewood Cliffs, New Jersey, Prentice-Hall, Inc., 1977, 247 pp.

(7) BERGIN, J.I., WAKE, F.R. Report to the Department of National Health and Welfare on Canadian Research on Psycho-Social Aspects of Cigarette Smoking: 1960-1972. Canadian Department of National Health and Welfare, 1974, 71 pp.

(8) BLOCK, J.R. Behavioral and demographic correlates of drug use among students in grades 7-12. In: Lettiere, D.J. (Editor). Predicting Adolescent Drug Abuse. National Institute on Drug Abuse, 1975, pp. 263-276.

(9) BORLAND, B.L., RUDOLPH, J.P. Relative effects of low socio-economic status, parental smoking and poor scholastic performance on smoking among high school students. Social Science and Medicine 9(1): 27-30, 1975.

(10) BOYLE, C.M. Some factors affecting the smoking habits of a group of teenagers. Lancet 2: 1287-1289, December 14, 1968.

(11) BRADSHAW, P.W. The problem of cigarette smoking and its control. International Journal of Addiction 8: 353-371, 1973.

(12) BRUNER, J.S. Beyond the Information Given. New York, W.W. Norton, 1973, 502 pp.

(13) BYNNER, J.M. The Young Smoker. Government Social Survey. London, Her Majesty's Stationary Office, 1969, 269 pp.

(14) CARAMANICA, V.P., FEILER, E.G., OLSEN, L.K. Evaluation of the effects of performance based teacher education on the health knowledge and attitudes of fifth grade students. Journal of School Health 44(8): 449-454, October 1974.

(15) CHEN, T.L., RAKIP, W.R. Are teachers prepared to implement smoking education in the schools? Journal of School Health 44(8): 438-441, October 1974.

(16) CHEN, T.L., RAKIP, W.R. The effect of the teachers' smoking behavior on their involvement in smoking education in the schools. Journal of School Health 45(8): 455-461, October 1975.

(17) CLAUSEN, J.A. Adolescent antecedents of cigarette smoking: Data from the Oakland growth study. Social Science and Medicine 1(4): 357-382, 1968.

(18) CRESWELL, W.H., JR., HUFFMAN, W.J., STONE, D.B. Youth Smoking Behavior Characteristics and Their Educational Implications. A Report of the University of Illinois Anti-Smoking Education Study, Champaign, University of Illinois, June 30, 1970, 164 pp.

(19) CRESWELL, W.H., JR., HUFFMAN, W.J., STONE, D.B., MERKI, D.J., NEWMAN, I.M. University of Illinois anti-smoking education study. Illinois Journal of Education 60: 27-37, 1969.

(20) CRESWELL, W.H., JR., STONE, D.B., HUFFMAN, W.J., NEWMAN, I.M. Anti-smoking education study at the University of Illinois. Health Service and Mental Health Administration. Health Reports 86: 565-576, 1971.

(21) DION, K.L., BARON, R.S., MILLER, N. Why do groups make riskier decisions than individuals? In: Berkowitz, L. (Editor). Advances in Experimental Social Psychology, Volume 5. New York, Academic Press, 1970, pp. 305-377.

(22) DUNN, W.L., JR. Experimental methods and conceptual models as applied to the study of motivation in cigarette smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 93-111.

(23) EDSON, L. Schools attacking the smoking problem. American Education 9(1): 10-14, January/February 1973.

(24) ERIKSON, E.H. Childhood and Society. New York, W.W. Norton and Company, 1963, 445 pp.

(25) EVANS, R.I. Dialogue with Erik Erikson. New York, Harper and Row, 1967, 142 pp.

(26) EVANS, R.I. Jean Piaget: The Man and His Ideas. New York, E.P. Dutton and Company, 1973, 189 pp.

(27) EVANS, R.I. Smoking in children: Developing a social psychological strategy of deterrence. Journal of Preventive Medicine 5: 122-127, 1976.

(28) EVANS, R.I., HANSEN, W.E., MITTELMARK, M.B. Increasing the validity of self-reports of smoking behavior in children. Journal of Applied Psychology 62(4): 521-523, 1977.

(29) EVANS, R.I., HENDERSON, A.H., HILL, P.C., RAINES, B.E. Current psychological, social and educational programs in control and prevention of smoking: A critical methodological review. Atherosclerosis Reviews. (In press)

(30) EVANS, R.I., ROZELLE, R.M., LASATER, T.M., DEMBROSKI, T.M., ALLEN, B.P. Fear arousal, persuasion, and actual versus implied behavioral change: New perspective utilizing a real-life dental hygiene program. Journal of Personality and Social Psychology 16(2): 220-227, 1970.

(31) EVANS, R.I., ROZELLE, R.M., MITTELMARK, M.B., HANSEN, W.B., BANE, A.L., HAVIS, J. Deterring the onset of smoking in children: Knowledge of immediate physiological effects and coping with peer pressure, media pressure, and parent modeling. Journal of Applied Social Psychology 8: 126-135, 1978.

(32) EVANS, R.I., ROZELLE, R.M., NOBLITT, R., WILLIAMS, D.L. Explicit and implicit persuasive communications over time to initiate and maintain behavior change: New perspective utilizing a real-life dental hygiene situation. Journal of Applied Social Psychology 5(2): 150-156, 1975.

(33) FESTINGER, L. A Theory of Cognitive Dissonance. Stanford, California, Stanford University Press, 1957, 291 pp.

(34) FISHBEIN, M. Consumer beliefs and behavior with respect to cigarette smoking: A critical analysis of the public literature. In: Federal Trade Commission. Report to Congress: Pursuant to the Public Health Cigarette Smoking Act. For the year 1976. Washington, D.C., May 1977, 113 pp.

(35) FODOR, J.T., GLASS, L.H. Curriculum development and implementation of smoking research: A longitudinal study. Journal of School Health 41(4): 199-202, April 1971.

(36) FODOR, J.T., GLASS, L.H., WEINER, J.M. Smoking behavior, cognitive skills and educational implications. Journal of School Health 38: 94-98, 1968.

(37) HASENFUS, J.L. Cigarette and health education among young people. Journal of School Health 41: 372-376, 1971.

(38) HILL, D. Peer group conformity in adolescent smoking and its relationship to affiliation and autonomy needs. Australian Journal of Psychology 23(2): 189-199, August 1971.

(39) HORNING, E.C., HORNING, M.G., CARROLL, D.I., STILLWELL, R.N., DZIDIC, I. Nicotine in smokers, non-smokers and room air. Life Science 13(10): 1331-1346, 1973.

(40) HRANCHUK, K.B., CHRISTIE, D., HRANCHUK, M., KENNEDY, C. Psycho-Social Aspects of Cigarette Smoking, 1972-76. Ottawa, Ontario, Canadian Council on Smoking and Health, March 1, 1978, 217 pp.

(41) IRWIN, R.P., CRESWELL, W.H., JR., STAUFFER, D.J. The effect of the teacher and three different classroom approaches on seventh grade students' knowledge, attitudes and beliefs about smoking. Journal of School Health 40(7): 355-359, September 1970.

(42) JARVIK, M.E., CULLEN, J.W., GRITZ, E.R., VOGT, T.M., WEST, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, 383 pp.

(43) JESSOR, R., JESSOR, S.L. Problem Behavior and Psychosocial Development. A Longitudinal Study of Youth. New York, Academic Press, 1977, 281 pp.

(44) JONES, E.E., DAVIS, K.E. From acts to dispositions: The attribution process in person perception. In: Berkowitz, L. (Editor). Advances in Experimental Social Psychology, Volume 2. New York, Academic Press, 1965, pp. 219-266.

(45) KELLEY, H.H. Attribution in Social Interaction. Morristown, New Jersey, General Learning Press, 1971, 26 pp.

(46) KELSON, S.R., PULLELLA, J.L., OTTERLAND, A. The growing epidemic. A survey of smoking habits and attitudes toward smoking among students in grades 7 through 12 in Toledo and Lucas County (Ohio) Public Schools—1964 and 1971. American Journal of Public Health 65(9): 923-938, 1975.

(47) KOHLBERG, L. Development of moral character and moral ideology. In: Hoffman, M.L., Hoffman, L.W. (Editors). Review of Child Development Research, Volume 1. New York, Russell Sage Foundation, 1964, pp. 383-431.

(48) LAOYE, J.A., CRESWELL, W.H., JR., STONE, D.B. A cohort study of 1,205 secondary school smokers. Journal of School Health 42(1): 47-52, January 1972.

(49) LEVITT, E.E. Reasons for smoking and not smoking given by school children. Journal of School Health 41: 101-105, February 1971.

(50) LEVITT, E.E., EDWARDS, J.A. A multivariate study of correlative factors in youthful cigarette smoking. Developmental Psychology 2(1): 5-11, 1970.

(51) MATTHEWS, V.L. The Saskatoon Smoking Study: Habits and Beliefs of Children in Grades Seven and Eight about Smoking. Department of Social and Preventative Medicine, College of Medicine, University of Saskatchewan, Saskatoon, May 1974, 64 pp.

(52) MCARTHUR, C., WALDRON, E., DICKINSON, J. The psychology of smoking. Journal of Abnormal and Social Psychology 56: 267-275, 1958.

(53) MCGUIRE, W.J. The nature of attitudes and attitude change. In: Lindzey, G., Aronson, E. (Editors). Handbook of Social Psychology. Volume 3, The Individual in a Social Context. Reading, Massachusetts, Addison-Wesley, 1969, pp. 136-314.

(54) MENDELSOHN, H. Mass communications and cancer control. In: Cullen, J.W., Fox, B.H., Isom, R.N. (Editors). Cancer: The Behavioral Dimensions. New York, Raven Press, 1976, pp. 197-204.

(55) MERKI, D.J., CRESWELL, W.H., STONE, D.B., HUFFMAN, W., NEWMAN, I. The effects of two educational methods and message themes on rural youth smoking behavior. Journal of School Health 38: 448-454, 1968.

(56) MILNE, A.M., MARSHALL-MIES, J., COLMEN, J.G. A Study of the Impact of the School Health Curriculum Project on Knowledge, Attitude and Behavior of Teenage Students. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, November 8, 1975, 41 pp.

(57) NATIONAL CANCER INSTITUTE. The Smoking Digest. Progress Report on a Nation Kicking the Habit. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, October, 1977, 127 pp.

(58) NATIONAL CANCER INSTITUTE. AMERICAN CANCER SOCIETY. Cigarette Smoking among Teenagers and Young Women. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1203, 1976, 31 pp.

(59) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Teenage Self-Test: Cigarette Smoking. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, DHEW Publication No. (CDC) 74-8723, 15 pp.

(60) NATIONAL INSTITUTES OF HEALTH. Respiratory Diseases: Task Force Report on Prevention, Control, and Education. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 77-1248, March 1977, 137 pp.

(61) NATIONAL INSTITUTES OF HEALTH. Teenage Smoking, National Patterns of Cigarette Smoking, Ages 12 through 18, in 1972 and 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 76-931, 1976, 125 pp.

(62) NEWMAN, A.N. How teachers see themselves in the exemplar role in smoking education as evidenced by their attitudes and practices. Journal of School Health 41: 275-279, May 1971.

(63) NEWMAN, I.M. Peer pressure hypothesis for adolescent cigarette smoking. School Health Review 1: 15-18, 1970.

(64) NEWMAN, I.M. Status configurations and cigarette smoking in a junior high school. Journal of School Health 40: 28-31, 1970.

(65) NEWMAN, I.M., MARTIN, G.L., IRWIN, R.P. Attitudes of adolescent cigarette smokers. New Zealand Medical Journal 78(499): 237-240, September 26, 1973.

(66) O'DONNELL, J.A., VOSS, H.L., CLAYTON, R.R., SLATIN, G.T., ROOM, R.G.W. Young Men and Drugs—A Nationwide Survey. NIDA Research Monograph 5. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, February 1976, 144 pp.

(67) O'ROURKE, T.W. Research on smoking behavior: Some limitations and suggestions for improvement. Public Health Reviews 2(1): 105-112, 1973.

(68) PALMER, A.B. Some variables contributing to the onset of cigarette smoking among junior high school students. Social Science and Medicine 4: 359-366, 1970.

(69) PIAGET, J. The Psychology of Intelligence. London, Routledge and Kegan Paul Limited, 1960, 182 pp.

(70) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study: Results of the second year. Canadian Journal of Public Health 65: 127-129, March/April 1974.

(71) PYSZKA, R.H., RUGGELS, W.L., JANOWICZ, L.M. Health Behavior Change: Smoking Cessation. Stanford Research Institute, Institute Research and Development Report, 1973, 31 pp.

(72) RABINOWITZ, H.S., ZIMMERLI, W.H. Effects of a health education program on junior high school students' knowledge, attitudes, and behavior concerning tobacco use. Journal of School Health 44(6): 324-330, June 1974.

(73) ROSENTHAL, R., ROSNOW, R.L. The Volunteer Subject. New York, Wiley, 1975, 266 pp.

(74) RUSSELL, M.A.H., WILSON, C., FEYERABEND, C., COLE, P.V. Effect of nicotine chewing gum on smoking behavior and as an aid to cigarette withdrawal. British Medical Journal 2: 391-393, 1976.

(75) SCHNEIDER, F.W., VANMASTRIGT, L.A. Adolescent-preadolescent differences in beliefs and attitudes about cigarette smoking. Journal of Psychology 87: 71-81, 1974.

(76) SCHWARTZ, J.L. Smoking cures: Ways to kick an unhealthy habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 308-336.

(77) SEELY, J.E., ZUSKIN, E., BOUHUYS, A. Cigarette smoking: Objective evidence for lung damage in teenagers. Science 172: 741-743, May 14, 1971.

(78) SHERIF, M., SHERIF, C.W. Reference Groups: Exploration into Conformity and Deviation in Adolescents. New York, Harper and Row, 1964, 360 pp.

(79) SMITH, G.M. Personality and smoking: A review of the empirical literature. In: Hunt, W.A. (Editor). Learning Mechanisms in Smoking. Chicago, Aldine Publishing Co., 1970, pp. 42-64.

(80) STREIT, W.K. Smoking in schools. Physical Educator 29: 25-26, March 1972.

(81) TEDESCHI, J.T., SCHLENKER, B.R., BONOMA, T.V. Cognitive dissonance: Private ratiocination or public spectacle? American Psychologist 26: 685-695, 1971.

(82) TERRY, D.E., WOODWARD, L.H. A five year plan for designing and implementing a statewide health education curriculum in Maryland. Journal of School Health 46: 282-285, 1976.

(83) THOMPSON, D.S., WILSON, T.R. Discontinuance of cigarette smoking: "Natural" and with "therapy." Journal of the American Medical Association 196: 1048-1052, 1966.

(84) THOMPSON, E.L. Smoking education programs 1960-1976. American Journal of Public Health 68: 250-257, 1978.

(85) TOMPKINS, V. Student smoking—Its prevention and cure. Health News 45: 12-15, 1968.

(86) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, National Clearinghouse for Smoking and Health, DHEW Publication No. (HSM) 72-7516, 1972, 158 pp.

(87) WARD, S. Television advertising and the adolescent. Clinical Pediatrics 10(8): 462-464, August 1971.

(88) WILLIAMS, T.M. Summary and Implications of Review of Literature Related to Adolescent Smoking. U.S. Department of Health, Education, and Welfare, Health Services and Mental Health Administration, Center for Disease Control, National Clearinghouse for Smoking and Health, September 1971, 59 pp.

(89) WOHLFORD, P. Initiation of cigarette smoking: Is it related to parental behavior? Journal of Consulting and Clinical Psychology 34(2): 148-151, 1970.

18. PSYCHOSOCIAL INFLUENCES ON CIGARETTE SMOKING.

National Institute on Drug Abuse

CONTENTS

Maintenance of Smoking

Many of the psychosocial influences on the establishment of smoking are discussed at length in other chapters of this report. This chapter begins with issues related to the maintenance of cigarette smoking. Much of the research which was reviewed, however, made no strict distinction between factors leading to the establishment and those leading to the maintenance of smoking. For a more far-ranging review than possible in this short space and for a somewhat different approach to the topic, the reader is advised to consult other sources (e.g. *47*, *48*).

Individual Factors

Personality and Smoking

In part because such research can be among the easiest to conduct, many studies have been undertaken to correlate scores on self-report personality inventories with smoking habits. Much of this research has been marred by too few subjects, inadequate samples, too little attention to other measurable and potent influences on cigarette smoking, such as peer pressure, parental influence, and socioeconomic status, and too little appreciation of the fact that studying the determinants of cigarette smoking is fundamentally a problem for multivariate analysis (see the criticisms in *19*, *22*, *49*, *65*, *90*).

In general, the personality research shows that even the most reliable personality predictors of cigarette smoking, such as extraversion, account for only about 3 to 5 percent of the variance in measures of smoking habits. Smith (*90*) concludes that the best univariate personality assessments are able to discriminate smokers from nonsmokers in only about 60 percent of the cases. His own multivariate studies are able to discriminate smokers from nonsmokers in 68 to 76 percent of the cases.

Personality research is intrinsically correlational. It describes associations between variables and does not establish causal connections. Researchers are in a position to manipulate at random (a requirement for true experimental designs) neither the personalities nor the chronic smoking habits of their subjects. To find that smokers are, to use the same example, more extraverted than nonsmokers gives no information about (1) whether smoking caused an increase in extraversion, or extraversion caused an increase in smoking, or (2) whether some unmeasured confounding variables, which are correlated with both smoking and extraversion, are the true cause of the observed association. Longitudinal studies that are able to assess personality before the onset of smoking are some help in dealing with the first problem, but they deal not at all with the second. Even with these limitations in mind, the search for correlations between personality and smoking has yielded some information worthy of consideration.

Wiggins (*105*) reviews studies which indicate that most of the various measures of temperament can be boiled down to two major factors—extraversion and neuroticism (anxiety).

Extraversion

Since the first major review of this area by Matarazzo and Saslow (*54*), a cluster of variables often called extraversion has been shown to be positively associated with cigarette smoking. Eysenck's work on extraversion-introversion has had a powerful influence on defining the field (*27*). According to his research, the typical extravert craves excitement, is willing to take risks, is sociable, likes parties, is carefree and easygoing, and may be aggressive. On the other hand, the introvert is introspective, retiring, bookish, prudent, emotionally-controlled, passive, and reliable. Eysenck considers the extraversion-introversion dimension to be comprised of varying degrees of four major traits: sociability, liveliness, impulsiveness, and jocularity. In a carefully sampled study (*28*), which also controlled for age and social class in British males, the amount smoked was related directly to greater extraversion.

Cattell's work with his 16PF inventory on a sample of college men and women (*14*) supports this finding on extraversion. Extraversion emerges as a second-order factor of the 16PF and correlates +.21 with smoking (a three-point scale of smoking habits). The primary factors which correlate most with smoking are Affectothymia (outgoing) ($r = +.16$) and Surgency (happy-go-lucky) ($r = +.29$). Both these factors are major components of the extraversion scores.

Smith (*91*) reviews the results of 15 reports describing 25 studies that he believes have provided adequate measures of extraversion (e.g., the Maudsley Personality Inventory, MMPI Social Introversion Scale, 16PF: Extraversion, Strong Vocational Interest Blank, and peer ratings of extraversion). Twenty-two of the twenty-four studies that describe statistical analyses showed that smokers were more extraverted than nonsmokers. It was noted that the effect has been found in several different populations (for example, U.S. adult males and females, British adult males, U.S. high school and junior high school males and females). Smith (*91*) treats impulsiveness as a separate personality category. But perhaps it is best to consider the impulsiveness findings as part of the general trend for smokers to be more extraverted. It has been argued that there are two basic components of extraversion: sociability and impulsiveness. Eysenck (*28*), for example, demonstrates that neither factor alone contributes inordinately to the association between smoking and extraversion.

More recent research (*15*, *18*, *69*) in general supports the association between smoking and extraversion. The Cherry and Kiernan paper (*15*) is of special interest because it describes the results of a large sample, longitudinal study. Personality scores were obtained on the Maudsley

Personality Inventory at the age of 16 years. (Neuroticism findings will be discussed below.) Smoking habits were measured when subjects were 25 years old. The total usable sample was 2,753 British males and females. Both male and female smokers were more extraverted than male and female nonsmokers ($p < .01$). An analysis of recruitment to smoking in those who had not been regular smokers by their 17th birthday showed that extraversion, neuroticism, and being male were each independently and positively associated with becoming a smoker. (There was an indication of interaction between the neuroticism and extraversion effects; those high in both were less likely to be smokers than would have been predicted.)

Russell (*73*) proposes that the following findings cluster with a degree of extraversion—that smokers are greater risk-takers, more impulsive, more prone to divorce and job changing, more interested in sex, and more likely to drink tea, coffee and alcohol.

Eysenck (*26*) has offered a biologically based theory as to why smoking should be more rewarding to extraverts than to introverts. Little additional social-psychological research has been done on how being extraverted might lead one to start or maintain smoking or on how being introverted might lead to not smoking. Likely hypotheses are easy to formulate. Since peer and parental pressures can be powerful influences on recruitment to smoking, it is interesting to note that extraverts are known to be more susceptible to social influence. Perhaps introverts are as resistant to social pressures to smoke as extraverts are prey to them. No research has been performed which attempts to hold these powerful social pressures constant to see the "purer" influence of extraversion on smoking. For example, the association between onset of smoking and extraversion may be moderated by some critical social variable. Future research should consider testing specific hypotheses about how extraversion and smoking could be related causally.

Neuroticism

Smith's review (*91*) uses the label "mental health" to loosely unite research that has gone under the more specialized labels of "neuroticism," "nervousness," "psychosomatic distress," "adjustment," "emotionality," and "anxiety." Just over half of the 50 or so studies in his review show smokers to have slightly poorer mental health than nonsmokers; the remaining studies show no relationship between smoking and neuroticism. The diversity of measures used and the lack of precise, consistent conceptualizations in this area may be responsible for much of the inconsistency. And it should be emphasized that the positive findings can in no way be interpreted to support the notion that smokers are substantially more neurotic, psychotic, or "crazy" than nonsmokers. At best, the data show a modest relationship

between neuroticism and smoking, accounting for 1 or 2 percent of the variance.

Matarazzo and Saslow (*54*) report that for the most part smokers have higher neuroticism scores. The first Surgeon General's Report on Smoking and Health (*98*) concluded tentatively that smoking and neuroticism were probably related. Eysenck (*27, 28*) has found no evidence that smokers are more neurotic in large representative samples of British adult males.

Two careful studies suggest that there may be sex differences in the relationship between smoking and neuroticism. Waters (*101*), in a random sample of 2,000 electors in Great Britain, was able to get completed questionnaires from 773 men and 945 women. For men, the correlation between smoking habits and neuroticism was essentially zero (Spearman's rank-order correlation coefficient between neurotic score and amount smoked was -.002); for women, the correlation was small, but statistically significant ($r = .127$, $p < .001$). Clausen (*17*), as part of the Oakland Growth Study, reports scores on psychoneurotic symptoms for boys and girls who would later grow up to be smokers. Males show a generally negative relationship between amount smoked during adulthood and their adolescent neuroticism scores; females show a generally positive association between smoking and neuroticism.

One other major British survey study, using a short form of the Maudsley Personality Inventory, finds no significant trend for neuroticism to increase among smokers as the amount smoked increased, but does find some indication that such a trend was present for women (*15*); when a simple nonsmoker-smoker classification was used, neuroticism was higher in both male and female respondents. In Indian males, who smoked either 0, 1 to 10, 11 to 20, or over 21 cigarettes per day, neuroticism decreased as smoking increased. Both linear and cubic trend were significant statistically (*43*).

In a detailed study on smoking and habits of nervous tension, Thomas (*96*) surveyed male medical students at Johns Hopkins University (437 nonsmokers, 144 ex-smokers, 251 continuing cigarette smokers) and found an anxiety scale significantly related to greater smoking in a stepwise discriminant function analysis.

At present, the most reasonable conclusion concerning smoking and neuroticism is that there are systematic relationships between them. Researchers do not yet understand, however, the interacting variables or moderating influences on the relationship. It is interesting to note here that Lebovits, et al. (*50*) evaluated the effects of defensiveness, age, education, and smoking habits on the MMPI scores of 1,572 white males, aged 40 to 56; they looked for statistical interactions which influenced the scores and found indications of some small interactive effects. More research along these lines might reveal the boundary

conditions that influence the relationship between neuroticism and smoking.

Some authorities, e.g., Russell (*73*), have proposed that slight neuroticism may be the result of being a dependent cigarette smoker rather than a cause of smoking; cigarette withdrawal syndromes may result in greater neuroticism. More careful evaluation of the characteristics of the individual's smoking habit—in particular, whether or not he or she is an *addicted* smoker—may help answer this question.

Antisocial Tendencies

Smith (*91*) considered 19 reports; 20 of 32 analyses showed that smokers had greater antisocial tendencies (belligerence, psychopathic deviance, misconduct, rebelliousness, defiance, and disagreeableness). Subsequent studies have supported this relationship (*49, 62, 69*).

Matarazzo and Saslow (*54*) and Weatherley (*102*) consider that smokers' greater antisocial tendencies may be due to a response bias. Perhaps smokers are more willing than nonsmokers to admit negative characteristics about themselves (*25, 84*), even though in actuality they may not differ from nonsmokers in these characteristics. Smith argues that ratings by peers support the belief that smokers have greater antisocial tendencies and that, therefore, the response bias explanation is not very persuasive.

Internal-External Control

At the time of Smith's review (*90*), there had been only five tests of the relationship between smoking and internal-external control. Internally-controlled individuals tend to believe that they are the masters of what happens to them; their effort and skills (intrinsic properties) will bring them rewards. Externally-controlled individuals tend to believe that fate, luck, or, in general, things beyond their control will bring them their rewards. Four out of five analyses showed smokers to be more externally controlled. (The disconfirming analysis revealed a probability level of about .06, rather than the standard $p < .05$.) Two more recent studies (*5, 36*) are divided in their support of the hypothesis that smokers are more externally controlled.

Miscellaneous Personality Variables

Orality has not been demonstrated conclusively to be related to more smoking (*91*). In addition, the concept of orality and its measurement are far from clear-cut. Some of the questionnaires intended to measure orality have depended on questions on beer drinking, coffee drinking, and medicine taking; hence, other drug use behaviors are being defined as "oral behaviors" (*40*).

The Edwards Personal Preference Schedule (EPPS) has shown some fairly consistent smoker-nonsmoker differences. Smokers tend to be

higher in "heterosexuality" and lower in "deference" and "order" (*89, 90*).

Personality and Attitudes Toward Drug Taking

Stokes (*94*) has argued that traditional personality constructs are likely to be inadequate to the task of finding strong predictors of drug use and that personality-attitude measures should be more tailored to the issues of drug use. Six personality factors were tested: fear of personal reaction to drugs; dissatisfaction and a desire to change oneself; respect for the illegality of psychedelic drug use; sensual hedonism; philosophical hedonism; and general tendency to try drugs. The two most important predictors of tobacco use were "general tendency to use drugs" ($r(735) = .29$, $p < .001$) and "fear of personal reaction to drugs" ($r = .26$, $p < .001$). In a multiple regression analysis, the multiple R of the six factors with tobacco use was .349, accounting for 12 percent of the variance. It should be kept in mind, however, that as questionnaires themselves become more targeted on drug use and less on general personality structure, the nature of the research is altered.

Smoking Typologies

The most common strategy for discovering why people smoke has been simply to ask them on a questionnaire to indicate their agreement with statements on reasons for smoking (e.g., "I smoke cigarettes to stimulate me, to perk myself up") or on occasions for smoking (e.g., "I like to smoke when at a party"). Ikard, et al. (*38*)—employing a theoretical analysis by Tomkins (*97*)—factor-analyzed responses to proposed reasons for smoking. This analysis revealed six factors: Habitual (e.g., "I smoke cigarettes automatically without being aware of it"), Addictive (e.g., "Between cigarettes I get a craving that *only* a cigarette will satisfy"), Reduction of Negative Affect (e.g., "When I feel 'blue' or want to take my mind off cares and worries, I smoke cigarettes"), Pleasurable Relaxation (e.g., "Smoking cigarettes is pleasant and relaxing"), Stimulation (e.g., "I smoke cigarettes to give me a 'lift' "), and Sensorimotor Manipulation (e.g., "Part of the enjoyment of smoking ... comes from the steps I take to light up"). For both men and women, moderate correlations were found between average number of cigarettes smoked per day and the Habitual, Addictive, and Negative Affect Reduction factor scores. Although second-order factors are not reported, inspection of the intercorrelation matrix for the scores on the six types of smoking discloses correlations ranging from .38 and .58 among the Habitual, Addictive, and Negative Affect Reduction scales.

McKennell (*58*) replicated his earlier work and the work of Horn and his associates. In both cases, the factor structures were remarkably stable. The only revision warranted was the addition of an eighth

factor to his own system—Reluctant Smoking. Reluctant Smoking was seen as similar to Horn's Habitual Smoking. In comparing the models, McKennell found that Horn's Pleasurable Relaxation was not measuring the same thing as was his own Relaxation Smoking. The Horn factor concerns smokers' general attitude toward smoking, that is, how pleasurable it is to smoke, while the McKennell factor concerns the desire to smoke in relaxed situations. The respective factors, Reduction of Negative Affect and Nervous Irritation Smoking, were found to be equivalent. McKennell concluded that it is possible to integrate the two models into a six-factors scheme. The first three factors load on a dimension of Inner Need (Inner Need/Relaxation, Inner Need/Stimulation, and Habit), the next two factors are concerned more with the sensorimotor and social aspects of smoking. The last and most tentative factor derives from Horn's Pleasurable Relaxation factor.

McKennell (*58*) used cluster analysis to determine if scores on these six integrated factors could be used to classify a random sample of 2,000 British respondents into distinct smoking types.

Six types were found(*58*, p. 10):

1. *Low Need-Pleasure* smokers, accounting for 14 percent of all smokers, tend more than others to be light smokers, with nonmanual occupations, who go to church, whose friends do not smoke, and who would not find it difficult to stop smoking.
2. *Medium Need* smokers, accounting for 30 percent of all smokers, differ from Low Need-Pleasure smokers chiefly in having a much more favourable attitude to smoking. Otherwise they are similar, although a little nearer the average in amount smoked.
3. *Medium Need/Handling-Social Confidence* smokers are a small group, comprising only 5 percent of all smokers. Apart from their motives for smoking, their most distinctive trait is their above-average frequency of drinking beer.
4. *Medium Need/Reluctant* smokers account for 28 percent of all smokers. They tend to disapprove of smoking but to be unable to escape from dependence on it. They tend to be young.
5. *High Need* smokers, who account for only 8 percent of all smokers, are distinct from High Need-Social smokers in scoring lower on the Handling and Social factors. In other respects they are similar.
6. *High Need-Social* smokers account for 15 percent of all smokers. They tend to smoke heavily, to have a manual occupation, to have friends who smoke, and to find it very difficult to stop smoking.

Coan (*18*) factor-analyzed an expanded version of the Horn scale and arrived at a classification scheme that is, in the main, compatible with the integration proposed by McKennell. Russell, et al. (*76*) compared the Horn and McKennell typologies, added new questions to their self-report inventories, and attempted to develop a typology that was more informed by recent developments in the psychopharmacology and

social psychology of cigarette smoking. Six oblique factors were obtained: Psychosocial Smoking, Indulgent Smoking, Sensorimotor Smoking, Stimulation Smoking, Addictive Smoking, and Automatic Smoking. One of the most provocative findings of this analysis was that Horn's Negative Affect Reduction factor did not appear on its own, but was split between the Addictive and Stimulation factors. What McKennell had been describing as a second-order "inner need" factor is here called Pharmacological Addiction and is comprised of the stimulation, automatic, and addictive factors. (The correlations among these factors ranged from .50 to .63). Scores on these three factors were able to discriminate the primary sample of 175 cigarette smokers from a second group of 103 addicted heavy smokers who were attending smoking treatment clinics. The authors propose that the single dimension of pharmacological addiction to nicotine may prove more important for significant classifications of cigarette smokers than would profiles based on the six types of smoking. Perhaps cluster analyses as in McKennell (*58*) would help answer this question.

Smoking typologies based on what smokers can tell us about their reasons and occasions for smoking are, until proven otherwise, of limited value. It is unclear what insights these verbal reports give us into smoking behavior. Recent work in psychology questions seriously the validity of any self-reports of motivation (*64*). It is also clear that processes at work well beneath the level of awareness can influence cigarette consumption (*83, 84*). A recent somewhat preliminary laboratory study indicates that there may be little behavioral validity to the self-reports about reasons for smoking; the classification of smokers into Positive Affect, Negative Affect, and Social Stimulation smokers did not relate to actual smoking behavior in various experimental conditions designed to elicit these types of smoking (*2*). Other research (*51*) suggests tentatively that verbal reports of reasons for smoking are more accurate for factors related to external cues (e.g., Pleasure-Taste and Habit) and less accurate for reports of internally defined states (Addiction).

Russell's (*74*) model of smoking proposes a progression from smoking for nonpharmacological rewards (that is, psychosocial and sensorimotor) to smoking to gain a positive effect from nicotine (indulgent, sedative, stimulation smoking). Finally, an addiction to nicotine develops and avoidance of the ill effects of nicotine withdrawal becomes an additional reinforcer of smoking.

It should be noted that Schwartz (*87*), using cluster analysis, detected 10 smoker types based on socioeconomic status, alcohol consumption-smoking environment, confidence-security adjustment, illness-anxiety, and attitudes toward smoking-beliefs about dangers. However, this result is not reported in enough detail so that it can be commented on at length.

The development of valid classification schemes for types of cigarette smoking could be a great boon to research on psychosocial influences on smoking. Perhaps, for example, the personality structure of addicted smokers is different from that of social smokers. Coan has conducted an interesting study which pursues this idea (*18*). Some greater standardization of behavioral classification of smoking habits is also advised. Clearly, a simple division of subjects into the categories of smoker versus nonsmoker is no longer excusable (*17*). Number of cigarettes smoked per day, number of months or years having been a smoker, nicotine content of preferred brands, and information about inhaling should be determined. (Eysenck (*28*) found that inhalers had a higher degree of neuroticism than those smokers who did not inhale.)

Self-reports of number of cigarettes consumed present their own problems of interpretation. First, there are strong pressures for the respondents to round-off their answers by saying "half a pack," "a pack," "pack and a half" and so on. Schachter has argued that, depending on the cut-off points that researchers use to establish their smoking categories, it is possible to arrive at some mistaken conclusions about the correlates of amount smoked (*82*). Using numbers of cigarettes smoked as the main indication of heavy or addicted smoking has had only modest success (*35, 38, 58, 76*). Another simple question promises to provide a surer link between addicted smoking and self-reports of the smoking habit—the time of the first cigarette in the morning. Kozlowski (*45*) and Schachter (*81*) have begun exploring the usefulness of this variable as a way of identifying addicted cigarette smokers.

The category of nonsmoker is also in need of refinement (*49*). Little attention has been given to developing a systematic typology for nonsmokers, although self-reported reasons for not smoking have been compiled. A typology of nonsmokers may prove useful and may help guide researchers to particular subsamples of nonsmokers in order to evaluate specific hypotheses. For example, some nonsmokers have never even tried a single cigarette and, hence, their own positive or negative biological responses to smoking cannot influence their recruitment to smoking; psychosocial factors in such cases might be said to have precluded the involvement of biological influences on becoming a smoker (*46*). These biologically-uncontaminated "never smokers" are ideal subjects for studies on psychosocial influences on smoking/not smoking.

Multiple Drug Use

One of the most reliable correlates of cigarette smoking is the use of other drugs. Smokers consume more coffee (caffeine), more alcohol, more psychotropic drugs, more marijuana, and more aspirin than do nonsmokers (*1*). The correlations between the various drug uses can be difficult to interpret. Consider the conditional probabilities of drug use

in a large sample of U.S. college students in 1969–70 (*33*). If a student used tobacco, the probability was .97 that the student had used alcohol; if alcohol, the probability of tobacco use was .62. If marijuana was used, the probability of tobacco use was .77; if tobacco, the probability of marijuana was .44. With such figures in mind, it becomes foolhardy to ignore possible multiple drug effects when studying any one drug.

The psychosocial pressures for adolescents to use one drug are similar to the pressures to use others (*31*). Kandel (*41*), in a large-sample study of adolescents in New York State, found that peer pressures had consistent and strong effects on drug use (marijuana, tobacco, alcohol, barbiturates, tranquilizers, and stimulants). Significant patterns of intrafamilial multiple drug use have been noted (*3*). Further, in a large longitudinal study (*42*), Kandel found systematic patterns of paths from one drug use to another. For example, though most respondents started with beer or wine, some went on to cigarettes next, while some went on to hard liquor. From either branch, liquor or cigarettes, some individuals went on to marijuana, while some persons became both liquor drinkers and cigarette smokers before trying marijuana. The conclusions of this study have important methodological implications:

> Whereas most studies compare youths within a total population on the basis of their use or non-use of a particular substance, my results suggest a different strategy. Since each style represents a cumulative pattern of drug use and generally contains fewer adolescents than the preceding stage or stages in the sequence, comparisons must be made among members of the restricted group of respondents who have already used the drug or drugs at the preceding stages, and those who have not. Unless this is done, the attributes identified as apparent characteristics of a particular class of drug users may actually reflect characteristics important for involvement in drugs at the preceding level (p. 914).

Kandel's suggestion demands large-sample research, and the larger the number of drugs of interest (for example, caffeine should probably be added), the larger the samples will have to be.

The methodological significance of the multiple drug use patterns has been clear to epidemiological researchers for years, particularly with respect to smoking (*105*). For example, it has been argued that the apparent association between coffee drinking and heart disease is actually due to an often unmeasured, but nonetheless confounding, correlation between smoking and heart disease (smoking and coffee drinking are positively correlated) (*21*). This interest in the confounding or interactive effects of multiple drug use has been slow to influence behavioral, physiological, or personality studies of cigarette smoking. The methodological implications are clear.

Consider, for example, a laboratory study in which subjects are asked to abstain from cigarettes for an hour before coming to the experiment. Since cigarette smokers are more likely to be coffee drinkers or alcohol drinkers, they are more likely to come to the study with significant doses of caffeine or alcohol in their systems. Without knowing it, the experimenter may be looking at the correlated effects of other drugs on the behaviors of interest. If the researchers deprive all subjects of caffeine well before the start of the study, they would not necessarily solve this problem, but rather they may unwittingly find themselves looking at the differential effects of caffeine withdrawal on their measures (*44, 45*). The effects of confounding drug use even on the filling out of personality inventories are not at all understood.

Social Factors

Family and Peer Pressures

Many of the social factors that are involved in the establishment of smoking are important for the maintenance of the habit. As the young adult begins to leave the direct sphere of influence of the family, presumably the effects of parental and sibling smoking habits (*7, 8, 66, 71*) would weaken; there is no reason to expect, however, that peer pressures to smoke (*66, 71*) will be any less strong during the early years of the individual's career as a smoker. The adult smoker is likely to have many smoking friends (*57*). Probably the most important family structure influence on the maintenance of cigarette smoking derives from the smoking habits of spouses or cohabitants (*59, 95*). A major survey by the American Cancer Society shows that 68 percent of young women smokers have boyfriends or husbands who smoke, compared with only 41 percent of the nonsmokers (*16*). The increasing militancy of nonsmokers and the increasing restriction on public opportunities to smoke (*99*) may be acting to tighten the ranks of cigarette smokers, making the support of a group of smoking friends all the more important to the maintenance of the habit. To our knowledge, no data have been gathered as yet on this point. Brecher and his associates (*10*) have proposed that the illusion that quitting is easy or the illusion that cigarettes are not dependence-producing helps the smoker to maintain the habit in the early years. Indeed, if one believes that cigarettes' damaging effects to health occur only after a long history of smoking and if, at the same time, one believes that he or she will be only a short-term smoker, the health consequences of smoking are, in effect, tabled as a reason for not smoking. Research reported by Green (*32*) isolates what is called a "rationalization factor" which is consistent with the preceding interpretation of what many young smokers believe about their smoking.

Some smokers do feel that there is room for doubt concerning the link between smoking and health. Such beliefs do at least give "rational" support to the maintenance of smoking.

Smokers do seem to gain some benefits from smoking. For example, the smoking typologies, discussed above, which are based on self-reports of why smokers smoke, indicate a range of perceived benefits from smoking. Green (*32*) describes the results of administering tests of the Horn typology to a large sample of smokers in the United States: the Pleasurable Relaxation, Tension Reduction and Craving factors were the most important reasons overall, and the Habit, Stimulation, and Handling factors were of substantial but lesser significance. If smoking can be used to relax or to stimulate the smoker (*63, 80*), it may genuinely contribute to successful performance in a variety of settings. Mausner (*55*) has discussed some particularly social gains from smoking, arguing that smoking is part of a complex social ritual and that it can be an important expressive behavior which helps to define the individual's self-concept.

Social Class and Social Mobility

In our culture, socioeconomic status, at least as measured by occupation, has had a stable relationship to cigarette smoking (*86*). White-collar workers (professional, technical) have the lowest smoking rates; blue-collar workers (laborers, craftsmen) have the highest smoking rates. Men show this relationship strongly, but women tend to show an opposite relationship. Employed white-collar female workers have a higher incidence of smoking than do the blue-collar female workers.

As Reeder (*68*) has pointed out, two excellent longitudinal studies have shown a relationship between social mobility and smoking behavior. Clausen (*17*) reports that upwardly mobile (relative to parents' SES) men were less likely to smoke; downwardly mobile men were more likely to be heavy smokers. Similarly, Srole and Fischer (*93*) report that for males upward mobility decreases the incidence of smoking, while downward mobility increases the incidence of smoking; the results for females do not show the same pattern and are difficult to interpret.

Sex Roles

One of the most striking findings to have emerged from basic surveys on the incidence of smoking in teenagers is the increase over the past 20 years in smoking among girls. No corresponding increase has been found among teenage boys. The latest survey in this series (1975) shows that teenage girls now equal boys, 20 to 21 percent, respectively, in the incidence of cigarette smoking (*68*). Reeder proposes that correlated changes in the sex role of women, as manifest in changes in

college attendance and in labor trends, may be responsible. For more discussion of these issues, see the Public Health Service report on cigarette smoking among teenagers and young women (*60*) and the report by Bosse and Rose (*9*).

Cessation of Smoking

Individual Factors

Two basic types of research are relevant to personality influences on stopping smoking. The first type concerns studies which have measured the personality characteristics of those who have become ex-smokers, with no particular regard to how they became ex-smokers. The second type deals with the personality correlates of success in specific smoking treatment programs.

Personality Characteristics of Ex-Smokers

Eysenck's research on British males (*28*) showed that ex-smokers were equal in extraversion to nonsmokers and to light smokers, but lower in this trait than were medium or heavy smokers; neuroticism was unrelated to smoking habits. In a longitudinal study of British men and women, Cherry and Kiernan (*15*) found that low daily cigarette consumption and high extraversion scores were each independently related to a greater incidence of giving up smoking. These relationships held for both men and women. Neuroticism had no relationship to smoking cessation in women, but for men, the more neurotic were less likely to give up smoking. A model was derived which has very impressive predictive powers. For men, neuroticism and extraversion scores were each divided into high and low categories and daily cigarette intake at age 20 was divided into three categories (1-10, 11-20, 21+). It was predicted that 47 percent of the high extraversion-low neuroticism-low consumption individuals would stop smoking, and 50 percent, in fact, did. Only 2 percent of the low extraversion-high neuroticism-high consumption individuals were predicted to give up cigarettes; none did. This study demonstrates the advantage to be gained from considering sex differences and from looking at more than one personality variable at a time.

In a small sample study (N=182) of college undergraduates, the Edwards Personal Preference Schedule (EPPS) showed that former smokers (N=22) expressed aggression more openly than either nonsmokers or smokers who never tried to stop; that they had a stronger need for achievement than any other group, including smokers who had tried to stop but failed; that they had a weaker need for close ties with peers (affiliation); and that they had more behavioral stability than the other groups (*101*). It should be noted, however, that this study failed to replicate EPPS differences that have been found for smokers versus nonsmokers.

Internal-External Locus of Control

It is not surprising that this dimension has made its way into several studies on this topic. "Internals" should believe in their own willpower and ability, while "Externals" should be much more fatalistic in outlook. One might therefore predict that Internals would be more successful than Externals in the efforts to quit smoking. Straits (*95*) and Foss (*30*) confirmed this prediction; Lichtenstein and Keutzer (*53*) and Burton (*12*) failed to confirm it. A third study showed only complicated interactions between type of treatment technique, Internal-External scores, and success at abstinence (*6*).

Extraversion and Neuroticism

Using general definitions of these two traits, it is possible to see a fairly consistent pattern of results which suggests that neuroticism and, in a more complicated way, extraversion are associated with ability to abstain from smoking. In a longitudinal study of Harvard males, McArthur, et al. (*56*) found slight indications that the heavier smokers who were able to give up cigarettes were best described as sociable and as having strong basic personalities, in other words, high in extraversion and low in neuroticism. Guilford (*34*) found that male quitters were less neurotic than those who were unsuccessful at quitting; this trend was not found in female smokers. In addition, male quitters were more sociable (an extraversion factor); this trend, too, was not found in women. Straits (*95*) found no relationship between extraversion and neuroticism, as measured by Eysenck's scales, and quitting. On the Cattell 16PF questionnaire, male quitters were less tense (that is, low in neuroticism) and had more "critical" and "independent" minds (perhaps this can be seen as more internal locus of control); female quitters had lower "tension" and "apprehension" scores (that is, low neuroticism) (*70*). Jacobs (*39*) found that successfully abstaining males were less "impulsive, defiant and manifestly distressed" and also were less "constricted, guarded and isolated." These two sets of traits were positively correlated with each other ($r(102) = .24$, $p < .05$); it is not obvious how an "impulsive, defiant" person could at the same time be "constricted" and "guarded." Perhaps the last two components, "manifestly distressed" and "isolated", account for the greatest share of the variance in this association. In a 5-year follow-up of a smoking withdrawal clinic (*103*), neuroticism as measured by an emotional status score and by a psychosomatic symptom score was related to quitting smoking; successful abstainers were less neurotic. Ryan (*77*), using the 16PF, found that the upper class male quitters were less neurotic and more extraverted; the lower class males did not show the same pattern, but the sample size of quitters here was very small (N = 11).

Self-Reported Reasons for Stopping

Four main reasons for quitting were identified by Green (*32*) in an analysis of data that had been gathered along with the large survey of adults carried out by the National Clearinghouse for Smoking and Health in 1975 (*61*). Health concerns, of course, weighed heavily as a reason for stopping. There was a desire to gain mastery of the habit which had been controlling their lives. Some smokers had come to believe that smoking was a messy, filthy, smelly habit and, therefore, aesthetic reasons had become prominent. Some smokers said that they were trying to quit because they felt that their smoking was setting a bad example for others who were under their influence, such as children or friends. Green tried to find out if economic concerns (the cost of cigarettes) were a major reason for stopping, but there was little evidence to support such a claim in this study. Perhaps more substantial increases in cigarette cost would have larger effects on attempts at cessation. Horn (*37*) and Russell (*72*) have argued that economic factors can have a major influence. Certainly among younger smokers the cost of smoking is a reason that is often given for wanting to stop (*78, 79*). Young ex-smokers in grades 7 to 12 gave the following reasons for not smoking, beginning with the most common: (1) no enjoyment of or a dislike of cigarettes, (2) health, (3) the influence of others, e.g., a doctor or a friend, (4) aesthetic or moral objections to smoking, (5) the cost of smoking, and (6) the desire to have athletic abilities unimpaired (this was a more important reason among males than females) (*79*).

Green (*32*) speculates that the increasing social pressures against smoking may be creating some new reasons for not smoking. For example, smokers are being made to feel more and more that their smoking is an unwelcome nuisance to other people, and this may motivate some smokers to try to give up cigarettes.

Horn (*37*) emphasizes four aspects of the perception of the health threats of smoking that may be crucial to the decision to try to stop smoking: (1) becoming aware of the threat, (2) accepting that the threat is important, (3) accepting that the threat is personally relevant, and (4) becoming aware that something can be done about the threat. Eisinger (*23*) has found that, of those reporting an acquaintance whose health has been affected by smoking, 27.1 percent quit smoking; only 9.7 percent of those reporting no such acquaintance quit smoking.

Many smokers come to realize that they are dependent on cigarettes; this realization can lead to low motivation to try to quit smoking (*75*). Mausner (*55*) has studied the reasons that successful and unsuccessful abstainers give for stopping smoking. He concludes that, in general, people decide to stop because of an increased expectation of the benefits derived from stopping, rather than because of the fear of the consequences of continuing to smoke. Most smokers believe that smoking is bad. The people who continue to smoke tend to find not

smoking more aversive than the prospect of continuing to smoke; those who stop tend to be able to convince themselves that not smoking would be worth the effort (*55*).

Multiple Drug Use

Unsuccessful abstainers from cigarettes, relative to quitters, are likely to be heavier users of other drugs, especially alcohol and caffeine (*34, 56, 96*). Little attention has been given to the special problems of people trying to abstain from more than one drug at once or to the possibilities of a user substituting for the absence of one drug by increasing the consumption of another (*45*). Thomas (*96*) analyzed correlates of quitting in light (less than 20 cigarettes per day) and heavy smokers (20 or more per day), and proposed that the greater alcohol and coffee consumption of the heavy smokers—along with higher anger and anxiety scores—made smoking cessation a more difficult feat for them to accomplish. There are some indications of sex differences in the relationship between alcohol intake and successful smoking cessation: among males, heavier drinkers were less likely to quit (*34, 93*); among females, heavier drinkers were more likely to quit (*93*), or no significant relationship between drinking and smoking cessation was found (*34*).

Social Factors

Social Class

The data on the effects of social class or socioeconomic status on quitting smoking are full of conflict. Eisinger (*23*) in a large sample study found no relationship between education level and smoking cessation. Ryan (*77*) found that among nonstudent males under age 60 (N = 206) in Greenfield, Iowa, successful abstention was much more common in those scored as being in the upper class. In the Midtown Manhattan study (*93*), for men, socioeconomic status was unrelated to becoming an ex-smoker; for women, there was some indication that lower class smokers were less likely to quit (no statistical tests are reported for this), but the authors assert that the sexes are "quite similar on all three SES levels in their smoking to non-smoking conversion percentages." Meyer, et al. (*59*) conclude from a study of approximately 200 individuals in the New York City area that blue-collar workers had less difficulty in quitting than did white-collar workers. An interesting theory was proposed to account for this finding: a member of the blue-collar group was felt to experience less pressure against becoming a smoker than was a white-collar group member; hence, white-collar workers constitute a specially selected group of high-need smokers for whom smoking, from the start, was important enough to maintain in spite of greater interpersonal pressures not to smoke. Unfortunately, this theory may be trying to

account for a phenomenon (white-collar smokers have a harder time quitting) that is far from reliable, as witnessed by the preceding review.

Family and Peer Pressures

The weight of evidence indicates that a smoker who has a spouse who smokes will be less likely to be a successful abstainer (*59, 88, 95, 103*). West, et al. (*103*) found that the smoking habits of the smoker's friends, work associates, siblings, mother or father were unrelated to being able to quit. Schwartz and Dubitzky (*88*) indicate that smoking friends can make a smoker less likely to be able to quit. Caplan, et al. (*13*) have described individual differences in a smoker's dependence on social support, not specifically related to smoking; smokers with low work loads and low social support were much more likely to be able to quit than were those with high work loads or with high social support. Smokers with Type A personality (hard-driving, persistent, competitive, involved in work, overloaded with work) were more likely to be unable to quit than those with Type B personality (having opposite characteristics to the Type A). This report is recommended highly for the appropriateness of its use of multivariate techniques to deal with complicated confounding influences on abstention. Eisinger (*24*) found that the "number of former smokers among their 20 best known friends" was directly related to successful abstention.

Sex Roles

Successful abstainers are more likely to be males than females; Eisinger reports 70.4 versus 29.6 percent (*24*). The smaller percentage of females who are able to quit smoking is one of the most reliable findings in the literature (*23, 24, 34, 103*). Bosse and Rose (*9*), using a national probability sample (N=5,704), tested the hypothesis that the growing convergence of male and female sex roles would lead to a decrease in the difference in male and female rates of smoking cessation. They found that younger male and female smokers were showing equivalent abstention rates; they described this effect as "the equalitarian shift." They found, then, that both age and sex were related to successful quitting, and, in addition, that "knowing someone whose health had been affected by smoking and who had quit" had an even greater effect on quitting.

Profiles of Successful Abstainers

In a cluster analysis performed on 252 male subjects attending a treatment clinic, Schwartz and Dubitzky (*88*) isolated 5 important factors (clusters) that combined to yield 12 types of subject. The first cluster concerned personal adjustment in work, achievement, sex, and social situations. The second cluster combined chronic illness and

anxiety along with recent respiratory ailments and use of psychiatric care. Cluster 3 was labeled perception of smoking; low scores here indicated belief in the health dangers of smoking. The fourth cluster was an equivalent to the chronic, habitual, addictive smoking syndrome described by Tomkins (*97*). The fifth cluster combined the Tomkins concepts of negative and positive affect smoking with positive attitudes toward smoking. For a detailed discussion of the 12 types, consult Schwartz and Dubitzky (*88*). These types were determined without regard to success in smoking withdrawal. When success in withdrawal is considered, the types can be reduced to more general groups of successful abstainers. Four of the types contained 60 percent of the continuing successes and only 20 percent of the failures. All these types had good adjustment, low chronic illness and anxiety, and low chronic, habitual, addictive smoking scores. Three of the types contained a significantly lower incidence of treatment successes. These types were distinguished either by very high chronic illness and anxiety or were high in chronic, habitual, addictive smoking. This latter finding underscores the need for more research on the dependence processes associated with cigarette smoking.

Two other factors were shown to discriminate successful individuals from recidivists. Those subjects who had friends or a wife who smoked were less likely to succeed, and those who had lower socioeconomic status were less likely to abstain. Based on earlier sections of this review, the first factor is more likely to be a significant influence on abstention than is the second.

Straits' (*95*) discriminant function analysis generally confirms the pattern found by Schwartz and Dubitzky. The roles of personal adjustment and chronic illness and anxiety in smoking cessation are generally supported by the earlier sections of the present review.

One final point needs to be made. There is mounting evidence, especially in some large sample studies like that of West and associates (*103*), that measures of cigarette dependence (for example, number of cigarettes smoked per day) are directly and often markedly related to increased inability to quit smoking (*15, 23, 39, 89, 103*).

Some General Psychosocial Influences On Smoking

Mass Media and Smoking

There is little persuasive empirical research available on the effects of television advertising, or its ban, on cigarette sales or on recruitment to the ranks of smoking. Bans on television advertising for cigarettes in several countries, including the United Kingdom, Denmark, Ireland, New Zealand, and Italy, seem to have had almost no effect on per capita cigarette consumption (*52*). A highly technical, econometric analysis has estimated that the 1965 ban on television advertising in the United Kingdom produced a statistically insignificant fall of 3

percent in cigarette consumption (*67*). In Communist countries, smoking is prevalent without advertising of any sort to support it. Four years after the 1970 ban on television advertising in the United States, there was little indication that this mass medium had a major influence on cigarette consumption (*104*). An econometric analysis by Warner (*100*) in 1977 suggested, however, that the sustained antismoking activities, including mass media, that have been conducted since 1964 may have prevented consumption of tobacco from rising even further than it already has.

Whiteside (*104*) has presented an interesting, though speculative, analysis of media influences on smoking. From 1922 to 1952 in the United States, cigarette sales increased 639 percent; over the same period, the population grew only 54 percent. Cigarette advertising, he argues, had a large effect on building the cigarette market. More recently, however, the cigarette market has been in a relatively mature, stable state and has had a much lower rate of growth. As the cigarette industry has asserted, the major action of cigarette advertising now seems to be to shift brand preferences, to alter market shares for a particular brand. Whiteside notes that, when television advertising was banned, the cigarette industry increased its use of direct marketing techniques, such as displays and promotions at the point of sale. This rechannelling of advertising makes it difficult to evaluate the independent effect of the television ban on cigarette sales.

Foote (*29*) proposes that the downturn in per capita cigarette sales in the United States from mid-1967 to 1970 was the result of the increase in antismoking ads on television. The Federal Communications Commission applied its so-called Fairness Doctrine to cigarette commercials in 1967, thereby requiring broadcasters to provide free time for the presentation of antismoking advertising. The application of the Fairness Doctrine led in 1970 to about $60 million of free television air time being provided to antismoking campaigns. After the ban on cigarette advertising, a major source of subsidy was removed from antismoking campaigns and they became a much less common sight on television. Per capita cigarette consumption began to increase again. The correlation between cigarette consumption trends and antismoking campaigns on television is provocative, but Foote's interpretation of this relationship is open to debate.

Economic Pressures and Smoking

Russell (*72*), in a regression analysis study of the relationship between cigarette costs and cigarette consumption, concluded that the smoking by British males was very sensitive to price changes. Such analyses are necessarily complex and, depending on the particular years considered, the correlations between cigarette consumption and cost ranged from -.52 to -.92. Another econometric analysis has challenged Russell's conclusions and suggests that males are relatively unresponsive to

price changes and that females are relatively responsive to them (*4*). Discussing both of the above projects and presenting a new analysis of British data, Peto (*67*) concluded that male cigarette consumption between 1951 and 1970 did show marked responsiveness to price changes. Schachter (*81*) has also argued that cigarette cost can have an influence on the composition of the ranks of smokers.

Economists have developed the concept of "elasticity" to refer to the demand for a product as a function of price. The elasticity of product demand is the percent change in consumption that results from a 1 percent price change. Russell's elasticity estimates for cigarettes indicate that for every 1 percent rise in price estimates, consumption fell by .6 percent. According to usual standards, this shows that cigarette demand is relatively inelastic.

Cross-cultural Perspectives

Damon (*20*) has studied the use of tobacco in seven preliterate or primitive societies, four in the Solomon Islands, Melanesia, and three in sub-Saharan Africa. All seven of the societies had access to locally grown tobacco, as well as cured tobacco. Damon was especially interested in evaluating social reasons for smoking. He found that, unless forbidden by religion, all adults smoked as much as possible. Four of the Melanesian tribes and one African tribe did not "report or recognize social factors as a major stimulus or support for smoking." Their dominant motive was personal gratification. Damon argues that physiological satisfaction is the major controlling influence on smoking in these five groups, even though each is aware that smoking is bad for health. The primacy of physiological factors is further supported by (1) the rapid adoption of smoking once it is introduced, (2) its widespread use unless forbidden by religion, and (3) the frequent inability of smokers to go without tobacco for even a few days. Two African tribes did recognize some social uses of tobacco, in addition to the underlying motive of physiological satisfaction. One of these groups, the Bushmen, had incorporated tobacco-smoking into some of their important social rituals. Damon concludes: "On the whole, among these seven societies personal gratification is much stronger than social influence in maintaining the smoking habit."

Personal gratification is often not considered a socially acceptable motive for drug use in the United States (*10*) and probably in many other Western industrialized cultures. The so-called Protestant work ethic is harsh toward such hedonistic motives and is likely to be much milder toward social motives. Perhaps we in industrialized cultures may have cultural "blinders" to the physiological pleasures of smoking and a special cultural need to emphasize social uses of smoking, although recent scientific research on smoking has been moving away from the long-defended notion that cigarettes produce only a psychological dependence and toward the idea that they produce a

physiological dependence (*75*, *82*). Conversely, perhaps some of the primitive groups have been biased against recognizing the social uses of tobacco and culturally predisposed to acknowledge the physiological pleasures of smoking.

Recommendations for Future Research

Specific recommendations about future research were made at a few points in this selective review of the literature, but several general points which echo the advice of other authorities (*19*, *22*, *49*, *68*) should be stated. There are multiple psychosocial influences on cigarette smoking. Multivariate research is needed—with as many as possible of the known factors measured within any one project. Only multivariate research can begin to deal with the problems of substantial intercorrelations and interactions among predictor variables. Large samples are needed for reliable multivariate work. Life-span longitudinal projects are much more valuable than one-shot cross-sectional studies. The small amount of longitudinal data already gathered has given us our most unambiguous and interesting information about psychosocial influences on smoking.

Psychosocial Influences on Cigarette Smoking: References

(1) ABELSON, H.I., FISHBURNE, P.M. Nonmedical Use of Psychoactive Substances. 1975/6 Nationwide Study Among Youth and Adults. Princeton, N.J., Response Analysis Corporation, September 1976, 189 pp.

(2) ADESSO, V.J., GLAD, W.R. A behavioral test of a smoking typology. Addictive Behaviors 3(1): 35-3°, 1978.

(3) ANNIS, H.M. Patterns of intra-familial drug use. British Journal of Addiction 69(4): 361-369, December 1974.

(4) ATKINSON, A.B., SKEGG, J.L. Control of smoking and price of cigarettes—a comment. British Journal of Preventive and Social Medicine 28: 45-48, 1974.

(5) BERMAN, A.L. Smoking behavior: How is it related to locus of control, death anxiety, and belief in afterlife? Omega 4(2): 149-155, 1973.

(6) BEST, J.A. Tailoring smoking withdrawal procedures to personality and motivational differences. Journal of Consulting and Clinical Psychology 43(1): 1-8, February 1975.

(7) BEWLEY, B.R., BLAND, J.M. Academic performance and social factors related to cigarette smoking by schoolchildren. British Journal of Preventive and Social Medicine 31: 18-24, 1977.

(8) BORLAND, B.R., RUDOLPH, J.P. Relative effects of low socio-economic status, parental smoking and poor scholastic performance on smoking among high school students. Social Science and Medicine 9(1): 27-30, January 1975.

(9) BOSSE, R., ROSE, C.L. Smoking cessation and sex role convergence. Journal of Health and Social Behavior 17(1): 53-61, March 1976.

(10) BRECHER, E.M. AND THE EDITORS OF CONSUMER REPORTS. Licit and Illicit Drugs. Boston, Little, Brown, and Company, 1972, pp. 209-244.

(11) BREHM, J. W. Responses to loss of freedom: A theory of psychological reactance. Morristown, New Jersey, General Learning Press, 1972, 26 pp.

(12) BURTON, D. Consistency versus internality as initiators of behavior change. International Journal of the Addictions 12(4): 553-563, June 1977.

(13) CAPLAN, R.D., COBB, S., FRENCH, J.R.P. Relationships of cessation of smoking with job stress, personality, and social support. Journal of Applied Psychology 60(2): 211-219, 1975.

(14) CATTELL, R.B., KRUG, S. Personality factor profile peculiar to the student smoker. Journal of Counseling Psychology 14(2): 116-121, March 1967.

(15) CHERRY, N., KIERNAN, K. Personality scores and smoking behaviour. A longitudinal study. British Journal of Preventive and Social Medicine 30(2): 123-131, June 1976.

(16) CLARK, R. Cigarette smoking among teen-age girls and young women: Summary of the findings of a survey conducted for the American Cancer Society. In: Wakefeld, J. (Editor). Public Education About Cancer: Recent Research and Current Programmes. UICC Technical Report Series, Volume 24, Geneva, 1976, pp. 39-46.

(17) CLAUSEN, J.A. Adolescent antecedents of cigarette smoking: Data from the Oakland growth study. Social Science and Medicine 1(4): 357-379, January 1968.

(18) COAN, R.W. Personality variables associated with cigarette smoking. Journal of Personality and Social Psychology 26(1): 86-104, April 1973.

(19) COAN, R.W. Research strategy in the investigation of personality correlates. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 133-141.

(20) DAMON, A. Smoking attitudes and practices in seven preliterate societies. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 219-230.

(21) DAWBER, T.R., KANNEL, W.B., GORDON, T. Coffee and cardiovascular disease. Observations from the Framingham Study. New England Journal of Medicine 291(17): 871-874, October 24, 1974.

(22) DUNN, W.L., JR. Experimental methods and conceptual models as applied to the study of motivation in cigarette smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 93-111.

(23) EISINGER, R.A. Psychosocial predictors of smoking behavior change. Social Science and Medicine 6(1): 137-144, February 1972.

(24) EISINGER, R.A. Psychosocial predictors of smoking recidivism. Journal of Health and Social Behavior 12: 355-362, December 1971.

(25) EVANS, R.R., BORGATTA, E.F., BOHRNSTEDT, G.W. Smoking and MMPI scores among entering freshmen. Journal of Social Psychology 73: 137-140, October 1967.

(26) EYSENCK, H.J. Personality and the maintenance of the smoking habit. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 113-146.

(27) EYSENCK, H.J. Smoking, Health and Personality. New York, Basic Books, 1965, pp. 75-106.

(28) EYSENCK, H.J. Smoking, personality and psychosomatic disorders. Journal of Psychosomatic Research 7(2): 107-130, October 1963.

(29) FOOTE, E. The time has come: Cigarette advertising must be banned. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 339-346.

(30) FOSS, R. Personality, social influence and cigarette smoking. Journal of Health and Social Behavior 14(3): 279-286, September 1973.

(31) GOODE, E. Cigarette smoking and drug use on a college campus. International Journal of the Addictions 7(1): 133-140, February 1972.

(32) GREEN, D.E. Psychological factors in smoking. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 149-155.

(33) GROVES, W.E. Patterns of college student drug use and lifestyles. In: Josephson, E., Carroll, E.E. (Editors). Drug Use: Epidemiological and Sociological Approaches. Washington, D.C., Halsted Press, 1974, pp. 241-275.

(34) GUILFORD, J.S. Factors Related to Successful Abstinence from Smoking: Final report. U.S. Public Health Service, Division of Chronic Diseases, Bureau of State Services, July 1966, 170 pp.

(35) HERMAN, C.P. External and internal cues as determinants of the smoking behavior of light and heavy smokers. Journal of Personality and Social Psychology 30(5): 664-672, November 1974.

(36) HJELLE, L.A., CLOUSER, R. Internal-external control of reinforcement in smoking behavior. Psychological Reports 26(2): 562, April 1970.

(37) HORN, D. Some factors in smoking and its cessation. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 12-21.

(38) IKARD, F.F., GREEN, D.E., HORN, D. A scale to differentiate between types of smoking as related to the management of affect. International Journal of the Addictions 4(4): 649-659, December 1969.

(39) JACOBS, M.A. The addictive personality: Prediction of success in a smoking withdrawal program. Psychosomatic Medicine 34(1): 30-38, January/February 1972.

(40) JACOBS, M.A., KNAPP, P.H., ANDERSON, L.S., KARUSH, N., MEISSNER, R., RICHMAN, S.J. Relationship of oral frustration factors with heavy cigarette smoking in males. Journal of Nervous and Mental Diseases 141(2): 161-171, August 1965.

(41) KANDEL, D. Interpersonal influences on adolescent illegal drug use. In: Josephson, E., Carroll, E.E. (Editors). Drug Use: Epidemiological and Sociological Approaches. Washington, D.C., Halsted Press, 1974, pp. 207-240.

(42) KANDEL, D. Stages in adolescent involvement in drug use. Science 190: 912-914, November 1975.

(43) KANEKAR, S., DOLKE, A.M. Smoking, extraversion, and neuroticism. Psychological Reports 26: 384, February-June 1970.

(44) KOZLOWSKI, L.T. Effect of caffeine on coffee drinking. Nature 264 (5584): 354-355, November 25, 1976.

(45) KOZLOWSKI, L.T. Effects of caffeine consumption on nicotine consumption. Psychopharmacology 47: 165-168, May 28, 1976.

(46) KOZLOWSKI, L.T., HARFORD, M.A. On the significance of never using a drug: An example from cigarette smoking. Journal of Abnormal Psychology 85(4): 433-434, August 1976.

(47) LARSON, P.S., HAAG, H.B., SILVETTE, H. Tobacco: Experimental and Clinical Studies: A Comprehensive Account of the World Literature. Baltimore, Williams and Wilkins Company, 1961, pp. 526-551.

(48) LARSON, P.S., SILVETTE, H. Tobacco: Experimental and Clinical Studies, Supplement I. Baltimore, Williams and Wilkins Company, 1968, pp. 259-322.

(49) LEBOVITS, B., OSTFELD, A. Smoking and personality: A methodological analysis. Journal of Chronic Diseases 23(10/11): 813-821, March 1971.

(50) LEBOVITS, B., OSTFELD, A.M., MOSES, V.K., PAUL, O. Cigarette smoking and personality. Journal of Chronic Diseases 25(10/11): 581-598, 1972.

(51) LEVENTHAL, H., AVIS, N. Pleasure, addiction, and habit: Factors in verbal report or factors in smoking behavior? Journal of Abnormal Psychology 85(5): 478-488, October 1976.

(52) LEVITT, E.E. The television cigarette commercial: Teenage transducer or paper tiger? Yale Scientific Magazine 45(1): 10-13, October 1970.

(53) LICHTENSTEIN, E., KEUTZER, C.S. Further normative and correlational data on the internal-external (I-E) control of reinforcement scale. Psychological Reports 21(3): 1014-1016, December 1967.

(54) MATARAZZO, J.D., SASLOW, G. Psychological and related characteristics of smokers and nonsmokers. Psychological Bulletin 57(6): 493-513, November 1960.

(55) MAUSNER, B. An ecological view of cigarette smoking. Journal of Abnormal Psychology 81(2): 115-126, April 1973.

(56) MCARTHUR, C., WALDRON, E., DICKINSON, J. The psychology of smoking. Journal of Abnormal Psychology 56(2): 267-275, March 1958.

(57) MCKENNELL, A.C. British research into smoking behavior. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 140-164.

(58) MCKENNELL, A.C. A comparison of two smoking typologies. Research Paper 12. London, Tobacco Research Council, 1973, 95 pp.

(59) MEYER, A.S., FRIEDMAN, L.N., LAZARSFELD, P.F. Motivational conflicts engendered by the on-going discussion of cigarette smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 243-254.

(60) NATIONAL CANCER INSTITUTE. AMERICAN CANCER SOCIETY. Cigarette Smoking Among Teen-agers and Young Women. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1203, 1975, 31 pp.

(61) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1976, 23 pp.

(62) NESBITT, P.D. Chronic smoking and emotionality. Journal of Applied Social Psychology 2(2): 187-196, April-June 1972.

(63) NESBITT, P.D. Smoking, physiological arousal, and emotional response. Journal of Personality and Social Psychology 25(1): 137-144, January 1973.

(64) NISBETT, R., WILSON, T.D. Telling more than we can know: Verbal reports on mental processes. Psychological Review 84(3): 231-259, May 1977.

(65) O'ROURKE, T.W. Research on smoking behavior: Some limitations and suggestions for improvement. Public Health Reviews 2(1): 105-112, February 1973.

(66) PALMER, A.B. Some variables contributing to the onset of cigarette smoking among junior high school students. Social Science and Medicine 4(3): 359-366, September 1970.

(67) PETO, J. Price and consumption of cigarettes: A case for intervention? British Journal of Preventive and Social Medicine 28: 241-245, 1974.

(68) REEDER, L.G. Sociocultural factors in the etiology of smoking behavior: An assessment. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 186-200.

(69) REYNOLDS, C., NICHOLS, R. Personality and behavioral correlates of cigarette smoking: One-year follow-up. Psychological Reports 38(1): 251-258, February 1976.

(70) RODE, A., ROSS, R., SHEPHARD, R.J. Smoking withdrawal programme. Personality and cardiorespiratory fitness. Archives of Environmental Health 24: 27-36, January 1972.

(71) RUDOLPH, J.P., BORLAND, B.L. Factors affecting the incidence and acceptance of cigarette smoking among high school students. Adolescence 11(44): 519-525, Winter 1976.

(72) RUSSELL, M.A.H. Changes in cigarette price and consumption by men in Britain, 1946-71: A preliminary analysis. British Journal of Preventive and Social Medicine 27: 1-7, 1973.

(73) RUSSELL, M.A.H. Cigarette smoking: Natural history of a dependence disorder. British Journal of Medical Psychology 44(1): 1-16, May 1971.

(74) RUSSELL, M.A.H. The smoking habit and its classification. Practitioner 212: 791-800, June 1974.

(75) RUSSELL, M.A.H. Smoking problems: An overview. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 13-34.

(76) RUSSELL, M.A.H., PETO, J., PATEL, U.A. The classification of smoking by factorial structure of motives. Journal of the Royal Statistical Society A 137 (Part 3): 313-332, 1974.

(77) RYAN, F.J. Cold turkey in Greenfield, Iowa: A follow-up study. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 231-241.

(78) SALBER, E.J., ABELIN, T.. Smoking behavior of Newton school children—5-year follow-up. Pediatrics 40 (3, part I): 363-372, September 1967.

(79) SALBER, E.J., WELSH, B., TAYLOR, S.V. Reasons for smoking given by secondary school children. Journal of Health and Human Behavior 4: 118-129, 1963.

(80) SCHACHTER, S. Nesbitt's paradox. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 147-155.

(81) SCHACHTER, S. Nicotine regulation in heavy and light smokers. Journal of Experimental Psychology: General 106(1): 5-12, March 1977.

(82) SCHACHTER, S. Pharmacological and psychological determinants of smoking. Annals of Internal Medicine 88(1): 104-114, January 1978.

(83) SCHACHTER, S., KOZLOWSKI, L.T., SILVERSTEIN, B. Effects of urinary pH on cigarette smoking. Journal of Experimental Psychology: General 106(1): 13-19, March 1977.

(84) SCHACHTER, S., SILVERSTEIN, B., PERLICK, D. Psychological and pharmacological explanations of smoking under stress. Journal of Experimental Psychology: General 106(1): 31-40, March 1977.

(85) SCHUBERT, D.S.P. Arousal seeking as a central factor in tobacco smoking among college students. International Journal of Social Psychiatry 11(3): 221-225, Summer 1965.

(86) SCHUMAN, L.M. Patterns of smoking behavior. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 36-65.

(87) SCHWARTZ, J.L. Insights into the smoker's profile. Journal of School Health 40: 127-131, March 1970.

(88) SCHWARTZ, J.L., DUBITZKY, M. Requisites for success in smoking withdrawal. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 231-247.

(89) SIMON, W.E., PRIMAVERA, L.H. The personality of the cigarette smoker: Some empirical data. International Journal of the Addictions 11(1): 81-94, February 1976.

(90) SMITH, G.M. Personality correlates of cigarette smoking in students of college age. Annals of the New York Academy of Sciences 142 (Article 1): 308-321, March 15, 1967.

(91) SMITH, G.M. Personality and smoking: A review of the empirical literature. In: Hunt, W.A. (Editor). Learning Mechanisms in Smoking. Chicago, Aldine Publishing Company, 1970, pp. 42-61.

(92) SPEVACK, M., PIHL, R.O. Nonmedical drug use by high school students: A three-year survey study. International Journal of the Addictions 11(5): 755-792, October 1976.

(93) SROLE, L., FISCHER, A.K. Smoking behavior 1953 and 1970: The midtown Manhattan study. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 255-265.

(94) STOKES, J.P. Personality traits and attitudes and their relationship to student drug using behavior. International Journal of the Addictions 9(2): 267-287, April 1974.

(*95*) STRAITS, B.C. The discontinuation of cigarette smoking: A multiple discriminant analysis. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tuscon, University of Arizona Press, 1967, pp. 79-81.

(*96*) THOMAS, C.B. The relationship of smoking and habits of nervous tension. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V.H. Winston and Sons, 1973, pp. 157-170.

(*97*) TOMKINS, S. A modified model of smoking behavior. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 165-186.

(*98*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. PHS Bulletin No. 1103, 1964, 387 pp.

(*99*) U.S. PUBLIC HEALTH SERVICE. State Legislation on Smoking and Health: 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, December 1976, 73 pp.

(*100*) WARNER, K.E. The effects of the antismoking campaign on cigarette consumption. American Journal of Public Health 67 (7): 645-650, 1977.

(*101*) WATERS, W.E. Smoking and neuroticism. British Journal of Preventive and Social Medicine 25(3): 162-164, August 1971.

(*102*) WEATHERLEY, D. Some personality correlates of the ability to stop smoking cigarettes. Journal of Consulting Psychology 29(5): 483-485, October 1965.

(*103*) WEST, D.W., GRAHAM, S., SWANSON, M., WILKINSON, G. Five year follow-up of a smoking withdrawal clinic population. American Journal of Public Health 67(6): 536-544, June 1977.

(*104*) WHITESIDE, T. Smoking still. New Yorker 50(39): 121-151, November 18, 1974.

(*105*) WIGGINS, J.S. Personality structure. In: Farnsworth, P.R., Rosensweig, M.R., Polefka, J.T. Annual Review of Psychology 19. Palo Alto, California, Annual Reviews, Inc., 1968, pp. 293-350.

(*106*) WYNDER, E.L. Interrelationship of smoking to other variables and preventive approaches. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education. and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 67-97.

19. MODIFICATION OF SMOKING BEHAVIOR.

National Institute on Drug Abuse

Contents

Introduction

Since the health consequences of smoking became more evident in the early 1960's, the development of techniques to aid smokers to quit have proliferated. The methods have ranged widely from gimmicks and over-the-counter cessation aids to formal programs and clinics (*368, 376*). Thus, the concerned professional or layman with an interest in assisting smokers in the process of cessation may find it very difficult to decide which intervention strategy is best or most useful. The social relevance of the topic has focused much of the effort in the field toward clinical presentations of what logically appeared to be the best withdrawal techniques or strategies rather than toward careful research to define what strategy, method, or program is most effective in producing long-term successes or positive changes in smoking behavior. Remarkably, a wide variety of interventions has been offered and recommended to the public, but outcome data needed for critical appraisal of them are scarce.

The task of evaluating the relative efficacy of programs and techniques has been very adequately done in numerous past and recent reviews (*24, 26, 29, 40, 171, 200, 224, 226, 230, 245, 366, 368, 376, 413*). Therefore, this review can be selective in order to allow discussion of critical topics and encourage new developments in the field. The reader is referred to the other available reviews to obtain a more detailed discussion of topics that are here given brief treatment.

Methodological Issues

Any reviewer of the literature on strategies to modify smoking behavior is faced with the difficult task of sorting through outcome research that is permeated by many methodological flaws and deficiencies (*24, 26, 224, 226, 366, 368, 376*). Despite the facts that smoking behavior offers an objectively measurable target behavior, that potential treatment participants are numerous, and that the normal treatment context affords the opportunity for both good internal and external validity (*24, 200, 226, 393*), a number of methodological inadequacies continues to plague the field (*26, 29, 226, 368, 376, 413*). Therefore, the methodology and design problems that most commonly limit the appraisal of existing outcome data will be briefly summarized. Anyone concerned with smoking withdrawal programs or research, however, should refer to other comprehensive evaulations of these issues presented by Bernstein (*24*), Schwartz (*366, 376*), Lichtenstein and Danaher (*226*), and the National Interagency Council on Smoking and Health's (NICSH) *Guidelines for Research on the Effectiveness of Smoking Cessation Programs* (*272*).

The most pervasive problem in the evaluation of outcome data from smoking cessation programs is the validity of the treatment results. Almost all clinics and research studies have relied primarily upon

unverified self-reports of smoking as their critical dependent measure. Unfortunately, the verbal or written requests for estimates of number of cigarettes currently smoked per unit of time depend upon the participant's accuracy and honesty (*226*), are subject to nonspecific demand characteristics (especially during and after treatment) (*226*), and appear to be highly influenced by digit-bias (that is, given in multiples of 5 or 1/2 pack units) (*423*). One study collecting global estimates under different conditions on the same day found questionable reliability (*423*). Thus, studies based only on global, unverified self-reports of smoking behavior must be viewed with skepticism.

Because of these factors, the rate measure based on such global estimates tends to be more an ordinal than a ratio variable (*396*). Nevertheless, rate-per-unit-of-time data often have been preferred over the dichotomous abstinent-nonabstinent or percent-reduction categories, which clearly require the use of less powerful nonparametric statistical analyses (*226, 393, 396*). The use of self-monitoring recording has been recommended in various forms (*109, 198, 226, 250, 272*) and commonly used in many studies to enhance both the reliability and psychometric qualities of the rate data. However, the procedure is known to be reactive (*198, 250*), is still susceptible to the demand characteristics (*198, 226*), and tends to underestimate the "real" baseline or follow-up rate (*109, 198, 226, 250*).

Studies not relying on smoking rates as the primary dependent measure have commonly utilized various and often undefined success-failure categories to minimize the problems of self-report data (*24, 366*). Standard categories have been suggested to avoid ambiguity (*272*); however, the primary evaluation of treatment-results based on abstinence data can be recommended for several reasons. First, abstinence is the primary goal of almost all smokers seeking treatment (*24, 25, 40, 171, 226, 366*). Second, follow-up data on smokers have indicated that most smokers who fail to attain abstinence eventually return to baseline smoking rates (*24, 26, 171, 251*). Third, analyses of rate data can yield statistically significant treatment effects even with a clinically insignificant proportion of participants abstinent at follow-up (*251, 366, 376*). Fourth, abstinence reports are less susceptible to nonspecific demand characteristics and the reactivity of self-monitoring (*226*). Nevertheless, when derived from reliably collected self-monitoring data, cigarettes-per-day rate data or the more precise percentage-or-baseline (current smoking ÷ pretreatment smoking rate x 100) variable (*199, 200, 226*) can be very helpful as secondary measures for testing finer theoretical questions with parametric statistical techniques (*24, 200, 226, 272*). Because treatment will often produce a marked, positive skewness in the distributions of rates (that is, greatly increased frequency of rates at or near zero), care should be taken to test the homogeneity of variance and to apply transforma-

tions as necessary before utilizing analysis-of-variance procedures, especially with cell frequencies of unequal size (*71, 292, 445*).

Optimally, self-report data on smoking should be validated by an objective measure. False reporting has now been documented in both children (*99, 154, 262*) and adults in cessation programs (*47, 82, 178, 283*). Natural-environment informants or observers have been recommended and used in many studies, but the systems are reactive, difficult to maintain, and, owing to possible collusion, have questionable validity (*47, 226*). Biochemical tests for objectively measuring smoking exposure are clearly more desirable. Measurements of blood carboxyhemoglobin (COHb) (*61, 192, 320, 330, 397, 427*) and thiocyanates (SCN^-) in biologic fluids (*18, 54, 75, 83, 238, 299, 300, 444*) have been demonstrated to be reliable indicators of smoking behavior. Concentrations of carbon monoxide (CO) in alveolar air is directly proportional to blood COHb concentrations (*61, 320, 330, 397*) and has been recommended as a simple validating tool (*208*). However, CO concentrations have a very short half-life (*330, 397*) and show high diurnal variability (*61, 258, 330*). Thus, SCN concentrations that have a biologic half-life of approximately 14 days (*299*) are more suited for validation of self-reports (*47, 54, 423, 424*). Determinations of serum SCN^- have been more common (*47, 54, 83, 423*), but tests of urine or saliva are also possible and may be more practical in many clinical settings (*18, 99, 262*). Unfortunately, COHb levels are affected by various environmental exposures (*192, 397, 427*) and SCN^- concentrations can be elevated by diet (*47*). Singly, however, they provide a crude measure of smoking rate (*423, 424*) with adequate discrimination between smokers and nonsmokers; together they appear to provide a very powerful test of abstinence (*423, 424*).

In summary, researchers should be aware that uncorroborated self-reports may lead to an overestimation of success, especially in situations where subjects are under social pressure to quit or to report quitting. The addition of objective biological assays can help to validate self-report data and improve the ability to assess outcome, using the self report as a low-cost, easily obtainable, dependent measure.

In addition to the problem of questionable validity of self-reports that faces all researchers, various design deficiencies also plague the field (*24, 200, 226, 272, 304, 366, 367, 376, 398*). First, attributions of causality of outcome results to independent treatment factors are virtually impossible without systematic designs, including appropriate experimental controls (*24, 56, 391*). Initial demonstrations of efficacy may be evaluated relative to commonly expected norms of success (*245, 304*); such clinical demonstrations must then be replicated versus appropriate control conditions, especially attention-placebo controls (*24, 26, 200, 226, 230, 245, 251, 272, 304, 366, 367, 376, 398*). Few procedures or programs developed in clinical settings have progressed

to experimental validation (*24, 40, 245, 304, 366, 367, 376, 398, 413*). Moreover, Straits (*398*) has suggested that the strength of laboratory research involves testing more complicated questions than treatment efficacy. Factorial designs enable one to evaluate specific treatment effects as well as more complex multidimensional and interactional effects and thus permit the simultaneous testing of several theoretical issues (*398*).

Systematic treatment evaluations must also include comprehensive and adequate follow-up of participants (*24, 26, 171, 272, 366, 368, 376*). Almost all treatments are able to show dramatic post-treatment effects, but rapid relapse in most participants has been the norm (*170, 171, 251, 366*). Therefore, no treatment can be adequately evaluated without long-term follow-up data. Recidivism tends to be the greatest during the first 3 to 4 months after treatment and relatively slight after 6 months (*170, 171*), but a 1-year follow-up remains highly recommended (*272, 366, 368, 376*).

Comprehensiveness of follow-up is as important as length, if not more so. Schwartz (*366, 368, 376*) has strongly emphasized that all participants, including early-treatment dropouts, should be used in computing treatment effectiveness. Additional analyses of subjects completing most treatments are useful to clarify theoretical issues (*24, 226*); however, the relative efficacy of the procedure should be judged on the stricter standard (*272, 366, 368, 376*). Follow-up results based only on participants who respond or who are readily available are especially suspect (*24, 272, 366, 368, 376*).

The final issue that commonly affects outcome data from smoking-modification studies involves the replicability and generalization of results. Programs and studies with reportedly very similar procedures have produced highly variable patterns of results (*24, 26, 40, 171, 200, 226, 230, 366, 376, 413*). This, it seems, is due in part to the variability introduced by small samples and population differences (*24, 171, 226, 272*) and the inadequacies of theoretical models guiding the descriptions of treatment variables (*24, 272, 306, 398*). In an effort to minimize these deficiencies, the NICSH *Guidelines* (*272*) stress the need to describe completely the recruitment and selection of participants, their characteristics, and the specifics of each aspect of treatment. Keutzer, et al. (*200*) have also discussed the problems of uncontrolled variability from group treatment and inexperience of the therapist or experimenter.

Thus, conclusions regarding the relative efficacy of treatments can be reliably made only when methodological deficiencies are at a minimum (*272*). The quality of the data has improved markedly since the early reviews (*24, 200, 366*), but almost all studies remain deficient in some respect (*368, 376*). Many programs have collected little or no objective follow-up data, and the lack of methodological rigor compromises the results of many others that have. Therefore, based

upon current data, the replicability and general utility of almost all procedures can be only tentatively assessed.

Review of General, Nonspecific Interventions

A variety of interventions has been developed and offered with the primary goal of aiding a group of smokers to become nonsmokers rather than testing how the procedures may work (*398*). Various reviewers have analyzed the data on this type of intervention, which includes public service and proprietary withdrawal clinics, individual or medical counseling, and large scale coronary prevention trials. Except for the coronary prevention trials, the clinical-treatment focus of these interventions has resulted in multiple uncontrolled clinical replications, often without adequate outcome data (*24, 40, 171, 200, 245, 366, 368, 376*). Additionally, the vast public health campaign of recent years should be considered as a special class of general, nonspecific interventions both to prevent smoking onset and to stimulate cessation (*24, 40, 200*).

Public Health Educational Campaigns

The public health campaign against cigarettes has produced notable changes in public awareness of the health consequences of cigarette smoking (*175, 269, 271, 422*). It appears that the dramatic changes noted in adult smoking, especially among middle-aged males and certain professional groups (*86, 100, 121, 271, 421*), can be attributed largely to the effectiveness of information and educational campaigns since 1964 (*130, 270*). Moreover, Warner (*428*) has estimated that the effect of specific "events," such as the 1964 Surgeon General's Report, on cigarette consumption (mean number of cigarettes consumed per day) may appear small and transitory, but that the cumulative effect of persistent publicity appears to have reduced consumption by 20 to 30 percent below its predicted 1975 level.

More specifically, O'Keefe (*284*), in a study on the impact of television anti-smoking commercials during the late 1960's, revealed changes in attitudes and reported reductions in consumption but little direct impact on smoking cessation. Forty-two percent of those motivated to quit felt the commercials acted as an incentive, but only 1 percent of the ex-smokers credited the commercials with helping them quit. Similar minor effects were noted in a smaller trial with anti-smoking posters (*5*). Ryan (*353*) reported the results of an entire community's attempt to quit in 1970. Thirty-seven percent of the adults attempted to quit, and 14.2 percent of the males and 3.9 percent of the females were still reporting abstinence 7 months later, with higher socioeconomic groups being more successful. The Avdel smoking project (*98*) also seemed to have produced small but meaningful changes in both smoking attitudes and behavior with a

worksite campaign. These specific and general results of the public health campaigns appear very similar to other British (*343*) and worldwide experiences (*130, 301*).

Public Service and Proprietary Clinics

It is interesting to note that Bernstein's (*24*) comment that the educational campaigns have affected research and clinical activities more than smoking behavior still seems valid. Public service and proprietary programs have proliferated since 1964. Schwartz and Rider (*376*) have provided a summary of the published and unpublished data on these types of programs. Many such smoking-withdrawal clinics offered by voluntary agencies have been intermittent and rarely evaluated. The group program of the American Cancer Society (ACS) (*2, 3, 160*) and the 5-Day Plans of the Church of the Seventh Day Adventists (*252, 253, 254*) have, however, remained very active in providing public service treatments to smokers. Unfortunately, while the two programs together have probably helped more smokers than any other organized effort (*245, 368, 376*), only limited published outcome data are available for consideration.

The 5-Day Plan has become standardized and involves five consecutive $1^1/_2$- to 2-hour sessions focusing on immediate cessation, and dietary, physical, and attitudinal changes to reduce withdrawal effects (*252, 254*). Because of its clinical focus, almost all evaluations have been without controls (*117, 146, 147, 148, 213, 252, 253, 254, 267, 298, 366, 376, 403, 412*), with good immediate abstinence rates of approximately 60 to 80 percent, but with an approximately 50 percent relapse by 1- to 3-months post-treatment. Unfortunately, clinical claims of abstinence among 33 to 40 percent of participants beyond a year post-treatment (*146, 147, 148, 253*) are markedly discrepant from other clinical demonstrations (*213, 267, 298, 361, 412*). Guilford's comparative study of the 5-Day Plan (*137, 138*) found abstinence rates of 16 to 20 percent at 1 year that may not differ from unaided attempts (*137, 138, 412*). Nevertheless, the program appeared to be more successful with males (*137, 138, 267, 403*) and when higher expectation of success was reported by participants (*361*). Results of all studies are based on unverified self-reports, often only from subjects completing all treatments (*366, 376*).

Available long-term abstinence outcome data on the ACS group programs (*2, 3*) also appear to be somewhat disappointing. The one available evaluation of the ACS groups, which focus on insight development, group support, and self-selected cessation techniques, was conducted on 29 clinics in Los Angeles from 1970 to 1973 (*318*). Telephone follow-ups were completed on 354 subjects selected from a random sample of 487 of the original 944 participants. Abstinence rates based on the total random sample were 41.7 percent at post-treatment, and 30 percent at 6-month, 22 percent at 12-month, and 18 percent at

18-month follow-up points (*245, 318, 378*). In the subsample group of 354 subjects who were contacted (*318*), 28.4 percent of the males and 20.3 percent of the females reported abstinence.

Other clinics with similar or more elaborate formats have reported fairly equivalent outcome data (*63, 81, 82, 114, 158, 178, 213, 274, 286, 289, 433, 438, 440, 448*). The Smoking Withdrawal Study Centre in Toronto (*81, 82, 378*) used comprehensive educational groups with 472 smokers and obtained successful abstinence in 28.6 percent of all participants at 1-year follow-up, with 33.9 percent of the men and 20.8 percent of the women being successful. However, carboxyhemoglobin (COHb) assessments revealed that 22 of the 107 (20.6 percent) reported ex-smokers had levels over 5 percent, which strongly suggested smoking. A 5 percent quit rate was noted among a no-treatment control group. In a population based sample, Isacsson and Janzon (*178*) were able to produce abstinence during an intensive 6-week program among 31 of 51 participants (60 percent), with 17 (33 percent) remaining nonsmokers at 8- to 9-month follow-up. Abstinence was verified by COHb determinations. West and his colleagues (*433*) followed up 559 smoking-cessation clinic participants 5 years later and found 17.8 percent of the contacted sample reporting abstinence. Approximately two-thirds of those who had quit during the clinic had returned to smoking, while only 8 percent of the unsuccessful participants were reporting abstinence at follow-up. Older males who had lighter smoking habits and more stable environments appeared to be most successful. Research clinics (to be discussed in more detail elsewhere in this report), offering similar treatment formats, have reported similar 15 to 20 percent long-term abstinence among participants (*341, 373, 374, 380, 381, 382*).

In light of these data on public service and research withdrawal groups and clinics, the claims of more impressive results by proprietary programs must be viewed with caution (*116, 245*). Schwartz and Rider (*376*) reviewed a variety of unpublished data on commercial methods, but only one published evaluation of a commercial method is currently available. In this study (*194*), records of 553 participants of the SmokEnders program in 1971 were examined and a $3\frac{1}{2}$- to 4-year follow-up was attempted on the 385 (70 percent) who were not smoking at treatment termination. Only 167 (43.4 percent) were contacted; of these, 57 percent of the males and 30 percent of the females were not smoking. Schwartz and Rider (*376*) noted, however, that, even if the smoking rates of those contacted at follow-up accurately represent the total successful sample, the long-term success based on all participants (including treatment dropouts) would be about 27 percent rather than the reported 39 percent. As the men and women were reported to have been about equally successful at treatment termination, the higher follow-up success rate for males would still seem valid.

In viewing the data from many clinics relative to the 16 to 19 percent success at 1-year follow-up noted in Guilford's (*137, 138*) and Schwartz and Dubitzky's (*373, 374*) unaided control groups, the impact of many programs appears to have been minimal. Bernstein's (*24*) conclusion still seems valid: clinics can serve a very useful purpose when more effective modification techniques are developed for general distribution, but uncontrolled use of nonvalidated notions cannot refine those procedures. The attempts to analyze more carefully the clinic format has produced some enlightening data (*81, 82, 137, 138, 178, 318, 341, 361, 373, 374, 380, 381, 382, 433*). Long-term results imply that males in these clinics fare better than females during maintenance (*81, 82, 137, 138, 267, 341, 376, 403, 433*). Moreover, the comprehensive follow-up and physiological validating of some studies (*81, 82, 178, 373, 374*) highlight how misleading early success based on self-reports can be. The placebo effect noted in control groups highlights the fact that many of the treatment effects of clinics remain undefined (*373, 374*). More effort should be made, therefore, to evaluate on-going clinical activities so that researchable hypotheses can be illuminated for further controlled study (*24, 394*).

Individual and Medical Counseling

Smoking-cessation counseling by professionals in private practice is known to exist, but published data on its efficacy are very rare. A report on two psychotherapist-led groups suggests that long-term therapy may help some smokers (*39*); however, the cost of such treatment would seem prohibitive (*245*). In controlled studies of the type of individual and group counseling formats that could be easily and less expensively disseminated, Schwartz and Dubitzky (*373, 374*) and the American Health Foundation (*380, 381, 382*) produced 1-year abstinence rates ranging from 13 to 30 percent with no clear superiority for individual or group therapy. While individual counseling styles seemed to affect initial success and dropout rates, there were no differences in effectiveness during follow-up (*186, 431*).

Since smokers have become almost uniformly aware of the health risks of smoking (*269, 271, 422*), they view the physician as an important person in the quit-smoking decision (*271*). However, only about 25 percent of smokers surveyed in a national telephone interview reported having been advised by their physician to quit (*271*). Almost all physicians are convinced of the health consequences of smoking and have made dramatic changes in their own smoking (*121, 421*), but many seem reluctant to confront their smoking patients until serious effects are present (*55, 338*). Nevertheless, numerous studies of ex-smokers have shown that linking the increase of symptoms, such as coughing or breathlessness, to smoking was a major precipitant for unaided quitting (*51, 128, 150, 152, 190, 294, 389, 390, 399, 400, 418, 419*).

Rose (*338*) and Lichtenstein and Danaher (*227*) have reviewed the issue of physician counseling and its efficacy. In general, it appears that physicians have been discouraged from this role (*338*) and are effective as counselors only when dramatic symptoms are present (*227*, *338*). Several uncontrolled studies, done primarily in England, have shown varying success. Early studies in this country showed minimal effects (*244*, *322*). Studies abroad, on the other hand, have evaluated several important aspects of the process. Porter and McCullough (*312*) produced only 5 percent abstinence at 6 months in a briefly-counseled group, while 4 percent quit in a randomly defined uncounseled group. Handel (*153*) reported more impressive results from one brief session with 17 of 45 (38 percent) males and 6 of 55 (11 percent) females reporting abstinence at 1-year follow-up. When patients presented current respiratory symptoms, Williams (*443*) and Burns (*51*) found a higher response to brief counseling. Burns (*51*) reported 35 of 66 (53 percent) males and 9 of 28 (32 percent) females reporting completely stopping 3 months after the visit. Similarly, Williams (*443*) found that, of 204 patients routinely counseled, 59 of the 160 (37 percent) who could be contacted at 6-month follow-up were reporting abstinence, with males and females being about equally receptive.

Some of the variability of response may be due to individual physician styles. Pincherle and Wright (*302*) followed up a total of 1,493 business executive smokers for 1 to 2 years after a regular physical where smoking-cessation advice was given. Thirteen percent reported quitting and 11 percent indicated a reduction in rate of 30 percent or more; however, when the results were analyzed across various physicians giving the message, success (quitting or 30+ percent reduction) rates varied from 35 percent to 17 percent. In a similar follow-up of antismoking advice given during annual physicals, Richmond found 118 of 543 (22 percent) quit for at least 1 year; 15 subsequently relapsed, leaving a long-term success rate of 19 percent (*329*). Unfortunately, no physician-counseling study has utilized techniques to validate self-reported behavior change.

Considering the brief nature of the contact and the lack of specific maintenance follow-up, the reported rates of abstinence seem encouraging. A study by Raw (*319*) has suggested that both a physician's message and counseling by a health professional in a white coat were important in producing cessation, also suggesting that health professionals other than physicians should become more involved. Peabody (*291*) reported that with a well-developed program, 25 percent of smokers will quit after the initial counseling, 25 percent will quit after several attempts, 20 percent will eventually stop with difficulty, and only 30 percent will never respond. These expectations may be high for a general patient population, but cessation data on special groups of patients with current medical problems related to smoking are encouraging.

Patients hospitalized with their first myocardial infarction (MI) provide a dramatic example of this. Thirty to fifty percent of the smokers in this group permanently stop smoking after only routine advice (*4, 11, 68, 157, 338, 430, 432, 442*). Follow-ups on hundreds of such patients reveal that relapses back to smoking are uncommon, with 50 percent quit rates often maintained for 1 or more years (*11, 68, 338, 430, 432*). When more intensive counseling and active follow-up support were undertaken in a study by Burt and associates (*52*), 70 of 114 (61 percent) of cigarette smokers and 9 of 11 (82 percent) of cigar and pipe smokers stopped smoking after hospitalization, and only 19 (15 percent) of the smokers made no changes. At the 1-year follow-up, 9 of the immediate quit group (11 percent) and 13 of 22 (59 percent) who quit later relapsed, leaving 79 of 125 smoking (cigarette, pipe, or cigar) patients reporting abstinence (63.2 percent) with 27 (21.6 percent) having reduced. Among 120 patients given conventional advice and not followed up in the special clinic, only 27 of 98 (27.5 percent) of the smokers were reporting abstinence and 27 (27.5 percent) reporting reduction at the 1-year follow-up.

Thus, physicians and other health professionals have great opportunities for anti-smoking counseling. Both Rose (*338*) and Lichtenstein and Danaher (*227*) warn, however, that the private practitioner should avoid unrealistic expectations and underestimations of the time required. Various guidelines have been offered on the office management of cigarette smoking (*113, 115, 166, 291, 307, 309, 402*); Lichtenstein and Danaher (*227*) provide a comprehensive format and suggestions. Clearly, health care professionals can play a dramatic role by being nonsmoking models, by linking current symptoms to smoking, and by aiding smokers in the decision to quit alone or with additional help. But as Rose (*338*) and Lichtenstein and Danaher (*227*) have pointed out, additional research is needed to test techniques applicable for office-guided cessation programs.

Large-Scale Coronary Prevention Trials

Middle-aged men judged at risk but not exhibiting coronary heart disease (CHD) provide a special challenge for smoking counseling (*336, 337*). Since cigarette smoking together with serum cholesterol and blood pressure levels are considered the major risk factors for CHD (*36, 420*), preventive trials have attempted to reduce the incidence of CHD in study samples by using a multifactor approach. The Coronary Prevention Evaluation Program (*391, 392*) was an initial 7-year feasibility test of this approach among 519 coronary-prone men aged 40 to 59 at intake. Only 116 of the original 191 smokers remained active in the study, and more emphasis was given to nutritional counseling than to smoking counseling. Nevertheless, 43 of the 116 (37.1 percent) remaining smokers eventually stopped smoking.

Subsequently, other trials were initiated in Europe (*449*). Wilhelmsen (*439*) established a comprehensive cessation program for use in a field trial in Sweden (*441*), but long-term results are not available. In a controlled trial of the effects of anti-smoking advice among 1,470 coronary-prone London civil servants (*324*), 51 percent of the 714 randomly assigned to anti-smoking clinics stopped smoking by the end of 1 year. Only 31 percent were reporting complete abstinence, as many converted to pipes and cigars (*338*). In general, the preliminary results of the European multifactor prevention trials are only moderately successful, with abstinence in 16 to 28 percent of the smokers after 1 year (*449*).

In 1972 the Multiple Risk Factor Intervention Trial (MRFIT) was initiated in this country (*265, 266*). One of the largest and most ambitious of the multicomponent efforts to influence cigarette smoking behavior among middle-aged men, this smoking intervention attempt is occurring within a broad 6-year coronary prevention program also intended to reduce serum cholesterol and blood pressure levels in over 6,000 men aged 35 to 57 at increased risk of coronary disease (*410*). Initial intense intervention involving multicomponent group or individual sessions produced abstinence in approximately 43 percent of the smokers by the first annual examination (*280*). Biochemical assessments are being made to validate the self-report data. Continued intervention and maintenance contacts have produced successful cessation in other participants who had not formerly quit and in participants who had returned to smoking (*280*).

Two studies have focused on total populations rather than selected high-risk groups. The North Karelia Project (*204, 316*) has been providing a comprehensive community program since 1972 to reduce the very high rate of cardiovascular disease in eastern Finland. By the end of the first year of intervention, the proportion of males aged 25 to 59 in the North Karelia district who smoked decreased from 54 percent to 43 percent, while female smoking rates have remained at about 11 to 13 percent throughout the 5 years of treatment. These encouraging changes in male smoking behavior were maintained, with the 5-year follow-up survey reporting 42 percent of the adult men still smoking.

More specific data are available on the field study conducted by the Stanford Heart Disease Prevention Program. An extensive 2-year, mass-media campaign (*234*) was presented to two California communities to persuade the general public to modify eating and smoking behaviors in order to reduce cardiovascular risk. A third community served as control (*101, 235*). Face-to-face behavioral counseling (*101, 247, 258*) was offered to two-thirds of the high-risk subjects in one of the media communities. Three years after the program started, the proportion of smokers had decreased by 3 percent in the control community, by 8 percent in the media-only community, and by 24 percent in the media-plus-counseling communities (*101, 248, 259*). Fifty

percent of the high-risk smokers receiving face-to-face counseling, but only 11 percent receiving just media, had quit (*101, 248, 259*). Thiocyanate monitoring was performed to validate self-reports.

When the risks of smoking are made more immediate and salient, and both skills and support to change are provided, meaningful reductions are possible. The multifactor trials reveal that when smokers are sufficiently educated regarding their risks, they respond much like the post-MI patient and quit immediately and relapse less than would be predicted. The most successful multifactor trials have involved expensive face-to-face intervention techniques and extensive follow-up contacts (*280, 410*) or costly and well-conceived behavioral and media programs (*101, 204, 235, 247, 316*). Hence, more work is needed to translate the skills developed from these research trials into office practice and public health campaigns (*227, 338*). It should be noted that the effective programs involved face-to-face intervention techniques which were both intensive and expensive.

Controlled Experimental Research on Intervention Strategies

A wealth of research data relevant to the modification of smoking behavior has been produced. Early controlled research tended to produce unimpressive results (*24, 200, 366*). Schwartz and Dubitzky (*373, 374*) conducted an exemplary study of what appeared to be the best treatment options available in the late 1960's (*24, 200, 366*). Initial results suggested that group or individual therapy had moderate effects on smoking; but, by the end of a 1-year follow-up, not one of the seven experimental conditions was superior to the no-contact or minimal-contact controls (*373, 374*). Recent progress has begun to highlight both what strategies may be more effective and why they may work. Because these data have been comprehensively evaluated and discussed in recent reviews (*26, 29, 226, 245, 368, 376*), this section will emphasize primarily the major trends in this research history.

Drug Treatments

The psychopharmacology of smoking and its relationship to smoking behavior and cessation are discussed in some length elsewhere in this report and in recent reviews (*46, 136, 181, 183, 349*). While research (*349, 359, 360*) continues to suggest that there are pharmacological determinants for smoking, the identification of chemical agents either to substitute for smoking or to minimize withdrawal symptoms has been frustrating and difficult (*136, 181, 183*).

Early research on Lobeline as a nicotine substitute was equivocal (*24, 200, 366*). The utilization of the substitute in a clinic format seemed to at least enhance short-term effectiveness (*93, 341*), but the double-blind study by Davison and Rosen (*77*) indicated that Lobeline was no more effective than an appropriate placebo. More recently, a nicotine

chewing gum has been developed and tested as a cessation aid (*41, 102, 103*). Double-blind studies using the gum in cessation clinics suggested that it is significantly more effective than placebos (*41, 185, 283, 352*), but, beyond the control of withdrawal symptoms (*364*), its effects appeared to be a small component in the overall success (*352*).

Combinations of drugs to reduce withdrawal symptoms have been used in various clinics (*180, 341, 438, 440*); however, the double-blind study by Schwartz and Dubitzky (*373, 374*) of meprobamate with and without individual or group therapy suggested that the placebo, if anything, was more effective. While all treatment conditions were initially superior to questionnaire and screened no-treatment controls, the prescription-only and prescription-plus-individual-counseling had lower (8.3 percent and 13.9 percent) abstinence rates at 1-year follow-up than the controls (16.7 and 19.4 percent) (*373, 374*).

Other chemicals have been tested in Europe with some initial success (*136, 363*), but additional evaluations are needed (*136, 376*). Rosenberg (*340*) reported initial success in reducing consumption in a double-blind study of an antismoking chewing gum that caused an unpleasant taste when tobacco was subsequently smoked. The gum's efficacy as a cessation aid was not tested. Current data suggest that the usefulness of pharmacological cessation aids has yet to be unequivocally demonstrated. While aids such as nicotine gum may be useful in the control of withdrawal symptoms in some smokers, current research suggests that they would need to be combined within a broader program to produce and maintain abstinence (*136, 352*).

Hypnosis

Clinicians have claimed from 42 to 86 percent of their clients treated with hypnotherapy were abstinent at 6- to 12-month follow-up (*66, 67, 143, 278, 358, 395, 429, 450*). Unfortunately, these claims have not been substantiated in controlled research. The early research was chaotic and methodologically poor, leading Johnston and Donoghue (*189*) to conclude that "there is almost no good research evidence attesting to the effectiveness of hypnosis in the elimination of smoking behavior" (p. 265). Moreover, Spiegel, a leading proponent of self-hypnosis, claimed that the actual success rate may be closer to 20 percent long-term abstinence (*387, 388*). Orne (*285*) considered both the theoretical foundations and research data for hypnosis and concluded that its effects can best be categorized as a placebo response which leads to nontraumatic cessation through both the mystique of the procedure and the hypnotic suggestions.

The data from several recent studies do not refute these conclusions. Pederson and associates (*295*) found that 9 out of 16 (54.3 percent) of the subjects in a hypnosis-plus-counseling group were reporting abstinence at 10-month follow-up as compared to 12.5 percent for counseling-only or waiting-list control groups. As there was only 8

percent abstinence for a group treated with hypnosis only, they concluded that hypnosis can enhance the effects of group counseling; alone, it may be insufficient as a cessation procedure. When Shewchuk and associates (*382*) allowed smokers attending clinics to choose group therapy, individual therapy, or hypnosis, 193 of 571 (34 percent) chose hypnosis. The group therapy-reported abstinence rate (49 percent) was significantly superior to those of both hypnosis (38 percent) and individual counseling (33 percent) at treatment termination. By 1-year follow-up, however, all three conditions showed marked relapse, leaving only 17 to 21 percent of the participants reporting abstinence. While assignment to conditions was self-selected and nonrandom, the failure of hypnosis to replicate clinical claims remains important.

Barkley and associates (*18*) found that group hypnosis did not significantly differ from an attention-placebo control in mean smoking rates at any point during treatment or follow-up, but it had more subjects claiming abstinence at the 12-week follow-up point (4 of 8 vs. 1 of 9). At the 9-month follow-up, only two of eight (25 percent) of the hypnosis subjects were reporting abstinence versus none for the control. Francisco's (*105*) unpublished dissertation appeared to have reached a similar conclusion. It has been suggested that a 15 to 20 percent success rate for hypnosis may reflect the expected proportion of subjects highly susceptible to hypnosis (*297*).

Social Psychological Approaches

Higbee (*159*), Leventhal (*216, 217, 218, 219*), and Rogers (*332*) have reviewed most of the data from field and laboratory studies conducted to test responsiveness to persuasive communication regarding cigarette smoking. While most studies on smoking have produced attitude changes without marked or lasting reductions in smoking behavior (*181, 182, 231, 239, 244, 303, 321, 401*), this area of research has clarified several basic aspects of the smoking cessation process. The results and implications of these studies have been summarized by Leventhal (*216, 217, 218, 219*) and Rogers (*332*).

Janis and Hoffman (*181*) demonstrated the facilitating effects of daily telephone contacts that persisted well into follow-up despite termination of the contacts. Unfortunately, mean-rate reductions rather than abstinence rates were reported. Rogers and associates (*333, 334*) have recently documented the long-term impact of several communication strategies on smoking behavior. They reported significantly higher abstinence for high-fear versus low-fear messages in a college sample at 3-month follow-up (22 percent vs. 7 percent), and in a community sample at 1-year follow-up (18.8 percent vs. 0 percent).

Suedfeld's unexpected results with a single exposure to 24-hour sensory deprivation (SD) are also impressive (*405, 406, 407*). In a pilot study with five subjects, four quit after treatment and were reporting abstinence for 1 to 3 months afterwards (*406*). In a controlled study

(*407*), almost all SD subjects were reported to be abstinent at treatment termination, and 10 of 37 (27 percent) appeared to remain so at 12-month follow-ups when only 4 of 35 (11.4 percent) of control-condition subjects were reporting abstinence. Recently, Suedfeld and Best (*405*) piloted a combination of SD with a complex behavioral program involving aversive smoking and reported abstinence in four of five subjects for over 8 months.

This latter finding is supportive of Leventhal's (*216, 219*) conclusion that attitude change without a meaningful plan for action will not produce behavioral change. Hence, additional integrations of attitude and behavior change procedures seem worthy of investigation.

Social Learning and Behavior Modification Approaches

Research based on experimental and social learning theories (*12, 14, 106, 168, 169, 172*) has produced a wide diversity of controlled studies. Unfortunately, most of the early research on techniques that had been successful with other behavioral problems (*106*) or were derived from the principles of experimental psychology and laboratory research on behavior change proved to be minimally effective in producing long-term changes in smoking behavior. While early reviewers (*24, 200, 230*) acknowledged these discouraging initial treatment results, they concluded that the more empirical approach of these procedures made them the most promising. These hopes have been only partially fulfilled (*243, 451*).

Specifically, many studies have been more concerned with theoretical comparisons based upon evaluations of smoking-rate changes than with developing techniques with documented efficacy based on long-term abstinence data. Techniques were often found to be at least temporarily superior to control conditions, but the effects either vanished during follow-up or no meaningful follow-up was conducted (*25, 53, 59, 64, 70, 107, 132, 135, 139, 155, 197, 199, 201, 206, 207, 209, 212, 215, 220, 221, 242, 255, 260, 273, 276, 280, 281, 287, 317, 377, 384, 394, 408, 409, 426, 434, 435, 436, 437, 447*).

This pattern has been especially common in dissertation research on smoking. Most such dissertation research has been conducted by doctoral candidates and supervised by committees who generally have solid experimental and methodological backgrounds but limited clinical experience with smokers (*225*). Armchair and theoretical analyses of smoking have too often led to experimental and control conditions of some theoretical interest but which typically produced no relative differences among groups at follow-up and weak absolute results as measured by abstinence rates (*225, 376*). Furthermore, graduation pressures usually lead to insufficient follow-ups of only 1 to 3 months (*225*). The number of unpublished doctoral dissertations of this type document how much well-meaning effort has been devoted to the production of largely inconclusive results (*10, 20, 34, 35, 38, 60, 69, 87,*

88, 96, 118, 123, 125, 127, 134, 146, 161, 187, 188, 191, 196, 236, 249, 268, 277, 292, 315, 328, 342, 357, 365, 385, 386, 411).

Overall, the methodology of the research based on learning-theory approaches has been improving (*26, 226, 376*). Most studies have utilized appropriate designs and controls, follow-ups are becoming longer, and, most encouraging, validation of self-reported abstinence has become more common. Confirmations by informants in the participant's natural environment have been the mainstay (*8, 21, 22, 27, 28, 31, 32, 59, 64, 71, 85, 123, 141, 142, 197, 202, 206, 210, 229, 240, 242, 251, 279, 292, 313, 362, 394, 446*). However, carbon monoxide monitoring (*71, 206, 351*), threatened or actual urine nicotine analyses (*308, 409*), a bogus marketing survey procedure (*94*), and attempted (*80*) or actual (*48, 246*) thiocyanate analyses have now been reported. Although the outcome data on most procedures have been quite variable, the stricter methodology of these studies has encouraged continued refinement of interventions. More recently, effective multicomponent programs have begun to develop from this earlier research. The wealth of studies will be discussed briefly, therefore, with special emphasis given to those research trends that have produced programs with documented effectiveness. More detailed discussions of the literature are available in past (*24, 200, 230, 366*) and recent (*26, 29, 226, 245, 368, 376, 413*) reviews.

The research in this area can be grouped loosely into two broad, but not mutually exclusive, categories: (1) behavioral self-control strategies utilizing high participant involvement and (2) aversion strategies designed to reduce the probability of the smoking response (*226*). However, the most effective programs have tended to be multicomponent interventions which combine certain strategies from both categories.

Self-Control Strategies

Stimulus Control

The basic philosophy of behavioral self-control treatments has been to provide the subject first with increased awareness of the target behavior and controlling stimuli and then with specific self-management skills to control the target behavior (*13, 14, 193, 241, 314, 414, 415*). Therefore, self-monitoring of individual smoking behaviors has been a fundamental element in all behavioral self-control programs. As a sole treatment, self-monitoring has rarely produced more than temporary treatment effects (*60, 87, 109, 250, 251, 288, 365, 411*) and has been classed with the nonspecific treatment factors common to almost all behavioral programs (*251*). Self-monitoring has usually been combined within stimulus control treatments to make subjects aware of the specific environmental and internal cues associated with smoking urges and behaviors.

These stimulus control programs have been based on learning-theory formulations (*168, 169, 172*) of smoking behavior that suggested cessation is difficult because smoking is prompted by such a variety and range of cues. Subjects were taught to reduce the strength of these cues either by eliminating smoking from an increasing number of situations or by making time intervals the only controlling cue (*24, 26, 226*).

While this process theoretically should, with rare exceptions (*311, 344, 345*), make cessation easier, most subjects were reported to have difficulty reducing below 10 to 12 cigarettes per day (*8, 10, 23, 59, 104, 139, 221, 242, 313, 377*). It has been suggested that, when most smokers reached that reduced level, each cigarette became more reinforcing and difficult to give up (*104, 243*).

Most studies involving a variety of stimulus control and other self-management techniques were shown to be at best only temporarily superior to control conditions. These studies have produced, in general, the common pattern of temporary reduction but rapid relapse and long-term abstinence rates that did not differ from those expected from nonspecific treatments (*10, 23, 60, 69, 87, 104, 125, 132, 139, 146, 155, 188, 191, 196, 197, 199, 221, 242, 260, 264, 273, 277, 279, 280, 328, 355, 365, 377, 385, 386, 411, 435*). Even when applied within more complex, multicomponent programs, the stimulus control-based treatments often produced only moderately encouraging findings (*48, 104, 155, 255, 273*). Some encouraging applications have been noted (*44, 45, 308, 416*), however, especially when the programs develop from systematic research and the programs offer behavioral training in a wide range of skills (*42, 310*).

Contingency Contracting

One specific technique that has produced some encouraging data involves the depositing of money for later disbursement based on attainment of specified goals. Early research on the technique was equivocal (*24, 200, 224, 230*), but several studies have produced impressive results. Elliot and Tighe (*95*) reported 84 percent abstinence at treatment termination, with 4 of 11 (36 percent) in two other groups followed up 15 to 17 months after treatment. However, the treatment also involved public pledges, stimulus control techniques, and group support.

Winett (*446*) found that 50 percent of the subjects in contingent repayment condition were abstinent, validated by informant reports, at 6-month follow-up, but only 23.5 percent of those in noncontingent repayment were abstinent. Multiple case studies by Axelrod and associates (*6*) and a study by Rovner (*342*) were also encouraging. Brengelmann (*44, 45*) has reported notable success in recent studies utilizing contingency contracting within a treatment-by-mail program. Forty-seven percent of those responding to the 15-month follow-up

were reporting abstinence. However, self-reports were not validated, and if one assumed that nonresponders were smoking, the success rate based on all subjects completing treatment would be only 23 percent (22 of 96). Some success has been noted utilizing contingency contracting as a maintenance aid within a broad-spectrum program (*210*). In sum, as a single technique, contingency contracting appears able to initiate some behavioral changes, and when used in combination with other procedures, to prevent relapse.

Other Self-Control Strategies

Several other techniques or procedures have been modified for treatment of smoking behavior. Systematic desensitization was one procedure that was adapted for use with smokers under the rationale that reducing the need for stress-related cigarettes would aid subjects in coping with cessation. Again, while the technique was theoretically attractive, long-term abstinence rates were unimpressive (*96, 200, 205, 215, 263, 301, 426*). Similarly, a direct test of meditation proved to be equivocal (*287*).

In a similar vein, the suggestions of Homme (*163*) have produced a number of treatments attempting to increase self-control over smoking. Homme focused on "covert operants" which were designed to be incompatible with smoking behavior. He also reinforced non-smoking alternatives. However, only temporary treatment effects were produced in control trials (*125, 188, 199, 212*), despite some clinical demonstrations (*416*). Several other studies tried some combination of techniques along these lines with only minimal success (*38, 120, 281*).

Aversion Strategies

Techniques designed to reduce the probability of smoking through the use of aversive stimuli have been very commonly utilized in behavioral research projects. The theoretical underpinnings of individual procedures remain only partially delineated, and different theoretical positions—such as operant versus classical conditioning perspectives (*12, 14, 106*)—can result in varying treatment predictions (*26, 226*). Possibly due in part to this lack of theoretical precision, early research on aversive strategies produced mixed results (*107, 135, 201, 279, 313, 326, 327, 435, 436, 437*). Continuing refinements and evaluations have led to more elaborate combinations that appear more effective.

Aversive control procedures can most easily be categorized according to the major stimuli used: electric shock, covert sensitization, or cigarette smoke. All but two studies (*242, 434*) reporting minimal long-term results for taste aversion fit easily into these categories. The three major stimuli have rarely been used in combination with each other, but more recently have been included in multicomponent packages that include aversion and self-control strategies. For clarity,

the research on the aversive control procedures applied in isolation will be examined first.

Electric Shock

Previous reviews (*24, 200, 230*) of early studies (*201, 279, 313, 435*) concluded that it was most likely that laboratory administered shock was ineffective because humans were too capable of discriminating between shock and no-shock situations. Thus, in spite of encouraging case study data (*338*), controlled experiments have failed to produce impressive long-term results (*20, 32, 64, 220, 350, 394*) or even superiority over attention-placebo controls (*20, 64, 350*). The nondifferential results from contingent and noncontingent shock conditions in the study by Russell and his collaborators (*350*) suggested that "traditional conditioning processes do not contribute significantly to the clinical response of human subjects to electric aversion therapy for cigarette smoking" (p. 103).

Some positive results are noteworthy, however. Berecz (*21, 22*) has presented interesting case study data suggesting that shocking imaginal urges rather than actual smoking may be more effective. Chapman and his colleagues (*58*) combined daily shock sessions with intensive self-management training to produce reported abstinence in 6 of 11 (54.5 percent) of the participants at a 12-month follow-up. Dericco, et al. (*85*) produced a clear treatment effect for electric shock therapy. Sixteen of twenty (80 percent) of the subjects receiving shock were abstinent at 6-month follow-ups with validation by informants. The treatment involved sessions 5 days per week for several weeks, with higher than normal shock intensities and the additive influence of other treatment factors. Thus, these results do not refute the basic conclusion of past reviewers that shock augmented by other procedures may produce an effective treatment package, although as a sole treatment it fails because the effects often do not generalize outside therapy (*200, 226, 230*).

Covert Sensitization

Cognitive processes have been commonly employed to produce aversion by pairing smoking with vivid images of extreme nausea or other unpleasant stimulation. This procedure of covert sensitization showed promise in case studies (*57, 416*), but experimental studies involving various types of control conditions or treatment comparisons have failed to produce either meaningful levels of long-term abstinence or superiority over controls (*14, 118, 212, 236, 249, 268, 280, 315, 355, 384, 426, 431, 447*). However, it has been suggested as a maintenance strategy (*29*), and variants of the technique have been utilized in the more elaborate multicomponent treatments to be discussed later.

Cigarette Smoke Aversion

The choice of cigarette smoke as the aversive stimulus in smoking treatment may be particularly appropriate because: (1) the reinforcing aspects of almost any stimulus are reduced if presented at sufficiently increased frequency or intensity, and (2) the aversion affects many of the endogenous cues that characterize smoking (*26*, *226*). Several main versions of this approach have been used: satiation (that is, doubling or tripling the daily consumption of cigarettes) prior to abstinence; and aversive conditioning through either smoking with warm, stale smoke blown into the face, or rapidly smoking with inhalations every 6 seconds.

Early research using artifically produced warm, stale smoke to affect aversion showed impressive initial results (*436*) followed by total failure during follow-up (*437*). Other early studies also produced minimal or no long-term successes (*107*, *135*). However, in a subsequent study with the warm, smoky air apparatus, Schmahl and his colleagues (*362*) produced both 100 percent termination abstinence and an impressive 57 percent (16 of 28) abstinence rate at 6-month follow-up, verified by random checks with informants. In the treatment, subjects were required to smoke rapidly (inhaling every 6 seconds) and continuously while facing into the blown smoke until further smoking could not be tolerated. Sessions were scheduled until the subject was abstinent a minimum of 24 hours and felt confident in maintaining abstinence (mean of about eight sessions).

A well controlled replication against a normal-paced, smoking attention-placebo control found 60 percent (18 of 30) abstinence among three experimental conditions at 6-month follow-ups, but only 30 percent (3 of 10) abstinence in the control (*229*); this was again verified by random checks of informants. As the rapid-smoking-only condition was as successful as the more involved procedures, abandonment of the inconvenient smoke blowing apparatus was recommended (*229*). Subsequent early research by Lichtenstein and his colleagues was also highly effective (*226*). The logic and supporting data for the procedure have been considered in more detail by Lichtenstein and Danaher (*226*).

Owing in part to the early effectiveness, convenience, and simplicity of the rapid smoking procedure, it became increasingly popular (*72*, *226*). Subsequent results are mixed and variable (*72*), however. A multiyear follow-up of the early studies has shown that some relapse did occur over the intervening years (*232*). Danaher (*72*) recently has comprehensively reviewed the existing data on the procedure and documented that termination and follow-up abstinence rates varied widely in subsequent research, with some studies reporting minimal or no (0 to 29 percent abstinence) long-term successes (*94*, *122*, *127*, *206*, *215*, *409*), others with moderate (30 to 49 percent abstinence) success (*28*, *31*, *104*, *202*, *207*, *209*, *276*, *292*, *325*, *452*), and a few approximately replicating the follow-up data of early studies (*71*, *94*, *144*, *246*).

Danaher (*72*) has attempted to clarify these data by highlighting the departures from original treatment procedures by the use of group presentation (*94, 127, 206, 209, 215, 246, 276, 292, 325, 452*), limiting the number of sessions (usually to six) (*123, 127, 202, 276, 292, 325*), offering treatment on a rigid or fixed schedule (*28, 71, 94, 123, 127, 202, 276, 292, 325, 409*), and omitting the contingently warm, supportive treatment context (*94, 206, 207, 209*). The most impressive recent outcome data have been produced with multicomponent approaches combining aversion and self-control procedures (*28, 31, 94, 144, 246*). Nevertheless, it is important to note that several multiple case studies and controlled studies on the rapid smoking procedure failed to demonstrate any improvement with the addition of self-control procedures (*70, 71, 123, 292*).

Thus, the rapid-smoking procedure appears to be a potentially very effective but complex intervention, dependent both upon the subject's active revivification of the aversion (*12, 226, 246*) and upon critical elements in the format, including a warm, personal client-therapist relationship offering social reinforcement and positive expectations (*72, 88, 226, 246*) and flexible or individualized treatment scheduling to insure total abstinence prior to treatment termination (*72, 226*). Numerous nonreplications and one direct test (*276*) have demonstrated that the production of only physiological aversion and conditioning effects are insufficient to produce long-term abstinence.

Satiation

Early research (*436, 437*) on the satiation technique was encouraging, with a 63-percent reported abstinence at 4-month follow-up. The success was partially replicated in a slightly modified, marathon format (*240*), but the weight of evidence on the procedure has been negative since that time. Controlled studies were unable to replicate the impressive cessation data or even to demonstrate superiority to control groups (*59, 211, 408*). Other comparative tests have also produced negative results (*32, 207, 242, 249, 280*). While the procedure as a sole treatment may have questionable effectiveness, more recent studies (*28, 31, 80, 210*), combining satiation with multicomponent treatment packages, have reported more impressive results.

Medical Risks of Aversive Smoking

Because the smoke-aversion procedures were developed to induce a degree of physiological discomfort by excessive smoking, the cardiopulmonary stress of increased nicotine and carbon monoxide exposure has been noted with concern, especially with regard to rapid smoking (*156, 164, 165, 223*). A number of studies have been undertaken to quantify the impact of rapid smoking on the cardiovascular system (*73, 78, 79, 144, 174, 261, 354*); much of the data has been summarized by

Lichtenstein and Glasgow (*228*). Recent studies by Hall and associates (*144, 354*) and Miller and associates (*261*) have documented that the rapid smoking procedure produces an acute and dramatic effect upon vital signs (respiratory rate, heart rate, and blood pressure), blood gases, and COHb saturations, which make the procedure contraindicated for individuals with potential or active cardiovascular or pulmonary diseases. Adequate medical screening of potential treatment participants has been strongly recommended (*144, 156, 223, 261, 354*).

Data have yet to be published on the relative risks of other smoke-aversion procedures. If heavy-smoking subjects double or triple their daily smoking consumption during the satiation procedure, notable acute effects on the cardiovascular system may also occur. It should be noted that in excess of 35,000 participants have been exposed to the rapid-smoking procedures, with an informally reported morbidity rate from nonspecific complications of about 0.023 percent and no reported mortality (*228*). Yet, until the relative risks of procedures have been adequately researched, all the smoke aversion procedures should be used with appropriate screening and monitoring (*144, 156, 228, 261, 354*).

Less Stressful Alternatives

The identification of the relative risks of the rapid smoking procedure has stimulated the development of smoke aversion interventions that involve less physiological stress. Because of the pattern of 20 to 30 percent long-term abstinence with a common normal-paced attention-placebo condition (*71, 123, 202, 206, 207, 209, 211, 229*), which self-control training seemed to enhance (*71*), initial clinical demonstrations have been undertaken combining normal-paced "focused" smoke aversion within broad, multicomponent treatment packages (*74, 141*). Preliminary demonstration data showed that a 6-month abstinence could be produced in approximately 50 percent (5 of 10) of the participants (*141*). A controlled test of a rapid-puffing-sans-inhalation procedure produced somewhat less optimistic results with only 6 of 21 (29.6 percent) of the participants who started treatment reporting abstinence at the 3-month follow-up; this was verified by random checks of informants (*292*). A recent report by Tori (*417*) found that a smoke-induced taste-aversion technique involving limited smoke inhalation produced reported abstinence in 17 of 25 (68 percent) of the participants versus 6 of 10 (60 percent) in a rapid smoking condition at a 26-week follow-up. Unfortunately, assignment to treatment was not random, abstinence reports were not validated, subjects were treated on a fee basis, and a variety of adjuncts including hypnosis were utilized as maintenance boosters. Nevertheless, this and other early data (*74, 141, 292*) on alternatives to rapid smoking involving similar treatment formats, rationales, and nonspecifics, but markedly reduced

physiological stress, appear encouraging and worthy of additional controlled research.

Multicomponent Interventions

As noted above, the research on techniques and procedures derived from learning theories and models has been mixed and often inconclusive. As recommended by early reviewers of the behavioral literature (*24, 366*), treatment packages combining multiple techniques are beginning to emerge. These comprehensive programs utilize some combination of the behavioral self-control techniques, and many also integrate aversive control procedures. The technology in this area is still developing; the early mixed results are to be expected. Still, recent reviews have uniformly concluded that the data from this emerging trend in programming are clearly encouraging (*26, 29, 226, 245*).

Treatment packages using behavioral self-control strategies alone have not produced notably effective results. Several complex programs have produced minimal long-term effects (*48, 104, 115, 255, 381, 382*). The later successes of Pomerleau and associates (*308*) and Brengelmann (*44, 45*) only came with refinements based on systematic developmental research. The most recent successful reports (*28, 31, 44, 45, 210, 246, 308*) thus appear to be a product of practical and in-depth knowledge of the problem which guides the application of the diverse elements in the treatment programs. Early and more recent successes (*28, 31, 39, 44, 45, 58, 80, 94, 140, 142, 210, 246, 308, 407*) suggest that planned extended contacts plus adaptation of techniques to individual needs are necessary for long-term success.

In a carefully evaluated clinical demonstration, Pomerleau and associates (*308*) reported success in 61 of the first 100 participants with 32 remaining abstinent (these were verified by urinary nicotine assays at 1-year post-treatment). Brengelmann (*42, 45*) has refined his complex treatment package (*42*) to the point where current results with treatment-by-mail are equal to face-to-face therapy, with 55 to 67 percent of the participants who complete treatment (86 percent reported completion rate) reporting abstinence at termination and 57 percent of those responding to follow-up reporting continued, but unverified, abstinence. Although the success rate based on the assumption that nonresponders were smoking would be 23 percent, the efficiency of the approach is clearly encouraging.

Other multicomponent treatments utilizing an aversion procedure to help induce cessation have also produced initially mixed but encouraging data. The early multiple case study of Chapman and associates (*58*) with electric shock plus extended self-management training is an often-cited example of this type of approach. In recent clinical evaluations of delivery formats, Best and associates (*28, 31*) have also documented the potential efficacy of a multicomponent program involving aversive smoking (satiation and rapid smoking) plus

behavioral self-control training. Abstinence rates at 6 months, verified by informant reports, have varied from 35 to 55 percent, with the best results in a take-home version involving minimal personal contact. In a controlled study of satiation plus self-control training, Delahunt and Curran (*80*) demonstrated the superiority of the multicomponent treatment over controls and individual components. Six-month abstinence data showed five out of nine subjects (56 percent) for the combined treatment, but only 0 to 22 percent for individual components and controls; self-report validity was enhanced by collected but unanalyzed saliva for thiocyanate assays. Elliott's (*94*) package of rapid smoking, self-control strategies, covert sensitization, and systematic desensitization likewise produced abstinence, verified by a bogus marketing survey, in 45 percent (9 of 20) of the participants at 6-month follow-up, versus 17 percent for rapid smoking only and 12 percent for attention-placebo control. McAlister (*246*) demonstrated that his multicomponent rapid-smoking package was equally effective at 3-month follow-up presented either in person (56 percent or 5 of 9 abstinence) or over television (62.5 percent or 5 of 8 abstinence), with self-reports validated by thiocyanate assays.

These very positive findings are tempered somewhat by several less successful combinations of self-control and aversive smoking procedures (*27, 71, 123, 292*). The analytical study of the multicomponent approaches by Flaxman (*104*) provided some data on the complexity of the issues involved. Although the study indicated that subjects who abruptly quit on a selected date after self-control training reported the best 6-month abstinence data either with subsequent aversive smoking (5 of 8 or 62.5 percent) or only supportive counseling (4 of 8 or 50 percent), gradual reduction strategies, especially for male subjects, were markedly less effective with or without aversive smoking. Though the cell frequencies were small and the abstinence data unverified, the results suggest that successful response to multicomponent treatments may be the product of many only partially understood variables.

Treatment Innovations

Older (*371*) and more recent (*119*) survey data clearly indicate that most smokers who are motivated to quit are less interested in formal programs than in do-it-yourself methods. The broadening of the mode of service delivery of behavioral treatments is thus another encouraging trend. A study by Dubren (*90*) suggested that brief interventions by television can produce small but meaningful abstinence rates on the order of 9 to 10 percent. He also demonstrated that taped telephone messages can be used to extend the intervention and support maintenance (*91*). McAlister's (*246*) experimental demonstration of the potential of the media-only treatment group was impressive. Rosen and Lichtenstein (*339*) evaluated a program independently developed

by the employer. They reported encouraging results using the resulting monetary contingency technique. These preliminary studies suggest that the best of the behavioral technology could be made available effectively by media or at the worksite to those smokers unwilling to attend formal programs.

The basics of successful clinical programs have also been reduced to self-study books (*310, 72a*). Consistent with the growing trend toward self-administered treatments (*124*), multicomponent treatments based on behavioral self-control strategies with or without aversive smoking techniques (*310, 72a*) are now available in self-study formats. Although initial tests of the self-study approach to smoking cessation are mixed (*28, 31, 123, 202*), their availability should facilitate further testing of programs similar to the successful self-managed clinic reported by Best and associates (*28, 31*).

Controlled Smoking

Most smokers want to reduce their risks from smoking (*49, 347*); this is evidenced by the dramatic changes that have occurred in the types of cigarettes being smoked (*151, 270, 287, 345*). Filter cigarettes are now the norm, and both the tar and nicotine content of the American cigarette have declined significantly (*279, 412*). These natural trends and apparent high interest among smokers in safer smoking have stimulated only preliminary interest in the development of interventions to maximize the reduction of risks (*49, 287, 347*). Frederiksen and associates (*108–112*), however, have pursued the topic and have experimentally demonstrated that exposure level can be controlled not only by rate of smoking and strength of cigarette, but also by altering the topography of the habit. They demonstrated that modifying the topography of smoking involves changing how much smoke is inhaled, how many puffs per cigarette are taken, and how much of each cigarette is smoked (*109, 110, 112*). Although the technology is still in the clinical-developmental stage, and the long-term stability of the changes will need to be verified, initial single-case demonstrations are encouraging and merit more emphasis. Data from the stimulus control studies suggest that reduction in exposure may be limited by the floor effect of 10 to 12 cigarettes per day (*8, 10, 23, 59, 104, 139, 221, 242, 313, 377*).

The controlled smoking technology may be useful to other groups of individuals. Physiological monitoring of ex-cigarette smokers who shift to pipes and cigars has documented that inhalation does occur (*81, 82, 351*). Because the inhalation may occur at an unconscious level and can lead to tobacco exposures as great as cigarette smoking, such smokers may need specific behavioral training to control the topography of their new habits. Similarly, some smokers who shift to lower tar and nicotine cigarettes to reduce their risk may also require the controlled

smoking technology to avoid increases in rate or attempts to compensate by altering the smoking topography.

Maintenance of Nonsmoking

Both early (*24, 200, 366*) and more recent (*26, 29, 40, 226, 245, 306, 368, 376*) reviews of the smoking intervention literature have focused on the need to devote more energy to developing procedures to assure long-term, robust behavior change. The continuing problems of nonreplications and minimal treatment effects have, however, kept most researchers searching for new or more effective *cessation* strategies. Yet past research has clearly indicated that most smokers motivated to quit relapse shortly after treatment termination (*170, 171*). Thus all interventions should recognize that the production of the initial cessation is only the start of treatment (*26, 226, 245, 306*). Detailed procedures to aid the recent ex-smoker learn the skills needed to solidify the behavior change should become an integral part of all treatments.

Existing attempts to add maintenance programming to various treatments have proven somewhat ineffective (*306*). When offered booster sessions or telephone support if problems arise, most participants fail to make use of the services (*27, 380*). Experimental tests of the booster treatment approach generally have shown equivocal results (*84, 202, 325*). Paradoxically, supportive phone calls during or after treatment seem to lead to significantly poorer long-term results (*28, 84, 380*). It has been suggested that maintenance programming must be offered in a fashion that will enhance rather than distract from self-attributions of success (*29, 203*).

Some initial positive findings are available, however. Dubren (*90*) reported some success utilizing tape-recorded telephone reinforcement messages during the follow-up of a televised smoking clinic. After some initial negative and inconsistent results (*206*), Lando (*210*) demonstrated, but was unable to replicate, that the long-term effectiveness of an aversive smoking program may be enhanced by a broad-spectrum, contingency-contracting program. Seven maintenance sessions over a 2-month period produced abstinence, validated by informant reports, in 76 percent (13 of 17) of the maintenance group subjects at 6-month follow-up, versus only 35 percent (6 of 17) of the controls given cessation treatment only. Case study data support the maintenance-contracting concept (*222*). Recent dissertation data also appear to provide some encouraging findings regarding maintenance programming (*84*).

Attempts to add on maintenance procedures have generally been ineffective (*27, 31, 202, 206, 292, 356*). However, several effective programs appear to have integrated into the total treatment package extended contacts and training in the behavioral skills (*28, 44, 45, 58, 210, 308*). These factors may be required to maintain abstinence. More

research is needed to define what types of maintenance procedures are needed and when and how they can be most effectively administered (*306*).

Research has begun to clarify the personal and situational factors which support smoking and which may induce ex-smokers back into the habit (*30, 97, 110, 111, 243, 256, 349, 359*). Individual difference factors have been overemphasized in the analysis of relapse, however, compared to situational factors (*29*). Retrospective analyses of individual differences that may be related to successful cessation have generally suggested that older males with lighter smoking habits and from higher social classes tend to be more successful (*92, 126, 149, 233, 271, 323, 389, 390*), but the magnitude of these differences has been small (*29*). Several studies have suggested that individuals who report using smoking to control negative affect or who have higher levels of anxiety also appear more susceptible to relapse (*89, 105, 179, 180, 292, 370, 375, 389, 390, 399, 400*). Efforts to utilize broad individual differences to maximize treatment effectiveness have been mixed and generally inconclusive (*27, 32, 33, 53, 205, 212, 292*). Given that broad smoking topographies (*1, 29, 176, 177, 256, 349*) and personality tests (*27, 179*) lack sufficient specificity, Best and Bloch (*29*) have suggested that emphasis should be placed on locating interactions between finer variations in the individual's situational cues and smoking patterns (*30, 97, 110, 111, 243*) and responsiveness to treatment modalities.

McAlister (*245, 246*) has outlined several other important areas that should be addressed in maintenance programming. Smokers need to be given a positive set regarding withdrawal symptoms and their ability to deal with them. Some data suggest that misattribution-type therapy can be helpful in achieving this goal (*16, 245*). Since most smokers, especially women, believe they will gain weight if they quit (*271*), fear of the documented weight gain after cessation (*37, 50, 62, 122*) should be directly countered (*245*). The role of negative self-evaluations and common rationalizations (*76*) also requires further clarification (*13, 245*). McAlister (*245*) has suggested that specific plans be formulated to aid ex-smokers confront their predicted problem areas.

Research interest in the important area of maintenance programming is beginning, but many issues remain to be defined and tested. Preliminary data suggest that multicomponent programs are more effective when extended contacts are planned into the program and diverse techniques are individualized to meet the special needs of all participants. Given the concern over smoking among women (*65, 162, 214, 335*), their special needs should be addressed.

General Overview of Data

Status of Methodology

As stated at the beginning of this section, there have been great improvements in the quality of data on smoking cessation methods in recent years (*26, 226, 368, 376*), especially in several research clinics (*81, 82, 178, 283, 381, 382*), large-scale coronary prevention trials (*101, 265, 266, 324, 441*), and in the behavioral research area (*26, 29, 226*). Yet the validity of the self-report data remains a critical concern. Since the validity of reported abstinence has been questioned by physiological measures in up to 20 percent of clinic participants (*47, 82, 178, 231*), it appears that many individuals may be reporting their commitment and expectations of success rather than their current smoking behavior. Ohlin and associates (*283*) revealed that, of the 19.2 percent (25 of 130) of the reportedly abstinent subjects who had COHb levels above a 0.8 percent nonsmoking cutoff at treatment termination, none was reporting abstinence at 6-month follow-up. With the current state of unverified self-report data, one must interpret cautiously even the commonly cited relapse curves (*170, 171*).

Random assignment to experimental conditions and the use of one or more control conditions have become much more common, especially in the behavioral research areas. Broad generalizations of the data continue to be made about the general efficacy of procedures with little regard for the interactive effects of age, gender, social class, or smoking topographies of successful participants. The small samples of almost all comparative research relegate these sources of possible interaction to the error variance. This, plus wide variability in the actual application of supposedly identical procedures, makes comparisons across individual studies difficult.

The continuing pattern of nonreplication and the lack of clear superiority of treatments over appropriate controls further suggest the need to balance these advances in research methodology with a practical and clinical sensitivity to the complexity of the problem (*7, 43, 224, 225, 304*). The guidelines offered by several comprehensive clinics (*43, 224, 304, 372, 375, 379, 380, 381, 383, 440*) should serve to direct initial clinical testing of procedures. As McAlister (*245*) has outlined, procedures should first be intensively piloted with single individuals or small groups. The technology for the use of quasi-experimental (*56, 393*) with other methods should make it possible to conduct multiple case studies with adequate statistical validity (*108, 158a, 293, 415*). When clinically refined, the treatment techniques can be tested against appropriate controls, especially attention-placebo controls (*24, 56, 226, 251, 272*). When the format and techniques are well understood and documented, they can be replicated by other researchers in diverse settings (*245, 304, 398*).

Although behavioral research has been advancing in experimental rigor, less progress has been made in public service and proprietary clinics. Objective and controlled evaluations are still needed in these settings. Though the treatment focus of these clinics makes classical experimental designs unattractive, alternative quasi-experimental designs should be investigated, since the technology exists to provide a degree of control in almost any field or applied setting (*56, 393*). If such evaluations were undertaken, a wealth of data would be available to guide more controlled research (*398*).

Most researchers now seem at least aware of the need to conduct long-term follow-ups of all participants. While various professional and financial constraints tend to limit this process, follow-ups of at least 6 months are becoming common. Innovative suggestions, such as obtaining the name of a contact who will know the future whereabouts of the participant, have been offered to aid in tracking participants during follow-up (*232*). The public service and proprietary clinics are only beginning to recognize their responsibility in this area, and little is known about the long-term efficacy of these programs.

In summary, the research on smoking-modification strategies over the past 15 years clearly indicates that past recommendations regarding adequate methodology still need to be heeded (*24, 26, 226, 251, 272, 366, 376*). Researchers also need to become more aware of social contingencies such as clinical zeal, publication pressures, and dissertation timetables which have led to poor adherence to these guidelines (*225*). Data on the reliability and validity of self-reports of smoking behavior now strongly suggest that unverified, global self-reports should no longer be accepted as the only outcome data. Objective techniques for measuring smoking exposure can be developed to validate and supplement self-report data. While great advances in methodology have been made in the past 15 years (*26, 226, 376*), new technical and design approaches now under study should serve to improve further the quality of the data collected in the future.

Implications of the Data

In light of the amount of research conducted over the past 15 years, it is remarkable that we have so little outcome data on the wide variety of treatments being offered and recommended. Equally astounding is how little we know about the millions of smokers who have quit on their own. As noted in other sections, it has been estimated that 95 percent of the 29 million smokers who have quit since 1964 have done so on their own (*270*). Various surveys have revealed that the cumulative quit rates for various age groups, social classes, and occupations are impressive (*92, 121, 133, 149, 271, 323, 421*). The sporadic and marginal quality of outcome data on treatment programs, however, makes it impossible to conclude how this broad social phenomenon has affected clinical and research programs. Survey data

have shown that only a third or less of smokers motivated to quit are interested in formal programs (*119, 371*), and only a small minority of those who do express an interest actually attend programs when they are offered (*195, 270*). It thus appears that objective outcome data that are available may be based on a small minority sample of smokers at large.

Objective data are lacking on most of the smokers who have been willing to attend formal programs. Public service clinics continue, but the lack of objective outcome data precludes the evaluation of their efficacy. Similarly, proprietary programs remain virtually unmonitored and unevaluated in an objective fashion. Smoking counseling by medical or health care personnel seems to be highly effective with symptomatic smokers (*227, 338*), but the efficacy of such an approach for other smokers has yet to be adequately evaluated. The data from the large scale coronary prevention trials (*101, 265, 266, 324, 441*) should help clarify some issues regarding medical counseling and smoking cessation among higher risk individuals, but the nonspecific treatment focus of these projects will limit the conclusions that can be drawn.

Controlled research has yet to produce a clearly superior intervention strategy. However, the rapidly accumulating and improving research data now suggest that multicomponent interventions offered by intervention teams with practical knowledge regarding the smoking problem are the most encouraging. In part, the added effectiveness of some programs may be due to the skills of the intervention team to present the available techniques as both credible and attractive to the participants (*173, 175*). It is important to recognize that improved success in recent studies may also be influenced by changes in social norms regarding smoking. More integration of diverse perspectives, including pharmacological, behavioral, medical, and social aspects of the smoking habit, should enhance the multicomponent treatment approach. It is encouraging to note that more research emphasis has begun to be focused on maintenance programming. Apparently the multicomponent programs enable participants to gain the new skills needed to deal with their individual problems in adjusting to the new nonsmoking lifestyle. Many issues remain to be researched, however, and special programs may be required to deal with the needs of smokers with personal or environmental factors that encourage recidivism.

Recommendations for Future Research

Objective Measures of Smoking

An adequate technology to validate self-report smoking data is critically needed. When physiological assessments have been done, inaccuracies in self-reported abstinence are common. Inaccuracies in

rate estimates among the continuing smokers cannot, however, be accurately evaluated with existing technology. If reliable physiological measures of smoking rate were available, the effects of various procedures in producing not only abstinence but meaningful and enduring reductions in smoke exposure could be objectively verified. Basic pharmacological and biological research is needed to formulate such objective measures of smoking.

Maximizing Unaided Cessation

The phenomenon of smoking cessation outside formal programs remains largely unexplored. Almost all successful ex-smokers quit on their own, but little is known about how to maximize this process. Existing survey data suggest that most smokers who are motivated to quit are not interested in attending formal programs. Most smokers report being interested in do-it-yourself quit methods or procedures. Therefore, precise information is needed regarding what types of treatments smokers view as credible, useful, and attractive. Controlled research is needed to evaluate the most cost-effective programs to make attractive and effective programs available to smokers who desire to quit. As treatments are refined in controlled research, they need to be translated into formats which are appropriate for testing with general population groups.

Development of Maintenance Strategies

The research on methods to assure that smokers who successfully quit have the behavioral skills and social supports needed to maintain and solidify the behavior change is currently at a very primitive stage. More basic research is needed to clarify the topography of smoking and relapse behavior so that the specific needs of various types of smokers can be fulfilled. Procedures and programs to aid smokers achieve cessation must be refined; past experience shows that the production of high rates of initial abstinence does not insure a noteworthy level of long-term abstinence. Different classes and types of smokers may require different levels of maintenance assistance. Specific smoking topography variables that predict such needs should be defined. Existing research on maintenance programming indicates that the maintenance procedures should be integrated into the treatment package rather than added on as an option at the end of the treatment. The development of maintenance strategies should be viewed as an integral part of the intervention package and should be evaluated accordingly.

Evaluation of Existing Programs and Procedures

As should be clear from the review of existing data, methodologically sound evaluations of all forms of smoking intervention are still greatly

needed. The increased rigor in the behavioral research area has begun to produce some tentative suggestions regarding effective strategies. However, the more promising multicomponent treatment packages pose new, more complex issues for evaluation. Alternative methods of effectively presenting the most effectual programs to the general public need to be explored and properly evaluated. In addition, the most attractive of the behavioral programs should be experimentally tested relative to other existing intervention strategies in order to produce relative outcome data for evaluation.

The potential efficacy of smoking cessation and reduction counseling by physicians and health care professionals also should be experimentally evaluated. The existing technology derived from behavioral and social psychological research should be integrated into interventions appropriate for use in medical settings.

All public service clinics and proprietary programs should be subjected to rigorous and continuing evaluation. Such programs must recognize their responsibility to the smoking public to present objective evaluations of long-term effectiveness. In addition, proper evaluations should lead to refinements in treatment procedures. As effective treatment strategies are developed and objectively evaluated within research programs, they should be translated into clinic formats for utilization and evaluation within the general population.

Modification of Smoking Behavior: References

(1) ADESSO, V.J., GLAD, W.R. A behavioral test of a smoking typology. Addictive Behaviors 3: 35-38, 1978.

(2) AMERICAN CANCER SOCIETY. Stop Smoking Program Guide. San Francisco, American Cancer Society, California Division, 1971, 178 pp.

(3) AMERICAN CANCER SOCIETY. Task Force on Tobacco and Cancer—Target 5. Report to the Board of Directors. American Cancer Society, Inc., 1976, 82 pp.

(4) ANDER, S. Who gives up smoking after a myocardial infarction? In: Richardson, R.G. (Editor). The Second World Conference on Smoking and Health. London, Pitman Medical, 1971, pp. 175-178.

(5) AUGER, T.J., WRIGHT, E., JR., SIMPSON, R.H. Posters as smoking deterrents. Journal of Applied Psychology 56(2): 169-171, April 1972.

(6) AXELROD, S., HALL, R.V., WEIS, L., ROHRER, S. Use of self-imposed contingencies to reduce the frequency of smoking behavior. In: Mahoney, M.J., Thoresen, C.E. (Editors). Self-Control: Power to the Person. Monterey, Brooks/Cole Publishing Company, 1974, pp. 77-85.

(7) AZRIN, N.H. A strategy for applied research. Learning based but outcome oriented. American Psychologist 32(2): 140-149, February 1977.

(8) AZRIN, N.H., POWELL, J. Behavioral engineering: The reduction of smoking behavior by a conditioning apparatus and procedure. Journal of Applied Behavior Analysis 1(3): 193-200, Fall 1968.

(9) BAER, P.E., FOREYT, J.P., WRIGHT, S. Self-directed termination of excessive cigarette use among untreated smokers. Journal of Behavior Therapy and Experimental Psychiatry 8(1): 71-74, March 1977.

(10) BAKEWELL, H.A. The relevance of goal-setting in a smoking reduction program. Doctoral dissertation, University of Utah, 1972, 119 pp. Dissertation Abstracts International 33(3): 1280-B, September 1972. (University Microfilms No. 72-24,574).

(11) BALL, K.H. Cigarettes and the prevention of heart disease. Rehabilitation 25(1-2): 17-20, 1972.

(12) BANDURA, A. Principles of Behavior Modification. New York, Holt, Rinehart and Winston, Inc., 1969, 677 pp.

(13) BANDURA, A. Self-efficacy: Toward a unifying theory of behavioral change. Psychological Review 84(2): 191-215, 1977.

(14) BANDURA, A. Social Learning Theory. Englewood Cliffs, New Jersey, Prentice-Hall, Inc., 1977, 203 pp.

(15) BARBARIN, O.A. III. A Comparison of Overt and Symbolic Aversion in the Self-Management of Chronic Smoking Behavior. Doctoral dissertation, Rutgers University, State University of New Jersey, 1975, 128 pp. Dissertation Abstracts International 36(5): 2457-B-2458-B, November 1975. (University Microfilms No. 75-24,655).

(16) BAREFOOT, J.C., GIRODO, M. The misattribution of smoking cessation symptoms. Canadian Journal of Behavioral Science 4(4): 358-363, 1972.

(17) BARIC, L, MACARTHUR, C., SHERWOOD, M. A study of health education aspects of smoking in pregnancy. International Journal of Health Education, Supplement to Volume 19(2): 1-17, April-June 1976.

(18) BARKLEY, R.A., HASTINGS, J.E., JACKSON, T.L., JR. The effects of rapid smoking and hypnosis in the treatment of smoking behavior. International Journal of Clinical and Experimental Hypnosis 25(1): 7-17, January 1977.

(19) BARYLKO-PIKIELNA, N., PANGBORN, R.M. Effect of cigarette smoking on urinary and salivary thiocyanates. Archives of Environmental Health 17(5): 739-745, November 1968.

(20) BEAVERS, M.E. Smoking Control: A Comparison of Three Aversive Conditioning Treatments. Doctoral dissertation, University of Arizona, 1973, 64 pp. Dissertation Abstracts International 34(6): 2919-B-2920-B, December 1973. (University Microfilms No. 73-28,782).

(21) BERECZ, J.M. Reduction of cigarette smoking through self-administered aversion conditioning: A new treatment model with implications for public health. Social Science and Medicine 6(1): 57-66, February 1972.

(22) BERECZ, J. Treatment of smoking with cognitive conditioning therapy: A self-administered aversion technique. Behavior Therapy 7(5): 641-648, October 1976.

(23) BERNARD, H.S., EFRAN, J.S. Case histories and shorter communications. Eliminating versus reducing smoking using pocket timers. Behavior Research and Therapy 10(4): 399-401, November 1972.

(24) BERNSTEIN, D.A. Modification of smoking behavior: An evaluative review. Psychological Bulletin 71(6): 418-440, 1969.

(25) BERNSTEIN, D.A. The modification of smoking behavior: A search for effective variables. Behavior Research and Therapy 8(2): 133-146, June 1970.

(26) BERNSTEIN, D.A., McALISTER, A. The modification of smoking behavior: Progress and problems. Addictive Behaviors 1(2): 89-102, 1976.

(27) BEST, J.A. Tailoring smoking withdrawal procedures to personality and motivational differences. Journal of Consulting and Clinical Psychology 43(1): 1-8, February 1975.

(28) BEST, J.A., BASS, F., OWEN, L.E. Mode of service delivery in a smoking cessation programme for public health. Canadian Journal of Public Health 68: 469-473, 1977.

(29) BEST, J.A., BLOCH, M. On improving compliance: Cigarette smoking. In: Haynes, R.B., Sackett, D.L. (Editors). Compliance. Baltimore, Johns Hopkins University Press, 65 pp. (to be published).

(30) BEST, J.A., HAKSTIAN, A.R. A situation-specific model for smoking behavior. Addictive Behaviors, 3(2): 79-92, 1978.

(31) BEST, J.A., OWEN, L.E., TRENTADUE, L. Comparison of satiation and rapid smoking in self-managed smoking cessation. Addictive Behaviors, 3(2): 71-78, 1978.

(32) BEST, J.A., STEFFY, R.A. Smoking modification procedures for internal and external locus of control clients. Canadian Journal of Behavioral Science/Revue Canadienne de Science du Comportement 7(2): 155-165, April 1975.

(33) BEST, J.A., STEFFY, R.A. Smoking modification procedures tailored to subject characteristics. Behavior Therapy 2(2): 177-191, April 1971.

(34) BIBIN, L.J. An Investigation of the Effectiveness of Covert Role Playing Using a Suggestion Oriented Relaxation Technique to Assist Smokers to Stop Smoking. Doctoral dissertation, United States International University, 1975, 229 pp. Dissertation Abstracts International 36(4): 1900-B, October 1975. (University Microfilms No. 75-22,652).

(35) BIRNBAUM, A.P. Smokers Differential Response to an Enriched Treatment Procedure as a Function of Motivation for Smoking. Doctoral dissertation, Southern Illinois University, 1975, 156 pp. Dissertation Abstracts International 36(12): 6350-B, June 1976. (University Microfilms No. 76-13,221).

(36) BLACKBURN, H. Progress in the epidemiology and prevention of coronary heart disease. In: Yu, P.N., Goodwin, J.F. (Editors). Progress in Cardiology, Volume 3. Philadelphia, Lea & Febiger, 1974, pp. 1-36.

(37) BLITZER, P.H., RIMM, A.A., GIEFER, E.E. The effect of cessation of smoking on body weight in 57,032 women: Cross-sectional and longitudinal analyses. Journal of Chronic Diseases 30(1): 415-429, July 1977.

(38) BOVILSKY, D.M. A Comparison of Confrontational and Non-Directive Group Experiences in Influencing Smoking Behavior. Doctoral dissertation, Columbia University, 1972, 154 pp. Dissertation Abstracts International 36(5): 2459-B-2460-B, November 1975. (University Microfilms No. 75-25,652).

(39) BOZZETTI, L.P. Group psychotherapy with addicted smokers. Psychotherapy and Psychosomatics 20(3/4): 172-175, 1972.

(40) BRADSHAW, P.W. The problem of cigarette smoking and its control. International Journal of the Addictions 8(2): 353-371, 1973.

(41) BRANTMARK, B., OHLIN, P., WESTLING, H. Nicotine-containing chewing gum as an anti-smoking aid. Psychopharmacologia 31(3): 191-200, 1973.

(42) BRENGELMANN, J.C. Manual on Smoking Cessation Therapy. Facts and Suggestions for the Treatment of Smoking. Geneva, International Journal of Health Education, 1975, 71 pp.

(43) BRENGELMANN, J.C. The organization of treatment for the cessation of smoking. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 655-663.

(44) BRENGELMANN, J.C., SEDLMAYR, E. Experimente zur behandlung des rauchens (Experiments for the treatment of smoking). Schriftenreihe des Bundesministers fuer Jugend, Familie und Gesundheit, Band 35. Stuttgart, Verlag W. Kohlhammer, 1976, 165 pp.

(45) BRENGELMANN, J.C., SEDLMAYR, E. Experiments in the reduction of smoking behavior. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 533-543.

(46) BRITISH MEDICAL JOURNAL. Do people smoke for nicotine? British Medical Journal 2(6094): 1041-1042, October 22, 1977. (Editorial)

(47) BROCKWAY, B.S. Chemical validation of self-reported smoking rates. Behavior Therapy, 6 pp. (to be published).

(48) BROCKWAY, B.S., KLEINMANN, G., EDLESON, J., GRUENEWALD, K. Non-aversive procedures and their effect on cigarette smoking. Addictive Behaviors 2(2): 121-128, 1977.

(49) BROSS, I.D.J. Less harmful ways of smoking. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, Publication No. (NIH) 76-1221, 1976, pp. 111-118.

(50) BROZEK, J., KEYS, A. Changes of body weight in normal men who stop smoking cigarettes. Science 125(3259): 1203, June 14, 1957.

(51) BURNS, B.H. Chronic chest disease, personality, and success in stopping cigarette smoking. British Journal of Preventive and Social Medicine 23(1): 23-27, February 1969.

(52) BURT, A., THORNLEY, P., ILLINGWORTH, D.,WHITE, P., SHAW, T.R.D., TURNER, R. Stopping smoking after myocardial infarction. Lancet 1(7852): 304-306, February 23, 1974.

(53) BURTON, D. Consistency versus internality as initiators of behavior change. International Journal of the Addictions 12(4): 553-563, 1977.

(54) BUTTS, W.C., KUEHNEMAN, M., WIDDOWSON, G.M. Automated method for determining serum thiocyanate, to distinguish smokers from nonsmokers. Clinical Chemistry 20(10): 1344-1348, 1974.

(55) CALIFORNIA MEDICAL ASSOCIATION. The Smoking Study. A report of the attitudes and habits of California physicians with respect to cigarette smoking. California Medicine 109(4): 339-344, October 1968.

(56) CAMPBELL, D.T., STANLEY, J.C. Experimental and Quasi-Experimental Designs for Research. Chicago, Rand McNally & Company, 1966, 84 pp.

(57) CAUTELA, J.R. Treatment of smoking by covert sensitization. Psychological Reports 26(2): 415-420, 1970.

(58) CHAPMAN, R.F., SMITH, J.W., LAYDEN, T.A. Elimination of cigarette smoking by punishment and self-management training. Behavior Research and Therapy 9(3): 255-264, 1971.

(59) CLAIBORN, W.L., LEWIS, P., HUMBLE, S. Stimulus satiation and smoking: A revisit. Journal of Clinical Psychology 28(7): 416-419, 1972.

(60) COCHRAN, N.N. A Methodological Analysis of Two Self-Control Procedures: Self-Monitoring and Thought-Stopping Applied to Smoking Behavior. Doctoral dissertation, University of Mississippi, 1976, 137 pp. Dissertation Abstracts International 37(1): 5826-B-5827B, May 1977. (University Microfilms No. 77-11,181).

(61) COHEN, S.I., PERKINS, N.M., URY, H.K., GOLDSMITH, J.R. Carbon monoxide uptake in cigarette smoking. Archives of Environmental Health 22(1): 55-60, January 1971.

(62) COMSTOCK, G.W., STONE, R.W. Changes in body weight and subcutaneous fatness related to smoking habits. Archives of Environmental Health 24(4): 271-276, April 1972.

(63) CONRAD, F.G. Smoking-withdrawal clinics. New England Journal of Medicine 285(1): 60, July 1, 1971.

(64) CONWAY, J.B. Behavioral self-control of smoking through aversive conditioning and self-management. Journal of Consulting and Clinical Psychology 45(3): 348-357, June 1977.

(65) CORTINES, C. Chronic disease and other aspects of women's smoking in the United States. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 293-297.

(66) CRASILNECK, H.B., HALL, J.A. Clinical hypnosis: Application in smoking and obesity problems. Dallas Medical Journal 62(6): 296-302, June 1976.

(67) CRASILNECK, H.B., Hall, J.A. Hypnosis in the control of smoking. In: Clinical Hypnosis: Principles and Applications. New York, Grune and Stratton, 1975, pp. 167-175.

(68) CROOG, S.H., RICHARDS, N.P. Health beliefs and smoking patterns in heart patients and their wives: A longitudinal study. American Journal of Public Health 67(10): 921-930, October 1977.

(69) CUDAHY, H.H. A Comparison of Two Operant Methods in the Treatment of Smoking. Doctoral dissertation, University of Utah, 1975, 127 pp. Dissertation Abstracts International 36(6): 3029-B, December 1975. (University Microfilms No. 75-28,866).

(70) CURTIS, B., SIMPSON, D.D., COLE, S.G. Rapid puffing as a treatment component of a community smoking program. Journal of Community Psychology 4(2): 186-193, April 1976.

(71) DANAHER, B.G. Rapid smoking and self-control in the modification of smoking behavior. Journal of Consulting and Clinical Psychology 45(6): 1068-1075, December 1977.

(72) DANAHER, B.G. Research on rapid smoking: Interim summary and recommendations. Addictive Behaviors 2(2): 151-166, 1977.

(72a) DANAHER, B.G., LICHTENSTEIN, E. Become an ex-smoker. Englewood Cliffs, N.J., Prentice Hall, 1978, 226 pp.

(73) DANAHER, B.G., LICHTENSTEIN, E., SULLIVAN, J.M. Comparative effects of rapid and normal smoking on heart rate and carboxyhemoglobin. Journal of Consulting and Clinical Psychology 44(4): 556-563, August 1976.

(74) DANAHER, B.G., SHISSLAK, C.M., THOMPSON, C.B., FORD, J.D. A smoking cessation program for pregnant women: An exploratory study. American Journal of Public Health, 68(9): 896-898, 1978.

(75) DASTUR, D.K., QUADROS, E.V., WADIA, N.H., DESAI, M.M., BHARUCHA, E.P. Effect of vegetarianism and smoking on Vitamin B_{12}, thiocyanate, and folate levels in the blood of normal subjects. British Medical Journal 3(5821): 260-263, July 29, 1972.

(76) DAVIDSON, H.A. Rationalizations for continued smoking. New York State Journal of Medicine 64: 2993-3001, December 15, 1964.

(77) DAVISON, G.C., ROSEN, R.C. Lobeline and reduction of cigarette smoking. Psychological Reports 31(2): 443-456, October 1972.

(78) DAWLEY, H.H. Jr., DILLENKOFFER, R.L. Letter to the Editor. Minimizing the risks in rapid smoking treatment. Journal of Behavior Therapy and Experimental Psychiatry 6(2): 174, August 1975.

(79) DAWLEY, H.H. JR., ELLITHORPE, D.B., TRETOLA, R. Aversive smoking: Carboxyhemoglobin levels before and after rapid smoking. Journal of Behavior Therapy and Experimental Psychiatry 7(1): 13-15, March 1976.

(80) DELAHUNT, J., CURRAN, J.P. Effectiveness of negative practice and self-control techniques in the reduction of smoking behavior. Journal of Consulting and Clinical Psychology 44(6): 1002-1007, December 1976.

(81) DELARUE, N.C. The anti-smoking clinic: Is it a potential community service? Canadian Medical Association Journal 108(9): 1164-65, 1168, 1171-1172, 1192, May 5, 1973.

(82) DELARUE, N.C. A study in smoking withdrawal. The Toronto smoking withdrawal study centre—description of activities. Canadian Journal of Public Health, Smoking and Health Supplement 64(2): S5-S19, March/April 1973.

(83) DENSEN, P.M., DAVIDOW, B., BASS, H.E., JONES, E.W. A chemical test for smoking exposure. Archives of Environmental Health 14(6): 865-874, June 1967.

(84) DERDEN, R.H., JR. The Effectiveness of Follow-up Strategies in Smoking Cessation. Doctoral dissertation, University of Pittsburgh, 1977, 204 pp. Dissertation Abstracts International 38(5): 2359-B-2360-B, November 1977. (University Microfilms No. 77-23,582).

(85) DERICCO, D.A., BRIGHAM, T.A., GARLINGTON, W.K. Development and evaluation of treatment paradigms for the suppression of smoking behavior. Journal of Applied Behavior Analysis 10(2): 173-181, Summer 1977.

(86) DICKEN, C., BRYSON, R. Psychology in action. The smoking of psychology. American Psychologist 33(5): 504-507, May 1978.

(87) DICKSON, C.R. The Effects of Self-Monitoring on Smoking Rate. Doctoral dissertation, University of Nevada, Reno, 1971, 102 pp. Dissertation Abstracts International 32(5): 5436-B, March 1972. (University Microfilms No. 72-9565).

(88) DITTRICH, R.A. An Investigation of Therapeutic Instructions, Progress Feedback, and Patient Expectation in Relation to Treatment Outcome. Doctoral dissertation, University of Oregon, 1975, 50 pp. Dissertation Abstracts International 36(7): 3597-B-3598-B, January 1976. (University Microfilms No. 76-922).

(89) DUBITZKY, M., SCHWARTZ, J.L. Ego-resiliency, ego-control, and smoking cessation. Journal of Psychology 70: 27-33, September 1968.

(90) DUBREN, R. Evaluation of a televised stop-smoking clinic. Public Health Reports 92(1): 81-84, January/February 1977.

(91) DUBREN, R. Self-reinforcement by recorded telephone messages to maintain nonsmoking behavior. Journal of Consulting and Clinical Psychology 45(3): 358-360, June 1977.

(92) EISINGER, R.A. Psychosocial predictors of smoking recidivism. Journal of Health and Social Behavior 12: 355-362, December 1971.

(93) EJRUP, B. A proposed medical regimen to stop smoking. The follow-up results. Swedish Cancer Society. Yearbook 3: 468-473, 1963-65.

(94) ELLIOTT, C.H. A Multiple Component Treatment Approach to Smoking Reduction. Doctoral dissertation, University of Kansas, 1976, 122 pp. Dissertation Abstracts International 38(2): 893-B-894-B, August 1977. (University Microfilms No. 77-16,272).

(95) ELLIOTT, R., TIGHE, T. Breaking the cigarette habit: Effects of a technique involving threatened loss of money. Psychological Record 18: 503-513, 1968.

(96) ENGELN, R.G. A Comparison of Desensitization and Aversive Conditioning as Treatment Methods to Reduce Cigarette Smoking. Doctoral dissertation, Washington State University, 1969, 86 pp. Dissertation Abstracts International 30(2): 1357-B, September 1969. (University Microfilms No. 69-14,447).

(97) EPSTEIN, L.H., COLLINS, F.L., JR. The measurement of situational influences of smoking. Addictive Behaviors 2(1): 47-53, 1977.

(98) EVANS, M.W. The Avdel smoking project. Health Education Journal 32(3): 76-81, 1973.

(99) EVANS, R.I., HANSEN, W.B., MITTELMARK, M.B. Increasing the validity of self-reports of smoking behavior in children. Journal of Applied Psychology 62(4): 521-523, 1977.

(100) EYRES, S.J. Public health nursing section report of the 1972 APHA smoking survey. American Journal of Public Health 63(10): 846-852, October 1973.

(101) FARQUHAR, J.W., MACCOBY, N., WOOD, P.D., ALEXANDER, J.K., BREITROSE, H., BROWN, B.W., JR., HASKELL, W.L., McALISTER, A.L., MEYER, A.J., NASH, J.D., STERN, M.P. Community education for cardiovascular health. Lancet 1(8023): 1192-1195, June 4, 1977.

(102) FERNO, O. The development of a chewing gum containing nicotine and some comments on the role played by nicotine in the smoking habit. In: Steinfeld, J., Griffiths, W.,Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 569-573.

(103) FERNO, O., LICHTNECKERT, S.J.A., LUNDGREN, C.E.G. A substitute for tobacco smoking. Psychopharmacologia 31(3): 201-204, 1973.

(104) FLAXMAN, J. Quitting smoking now or later: Gradual, abrupt, immediate, and delayed quitting. Behavior Therapy 9(2): 260-270, March 1978.

(105) FRANCISCO, J.W. Modification of Smoking Behavior: A Comparison of Three Approaches. Doctoral dissertation, Wayne State University, 1972, 87 pp. Dissertation Abstracts International 33(11): 5511-B-5512-B, May 1973. (University Microfilms No. 73-12,511).

(*106*) FRANKS, C.M. Behavior Therapy Appraisal and Status. New York, McGraw-Hill Book Company, 1969, 780 pp.

(*107*) FRANKS, C.M., FRIED, R., ASHEM, B. An improved apparatus for the aversive conditioning of cigarette smokers. Behavior Research and Therapy 4(4): 301-308, November 1966.

(*108*) FREDERIKSEN, L.W. Single-case designs in the modification of smoking. Addictive Behaviors 1(4): 311-319, 1976.

(*109*) FREDERIKSEN, L.W., EPSTEIN, L.H., KOSEVSKY, B.P. Reliability and controlling effects of three procedures for self-monitoring smoking. Psychological Record 25(2): 255-264, 1975.

(*110*) FREDERIKSEN, L.W., FRAZIER, M. Temporal distribution of smoking. Addictive Behaviors. 2(3): 187-192, 1977.

(*111*) FREDERIKSEN, L.W., MILLER, P.M., PETERSON, G.L. Topographical components of smoking behavior. Addictive Behaviors. 2(1): 55-61, 1977.

(*112*) FREDERIKSEN, L.W., PETERSON, G.L., MURPHY, W.D. Controlled smoking: Development and maintenance. Addictive Behaviors 1(3): 193-196, 1976.

(*113*) FREDRICKSON, D.T. Cigarette smoking: Questions patients ask doctors (Part I and II) Chest 58(2 and 4): 147-151, 369-372, August and October 1970.

(*114*) FREDRICKSON, D.T. The community's response to substance misuse. New York City Smoking Withdrawal Clinic. International Journal of the Addictions 3(1): 81-89, Spring 1968.

(*115*) FREDRICKSON, D.T. How to help your patient stop smoking—Guidelines for the office physician. Diseases of the Chest 54(3): 196-202, September 1968.

(*116*) FREDRICKSON, D.T., MCALISTER, A., DANAHER, B.G. Giving up smoking: How the various programs work. Medical World News 17(24): 52-57, November 1, 1976.

(*117*) FRITZ, R. Erfahrungen mit dem "Fuenf-Tage-Plan zur Raucherentwohnung" (Experiences with the "five-day plan to quit smoking"). Zeitschrift fuer Allgemeinmedizin 50(13): 628-630, May 10, 1974.

(*118*) FUHRER, R.E. The Effects of Covert Sensitization with Relaxation Induction, Covert Sensitization Without Relaxation Induction, and Attention-Placebo on the Reduction of Cigarette Smoking. Doctoral dissertation, University of Montana, 1971, 133 pp. Dissertation Abstracts International 32(11): 6644-B-6645-B, May 1972. (University Microfilms No. 72-13,449).

(*119*) GALLUP OPINION INDEX. Public puffs on after ten years of warnings. Gallup Opinion Index (Report No. 108): 20-21, June 1974.

(*120*) GARDNER, R.M. A Test of Coverant Control Therapy to Reduce Cigarette Smoking: A Comparative Study of the Effectiveness of Two Different Strategies with a Direct Test of the Effectiveness of Contingency Management. Doctoral dissertation, University of Louisville, 1970, 95 pp. Dissertation Abstracts International 32(05): 3001-B, September 1971. (University Microfilms No. 71-29,132).

(*121*) GARFINKEL, L. Cigarette smoking among physicians and other health professionals, 1959-1972. CA—A Cancer Journal for Clinicians 26(6): 373-375, November/December 1976.

(*122*) GARVEY, A.J., BOSSE, R., SELTZER, C.C. Smoking, weight change, and age. A longitudinal analysis. Archives of Environmental Health 28(6): 327-329, June 1974.

(*123*) GLASGOW, R.E. Effects of a Self-Control Manual, Rapid Smoking, and Amount of Therapist Contact on Smoking Reduction. Doctoral dissertation, University of Oregon, 1977, 137 pp. Dissertation Abstracts International 38(10): 5014-B, April 1978. (University Microfilms No. 7802521).

(*124*) GLASGOW, R.E., ROSEN, G.M. Behavioral bibliotherapy: A review of self-help behavior therapy manuals. Psychological Bulletin 85(1): 1-23, January 1978.

(*125*) GORDON, S.B. Self-Control with a Covert Aversive Stimulus: Modification of Smoking. Doctoral dissertation, West Virginia University, 1971, 73 pp. Dissertation Abstracts International 32(8): 4858-B-4859-B, February 1972. (University Microfilms No. 72-5154).

(*126*) GORDON, T., KANNEL, W.B., DAWBER, T.R., MCGEE, D. Changes associated with quitting cigarette smoking: The Framingham Study. American Heart Journal 90(3): 322-328, September 1975.

(*127*) GORDON, W.M. The Effects of Instructions to Abstain, Rapid Smoking, and Individually Tailored Treatment on Chronic Smoking Behavior. Doctoral dissertation, Rutgers University, State University of New Jersey, 1976, 48 pp. University Microfilms, Inc., Ann Arbor, Michigan, July 1976. (University Microfilms No. 76-16,402).

(*128*) GRAHAM, S., GIBSON, R.W. Cessation of patterned behavior: Withdrawal from smoking. Social Science and Medicine 5(4): 319-337, August 1971.

(*129*) GREEN, L.W. Diffusion and adoption of innovations related to cardiovascular risk behavior in the public. In: Enelow, A.J., Henderson, J.B. (Editors). Applying Behavioral Science to Cardiovascular Risk. Proceedings of a Conference. American Heart Association, Inc., 1975, pp. 84-108.

(*130*) GREEN, P. The mass media anti-smoking campaign around the world. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 245-253.

(*131*) GREENBERG, I., ALTMAN, J.L. Modifying smoking behavior through stimulus control: A case study. Journal of Behavior Therapy and Experimental Psychiatry 7(1): 97-99, March 1976.

(*132*) GREENE, R.J. Modification of smoking behavior by free operant conditioning methods. Psychological Record 14(2): 171-178, April 1964.

(*133*) GREENE, S.B., AAVEDAL, M.J., TYROLER, H.A., DAVIS, C.E., HAMES, C.G. Smoking habits and blood pressure change: A seven year follow-up. Journal of Chronic Diseases 30(1): 401-413, July 1977.

(*134*) GREENSPUN, I.F. Modification of Smoking Behavior Through Commitment Enhancement. Doctoral dissertation, State University of New York at Stony Brook, 1974, 158 pp. Dissertation Abstracts International 35(9): 4650-B, March 1975. (University Microfilms No. 75-4571).

(*135*) GRIMALDI, K.E., LICHTENSTEIN, E. Hot, smoky air as an aversive stimulus in the treatment of smoking. Behavior Research and Therapy 7(3): 275-282, September 1969.

(*136*) GRITZ, E.R., JARVIK, M.E. Pharmacological aids for the cessation of smoking. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 575-591.

(*137*) GUILFORD, J.S. Group treatment versus individual initiative in the cessation of smoking. Journal of Applied Psychology 56(2): 162-167, April 1972.

(*138*) GUILFORD, J.S. Sex differences between successful and unsuccessful abstainers from smoking. In: Zagona, S.V. Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 95-102.

(*139*) GUTMANN, M., MARSTON, A. Problems of S's motivation in a behavioral program for reduction of cigarette smoking. Psychological Reports 20(4): 1107-1114, June 1967.

(*140*) HACKETT, G., HORAN, J.J. Behavioral control of cigarette smoking: A comprehensive program. Journal of Drug Education 7(1): 71-79, 1977.

(*141*) HACKETT, G., HORAN, J.J. Focused smoking: An unequivocably safe alternative to rapid smoking. Journal of Drug Education 8(3): 261-265, 1978.

(*142*) HACKETT, G., HORAN, J.J., STONE, C.I., LINBERG, S.E., NICHOLAS, W.C., LUKASKI, H.C. Further outcomes and tentative predictor variables from an evolving comprehensive program for the behavioral control of smoking. Journal of Drug Education 7(3): 225-229, 1977-78.

(*143*) HALL, J.A., CRASILNECK, H.B. Development of a hypnotic technique for treating chronic cigarette smoking. International Journal of Clinical and Experimental Hypnosis 18(4): 283-289, October 1970.

(*144*) HALL, R.G., SACHS, D.P.L., HALL, S.M. Medical risk and therapeutic effectiveness of rapid smoking. Behavior Therapy, 28 pp. (to be published)

(*145*) HALLAQ, J.H. The pledge as an instrument of behavioral change. Journal of Social Psychology 98: 147-148, February 1976.

(*146*) HAMMEN, C.L. Factors which Affect Self-Controlling Responses in Smoking Cessation. Doctoral dissertation, University of Wisconsin, 1971, 123 pp. Dissertation Abstracts International 32(6): 3636-B, December 1971. (University Microfilms No. 71-23,304).

(*147*) HAMMER, O. 5 Jahre Bad Nauheimer Raucher-Entwohnungstherapie und Nichtraucher-Training. (Five years of the Bad Nauheim nicotine withdrawal therapy and nonsmoker's training). Muenchener Medizinische Wochenschrift 116(11): 565-568, March 15, 1974.

(*148*) HAMMER, O., ADOLPH, E., HAMMER, R. Gruppentherapie "Frei von Rauchen." Zweijaehrige erfahrungen mit dem Bad Nauheimer 5-Tage-Plan. (Group therapy "Free of Smoking". Two years' experience with the Bad Nauheimer 5-day-plan). Muenchener Medizinische Wochenschrift 112(28): 1329-1335, July 10, 1970.

(*149*) HAMMOND, E.C., GARFINKEL, L. Changes in cigarette smoking. Journal of The National Cancer Institute 33(1): 49-64, July 1964.

(*150*) HAMMOND, E.C., GARFINKEL, L. The influence of health on smoking habits. Study of Cancer and Other Chronic Diseases. National Cancer Institute Monograph 19: 269-285, 1966.

(*151*) HAMMOND, E.C., GARFINKEL, L., SEIDMAN, H., LEW, E.A. "Tar" and nicotine content of cigarette smoke in relation to death rates. Environmental Research 12(3): 263-274, December 1976.

(*152*) HAMMOND, E.C., PERCY, C. Ex-smokers. New York State Journal of Medicine 58: 2956-2959, September 15, 1958.

(*153*) HANDEL, S. Change in smoking habits in a general practice. Postgraduate Medical Journal 49: 679-681, October 1973.

(*154*) HARLIN, V.K. The influence of obvious anonymity on the response of school children to a questionnaire about smoking. American Journal of Public Health 62(4): 566-574, April 1972.

(*155*) HARRIS, M.B., ROTHBERG, C. A self-control approach to reducing smoking. Psychological Reports 31(1): 165-166, August 1972.

(*156*) HAUSER, R. Rapid smoking as a technique of behavior modification: Caution in selection of subjects. Journal of Consulting and Clinical Psychology 42(4): 625, August 1974.

(*157*) HAY, D.R., TURBOTT, S. Changes in smoking habits in men under 65 years after myocardial infarction and coronary insufficiency. British Heart Journal 32: 738-740, 1970.

(*158*) HEPPER, N.G.G., CARR, D.T., ANDERSEN, H.A., FONTANA, R.S., ROSENOW, E.C., III, HANSON, C. Antismoking clinic: Report of an experience and comparison with published results. Mayo Clinic Proceedings 45(3): 189-196, March 1970.

(158a) HERSEN, M., BARLOW, D.E. Single Case Experimental Designs: Strategies for Studying Behavior Changes. New York, Pergamon Press, 1976, 374 pp.

(159) HIGBEE, K.L. Fifteen years of fear arousal: Research on threat appeals: 1953-1968. Psychological Bulletin 72(6): 426-444, December 1969.

(160) HILDEBRAND, G.I. Improving the adult community through hospital based smoking education and cessation programs. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 283-288.

(161) HILDEBRANDT, D.E. The Impact of Commitment and Technique Training on Smoking. Doctoral dissertation, Northern Illinois University, 1975, 256 pp. Dissertation Abstracts International 36(4): 1919-B, October 1975. (University Microfilms No. 75-23,120).

(162) HILL, H. Situational analysis: Women and smoking. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 291-292.

(163) HOMME, L.E. Perspectives in psychology: XXIV. Control of coverants, the operants of the mind. Psychological Record 15(4): 501-511, October 1965.

(164) HORAN, J.J., HACKETT, G., NICHOLAS, W.C., LINBERG, S.E., STONE, C.I., LUKASKI, H.C. Rapid smoking: A cautionary note. Journal of Consulting and Clinical Psychology 45(3): 341-343, June 1977.

(165) HORAN, J.J., LINBERG, S.E., HACKETT, G. Nicotine poisoning and rapid smoking. Journal of Consulting and Clinical Psychology 45(3): 344-347, June 1977.

(166) HORN, D. An approach to office management of the cigarette smoker. Diseases of the Chest 54(3): 203-209, September 1968.

(167) HORN, D. Epidemiology and psychology of cigarette smoking. Chest 59 (5, supplement): 22S-24S, May 1971.

(168) HUNT, W.A. (Editor). Learning Mechanisms in Smoking. Chicago, Aldine Publishing Company, 1970, 237 pp.

(169) HUNT, W.A. (Editor). New approaches to behavioral research on smoking. Journal of Abnormal Psychology 81(2): 107-198, April 1973.

(170) HUNT, W.A., BARNETT, L.W., BRANCH, L.G. Relapse rates in addiction programs. Journal of Clinical Psychology 27(4): 455-456, October 1971.

(171) HUNT, W.A., BESPALEC, D.A. An evaluation of current methods of modifying smoking behavior. Journal of Clinical Psychology 30(4): 431-438, October 1974.

(172) HUNT, W.A., MATARAZZO, J.D. Habit mechanisms in smoking. In: Hunt, W.A. (Editor). Learning Mechanisms in Smoking. Chicago, Aldine Publishing Company, 1970, pp. 65-106.

(173) HYND, G.W., CHAMBERS, C., STRATTON, T.T., MOAN, E. Credibility of smoking control strategies in non-smokers: Implications for clinicians. Psychological Reports 41(2): 503-506, October 1977.

(174) HYND, G.W., O'NEAL, M., SEVERSON, H.H. Cardiovascular stress during the rapid-smoking procedure. Psychological Reports 39(2): 371-375, October 1976.

(175) HYND, G.W., STRATTON, T.T., SEVERSON, H.H. Smoking treatment strategies, expectancy outcomes, and credibility in attention-placebo control conditions. Journal of Clinical Psychology 34(1): 182-186, January 1978.

(176) IKARD, F.F., GREEN, D.E., HORN, D. A scale to differentiate between types of smoking as related to the management of affect. International Journal of the Addictions 4(4): 649-659, December 1969.

(177) IKARD, F.F., TOMKINS, S. The experience of affect as a determinant of smoking behavior: A series of validity studies. Journal of Abnormal Psychology 81(2): 172-181, April 1973.

(178) ISACSSON, S.-O., JANZON, L. Results of a quit-smoking research project in a randomly selected population. Scandinavian Journal of Social Medicine 4(1): 25-29, 1976.

(179) JACOBS, M.A. The addictive personality: Prediction of success in a smoking withdrawal program. Psychosomatic Medicine 34(1): 30-38, January/February 1972.

(180) JACOBS, M.A., SPILKEN, A.Z., NORMAN, M.M., WOHLBERG, G.W., KNAPP, P.H. Interaction of personality and treatment conditions associated with success in a smoking control program. Psychosomatic Medicine 33(6): 545-556, November/December 1971.

(181) JANIS, I.L., HOFFMAN, D. Facilitating effects of daily contact between partners who make a decision to cut down on smoking. Journal of Personality and Social Psychology 17(1): 25-35, April 1970.

(182) JANIS, I.L., MANN, L. Effectiveness of emotional role-playing in modifying smoking habits and attitudes. Journal of Experimental Research in Personality 1(1): 84-90, June 1965.

(183) JARVIK, M.E. Biological factors underlying the smoking habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 122-148.

(184) JARVIK, M.E. Further observations on nicotine as the reinforcing agent in smoking. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. Washington, D.C., V. H. Winston and Sons, 1973, pp. 33-49.

(185) JARVIK, M.E., GLICK, S.D., NAKAMURA, R.K. Inhibition of cigarette smoking by orally administered nicotine. Clinical Pharmacology and Therapeutics 11(4): 574-576, July/August 1970.

(186) JENKS, R., SCHWARTZ, J.L., DUBITZKY, M. Effect of the counselor's approach to changing smoking behavior. Journal of Clinical Psychology 16: 215-221, 1969.

(187) JOHNSON, E.K. The Treatment of Smoking as a Self-Defeating Behavior and Prediction of Behavior Change and Maintenance. Doctoral dissertation, Brigham Young University, 1975, 144 pp. Dissertation Abstracts International 36(7): 3610-B, January 1976. (University Microfilms No. 76-710).

(188) JOHNSON, S.S. The Effects of Self Control Techniques Upon Differing Types of Smoking Behavior. Doctoral dissertation, University of Colorado, 1968, 97 pp. University Microfilms, Inc., Ann Arbor, Michigan, 1972. (University Microfilms No. 69-4370).

(189) JOHNSTON, E., DONOGHUE, J.R. Hypnosis and smoking: A review of the literature. American Journal of Clinical Hypnosis 13(4): 265-272, April 1971.

(190) JONES, J.S. Cigarette abandonment: Its significance. British Journal of Diseases of the Chest 71(4): 285-288, October 1977.

(191) JORGENSEN, G.T. An Experimental Test of a Treatment Program to Modify Cigarette Smoking. Doctoral dissertation, Colorado State University, 1973, 118 pp. Dissertation Abstracts International 34(9): 4666-B, March 1974. (University Microfilms No. 74-5424).

(*192*) KAHN, A., RUTLEDGE, R.B., DAVIS, G.L., ALTES, J.A., GANTNER, G.E., THORNTON, C.A., WALLACE N.D. Carboxyhemoglobin sources in the metropolitan St. Louis population. Archives of Environmental Health 29: 127-135, September 1974.

(*193*) KANFER, F.H., KAROLY, P. Self-control: A behavioristic excursion into the lion's den. Behavior Therapy 3(3): 398-416, July 1972.

(*194*) KANZLER, M., JAFFE, J.H., ZEIDENBERG, P. Long- and short-term effectiveness of a large-scale proprietary smoking cessation program—a four-year follow-up of Smokenders participants. Journal of Clinical Psychology 32(3): 661-669, July 1976.

(*195*) KANZLER, M., ZEIDENBERG, P., JAFFE, J.H. Response of medical personnel to an on-site smoking cessation program. Journal of Clinical Psychology 32(3): 670-674, July 1976.

(*196*) KAPLAN, J.M. An Individualized Stimulus-Control Procedure in the Treatment of Cigarette Smoking. Doctoral dissertation, Florida State University, 1976, 52 pp. Dissertation Abstracts International 37(1): 463-B-464-B, July 1976. (University Microfilms No. 76-16,527).

(*197*) KATZ, R.C., HEIMAN, M., GORDON, S. Effects of two self-management approaches on cigarette smoking. Addictive Behaviors 2(1): 113-119, 1977.

(*198*) KAZDIN, A.E. Self-monitoring and behavior change. In: Mahoney, M.J., Thoresen, C.E. (Editors). Self-Control: Power to the Person. Monterey, Brooks/Cole Publishing Company, 1974, pp. 218-246.

(*199*) KEUTZER, C.S. Behavior modification of smoking: The experimental investigation of diverse techniques. Behaviour Research and Therapy 6(2): 137-157, May 1968.

(*200*) KEUTZER, C.S., LICHTENSTEIN, E., MEES, H.L. Modification of smoking behavior: A review. Psychological Bulletin 70(6): 520-533, December 1968.

(*201*) KOENIG, K.P., MASTERS, J. Experimental treatment of habitual smoking. Behavioral Research and Therapy 3 (4): 235-243, December 1965.

(*202*) KOPEL, S.A. The Effects of Self-Control, Booster Sessions, and Cognitive Factors on the Maintenance of Smoking Reduction. Doctoral dissertation, University of Oregon, 1974, 67 pp. Dissertation Abstracts International 35(8): 4182-B-4183-B, February 1975. (University Microfilms No. 75-3895).

(*203*) KOPEL, S., ARKOWITZ, H. The role of attribution and self-perception in behavior change: Implications for behavior therapy. Genetic Psychology Monographs 92: 175-212, 1975.

(*204*) KOSKELA, K., PUSKA, P., TUOMILEHTO, J. The North Karelia project: A first evaluation. International Journal of Health Education 19(1): 59-66, 1976.

(*205*) KREITLER, S., SHAHAR, A., KREITLER, H. Cognitive orientation, type of smoker and behavior therapy of smoking. British Journal of Medical Psychology 49(2): 167-175, June 1976.

(*206*) LANDO, H.A. Aversive conditioning and contingency management in the treatment of smoking. Journal of Consulting and Clinical Psychology 44(2): 312, April 1976.

(*207*) LANDO, H.A. A comparison of excessive and rapid smoking in the modification of chronic smoking behavior. Journal of Consulting and Clinical Psychology 43(3): 350-355, June 1975.

(*208*) LANDO, H.A. Measurement and technique innovations. An objective check upon self-reported smoking levels: A preliminary report. Behavior Therapy 6(4): 547-549, July 1975.

(*209*) LANDO, H.A. Self-pacing in eliminating chronic smoking: Serendipity revisited? Behavior Therapy 7(5): 634-640, October 1976.

(*210*) LANDO, H.A. Successful treatment of smokers with a broad-spectrum behavioral approach. Journal of Consulting and Clinical Psychology 45(3): 361-366, June 1977.

(*211*) LANDO, H.A., DAVISON, G.C. Cognitive dissonance as a modifier of chronic smoking behavior: A serendipitous finding. Journal of Consulting and Clinical Psychology 43(5): 750, October 1975.

(*212*) LAWSON, D.M., MAY, R.M. Three procedures for the extinction of smoking behavior. Psychological Record 20(2): 151-157, April 1970.

(*213*) LAWTON, M.P. Group methods in smoking withdrawal. Archives of Environmental Health 14(2): 258-265, February 1967.

(*214*) LE MEITOUR-KAPLAN, A. Situational analysis: Profile of women's smoking habits in continental Western Europe. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department, of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 309-327.

(*215*) LEVENBERG, S.B., WAGNER, M.K. Smoking cessation: Long-term irrelevance of mode of treatment. Journal of Behavior Therapy and Experimental Psychiatry 7(1): 93-95, March 1976.

(*216*) LEVENTHAL, H. Changing attitudes and habits to reduce risk factors in chronic disease. American Journal of Cardiology 31(5): 571-580, May 1973.

(*217*) LEVENTHAL, H. Effect of fear communications in the acceptance of preventive health practices. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 17-27.

(*218*) LEVENTHAL, H. Experimental studies of anti-smoking communications. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 95-121.

(*219*) LEVENTHAL, H. Fear appeals and persuasion: The differentiation of a motivational construct. American Journal of Public Health 61(6): 1208-1224, June 1971.

(*220*) LEVINE, B.A. Effectiveness of contingent and non-contingent electric shock in reducing cigarette smoking. Psychological Reports 34: 223-226, February 1974.

(*221*) LEVINSON, B.L., SHAPIRO, D., SCHWARTZ, G.E., TURSKY, B. Smoking elimination by gradual reduction. Behavior Therapy 2(4): 477-487, October 1971.

(*222*) LEWITTES, D.J., ISRAEL, A.C. Responsibility contracting for the maintenance of reduced smoking: A technique innovation. Behavior Therapy 6 (5): 696-698, 1975.

(*223*) LICHTENSTEIN, E. Lichtenstein replies. Journal of Consulting and Clinical Psychology 42(4): 625-626, August 1974.

(*224*) LICHTENSTEIN, E. Modification of smoking behavior: good designs—ineffective treatments. Journal of Consulting and Clinical Psychology 36(2): 163-166, April 1971.

(*225*) LICHTENSTEIN, E. Social learning. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 348-354.

(*226*) LICHTENSTEIN, E., DANAHER, B.G. Modification of smoking behavior: A critical analysis of theory, research, and practice. In: Hersen, M., Eisler, R.M., Miller, P.M. (Editors). Progress in Behavior Modification, Volume 3. New York, Academic Press, Inc., 1976, pp. 79-132.

(227) LICHTENSTEIN, E., DANAHER, B.G. What can the physician do to assist the patient to stop smoking? In: Brashear, R.E., Rhodes, M.L. (Editors). Chronic Obstructive Lung Disease: Clinical Treatment and Management. St. Louis, Mosby, 1978, pp. 227-241.

(228) LICHTENSTEIN, E., GLASGOW, R.E. Rapid smoking: Side effects and safeguards. Journal of Consulting and Clinical Psychology 45(5): 815-821, October 1977.

(229) LICHTENSTEIN, E., HARRIS, D.E., BIRCHLER, G.R., WAHL, J.M., SCHMAHL, D.P. Comparison of rapid smoking, warm, smoky air, and attention placebo in the modification of smoking behavior. Journal of Consulting and Clinical Psychology 40(1): 92-98, February 1973.

(230) LICHTENSTEIN, E., KEUTZER, C.S. Modification of smoking behavior: A later look. In: Rubin, R.D., Fensterheim, H., Lazarus, A.A., Franks, C.M. (Editors). Advances in Behavior Therapy. Proceedings of the Third Conference of the Association for Advancement of Behavior Therapy. New York, Academic Press, 1971, pp. 61-75.

(231) LICHTENSTEIN, E., KEUTZER, C.S., HIMES, K.H. "Emotional" role-playing and changes in smoking attitudes and behavior. Psychological Reports 25(2): 379-387, October 1969.

(232) LICHTENSTEIN, E., RODRIGUES, M.-R.P. Long-term effects of rapid smoking treatment for dependent cigarette smokers. Addictive Behaviors 2(2): 109-112, 1977.

(233) LINDENTHAL, J.J., MYERS, J.K., PEPPER, M.P. Smoking, psychological status and stress. Social Science and Medicine 6(5): 583-591, October 1972.

(234) MACCOBY, N., FARQUHAR, J.W. Communication for health: Unselling heart disease. Journal of Communication 25(3): 114-126, Summer 1975.

(235) MACCOBY, N., FARQUHAR, J.W., WOOD, P.D., ALEXANDER, J. Reducing the risk of cardiovascular disease: Effects of a community-based campaign on knowledge and behavior. Journal of Community Health 3(2): 100-114, Winter 1977.

(236) MADOF, F. The Effect of Certain Learning Variables, Applied in Imagination, on the Modification of Smoking Behavior. Doctoral dissertation, Temple University, 1976, 208 pp. Dissertation Abstracts International 36(12 part 1): 6360-B, June 1976. (University Microfilms No. 76-12,015).

(237) MAIR, J.M.M. Psychological problems and cigarette smoking. Journal of Psychosomatic Research 14(3): 277-283, September 1970.

(238) MALISZEWSKI, T.F., BASS, D.E. "True" and "apparent" thiocyanate in body fluids of smokers and nonsmokers. Journal of Applied Physiology 8(3): 289-291, November 1955.

(239) MANN, L., JANIS, I.L. A follow-up study on the long-term effects of emotional role playing. Journal of Personality and Social Psychology 8(4): 339-342, 1968.

(240) MARRONE, R.L., MERKSAMER, M.A., SALZBERG, P.M. A short duration group treatment of smoking behavior by stimulus saturation. Behavior Research and Therapy 8(4): 347-352, November 1970.

(241) MARSTON, A.R., FELDMAN, S.E. Toward the use of self-control in behavior modification. Journal of Consulting and Clinical Psychology 39(3): 429-433, December 1972.

(242) MARSTON, A.R., MCFALL, R.M. Comparison of behavior modification approaches to smoking reduction. Journal of Consulting and Clinical Psychology 36(2): 153-162, April 1971.

(243) MAUSNER, B. Some comments on the failure of behavior therapy as a technique for modifying cigarette smoking. Journal of Consulting and Clinical Psychology 36(2): 167-170, April 1971.

(244) MAUSNER, B., MAUSNER, J.S., RIAL, W.Y. The influence of a physician on the smoking behavior of his patients. In: Zagona, S.V. Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 103-106.

(245) MCALISTER, A. Helping people quit smoking: Current progress. In: Enelow, A.J., Henderson, J.B. (Editors). Applying Behavioral Science to Cardiovascular Risk. Proceedings of a Conference, Seattle, Washington, June 17-19, 1974. American Heart Association, Inc., 1975, pp. 147-165.

(246) MCALISTER, A.L. Toward the Mass Communication of Behavioral Counseling: A Preliminary Experimental Study of a Televised Program to Assist in Smoking Cessation. Doctoral dissertation, Stanford University, June 1976, 134 pp. University Microfilms, Inc., Ann Arbor, Michigan, 1975. (University Microfilms No. 77-7128).

(247) MCALISTER, A.L., FARQUHAR, J.W., THORESEN, C.E., MACCOBY, N. Behavioral science applied to cardiovascular health: Progress and research needs in the modification of risk-taking habits in adult populations. Health Education Monographs 4(1): 45-74, 1976.

(248) MCALISTER, A., MEYER, A.J., MACCOBY, N. Long-term results of education to reduce smoking: Stanford three community study. Circulation (Abstracts) 53, 54 (Supplement II)II-226, October 1976.

(249) MCCALLUM, R.N. The Modification of Cigarette Smoking Behavior: A Comparison of Treatment Techniques. Doctoral dissertation, University of Missouri, Columbia, 1970, 211 pp. Dissertation Abstracts International 31(10): 6264-B, April 1971. (University Microfilms No. 71-8360).

(250) MCFALL, R.M. Effects of self-monitoring on normal smoking behavior. Journal of Consulting and Clinical Psychology 35(2): 135-142, October 1970.

(251) MCFALL, R.M., HAMMEN, C.L. Motivation, structure, and self-monitoring: Role of nonspecific factors in smoking reduction. Journal of Consulting and Clinical Psychology 37(1): 80-86, 1971.

(252) MCFARLAND, J.W. Physical measures used in breaking the smoking habit. Archives of Physical Medicine and Rehabilitation 46(4): 323-327, April 1965.

(253) MCFARLAND, J.W. The role of church groups in smoking and health. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 949-952.

(254) MCFARLAND, J.W., GIMBEL, H.W., DONALD, W.A.J., FOLKENBERG, E.J. The five-day program to help individuals stop smoking. A preliminary report. Connecticut Medicine 28(12): 885-890, December 1964.

(255) MCGRATH, M.J., HALL, S.M. Self-management treatment of smoking behavior. Addictive Behaviors 1(4): 287-292, 1976.

(256) MCKENNELL, A.C. Smoking motivation factors. British Journal of Social and Clinical Psychology 9(1): 8-22, February 1970.

(257) MEADE, T.W., WALD, N.J. Cigarette smoking patterns during the working day. British Journal of Preventive and Social Medicine 31(1): 25-29, March 1977.

(258) MEYER, A.J., HENDERSON, J.B. Multiple risk factor reduction in the prevention of cardiovascular disease. Preventive Medicine 3(2): 225-236, June 1974.

(259) MEYER, A.J., MCALISTER, A., NASH, J., MACCOBY, N., FARQUHAR, J.W. Maintenance of cardiovascular risk reduction: Results in high risk subjects. Circulation (Abstracts) 53, 54 (Supplement II): II-226, October 1976.

(260) MILLER, A., GIMPL, M. Operant conditioning and self-control of smoking and studying. Journal of Genetic Psychology 119(2): 181-186, December 1971.

(261) MILLER, L.C., SCHILLING, A.F., LOGAN, D.L., JOHNSON, R.L. Potential hazards of rapid smoking as a technic for the modification of smoking behavior. New England Journal of Medicine 297(11): 590-592, September 15, 1977.

(262) MITTELMARK, M.B. Information on Imminent Versus Long-Term Health Consequences: Impact on Children's Smoking Behavior, Intentions, and Knowledge. Doctoral dissertation, University of Houston, May 1978, 166 pp.

(263) MORGANSTERN, K.P., RATLIFF, R.G. Systematic desensitization as a technique for treating smoking behavior: a preliminary report. Behavior Research and Therapy 7: 397-398, 1969.

(264) MOZER, M.H. The Intensive Application of Self Control Procedures in the Reduction of Smoking. Doctoral dissertation, University of Montana, 1972, 171 pp. Dissertation Abstracts International 33(7): 3318-B, January 1973. (University Microfilms No. 72-33,062).

(265) MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT). A national study of primary prevention of coronary heart disease. Journal of the American Medical Association 235(8): 825-827, February 23, 1976.

(265a) MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT). Multiple Risk Factor Intervention Trial (MRFIT):Smoking cessation procedures and cessation and recidivism patterns for a large cohort of MRFIT participants. In: Schwartz, J.L. Progress in Smoking Cessation: Proceedings of the International Conference on Smoking Cessation, June 21-23, 1978. New York, American Cancer Society, 1979, 15 pp.

(266) MULTIPLE RISK FACTOR INTERVENTION TRIAL GROUP. Statistical design considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). Journal of Chronic Diseases 30(5): 261-275, May 1977.

(267) MURDOCK, R., EVA, J. Smoking clinics—whither? Community Health 6(3): 155-159, December 1974.

(268) MURPHY, W.D. The Contribution of Relaxation and Relief to Covert Sensitization in the Treatment of Smoking. Doctoral dissertation, Ohio University, 1976, 107 pp. Dissertation Abstracts International 37(8): 4157-B, February 1977. (University Microfilms No. 77-3487).

(269) NATIONAL CANCER INSTITUTE. AMERICAN CANCER SOCIETY. Cigarette Smoking Among Teen-Agers and Young Women. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1208, 1977, 31 pp.

(270) NATIONAL CANCER INSTITUTE. The Smoking Digest. Progress Report on a Nation Kicking the Habit. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, October 1977, 127 pp.

(271) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U.S. Department of Health, Education and Welfare, Public Health Service, June 1976, 133 pp.

(272) NATIONAL INTERAGENCY COUNCIL ON SMOKING AND HEALTH. Guidelines for Research on the Effectiveness of Smoking Cessation Programs. A Committee Report. New York, National Interagency Council on Smoking and Health, October 1974, 46 pp.

(273) NELSON, S.K. Behavioral control of smoking with combined procedures. Psychological Reports 40(1): 191-196, February 1977.

(274) NEMZER, D.E. Results of Four Cigarette Cessation Clinics in Nassau and Suffolk Counties, New York. Riverhead, New York, American Lung Association of Nassau-Suffolk, 1973. 24 pp.

(*275*) NEWMAN, A. The effect of reinforcement of intention statements and/or execution of self-control in smokers and ex-smokers. Addictive Behaviors 2(1): 15-20, 1977.

(*276*) NORTON, G.R., BARSKE, B. The role of aversion in the rapid-smoking treatment procedure. Addictive Behavior 2(1): 21-25, 1977.

(*277*) NOVAR, L.G. Self-Control of Smoking Behavior—A Comparative Study of Constructional and Eliminative Approaches. Doctoral dissertation, University of Chicago, 1976. Dissertation Abstracts International 38(2): 709-A, August 1977.

(*278*) NULAND, W., FIELD, P.B. Smoking and hypnosis: A systematic clinical approach. International Journal of Clinical and Experimental Hypnosis 18(4): 290-305, October 1970.

(*279*) OBER, D.C. Modification of smoking behavior. Journal of Consulting and Clinical Psychology 32(521): 543-549, October 1968.

(*280*) O'BRIEN, R.M., DICKINSON, A.M. Contingency factors in negative practice of smoking. Psychological Reports 40(2): 495-505, April 1977.

(*281*) OCHSNER, A., DAMRAU, F. Control of cigarette habit by psychological aversive conditioning: Clinical evaluation in 53 smokers. Journal of the American Geriatrics Society 18(5): 365-369, May 1970.

(*283*) OHLIN, P., LUNDH, B., WESTLING, H. Carbon monoxide blood levels and reported cessation of smoking. Psychopharmacology 49(3): 263-265, 1976.

(*284*) O'KEEFE, M.T. The anti-smoking commercials: A study of television's impact on behavior. Public Opinion Quarterly 35(2): 242-248, 1971.

(*285*) ORNE, M.T. Hypnosis in the treatment of smoking. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 489-507.

(*286*) ORR, R.G. Smoking-withdrawal clinics. New England Journal of Medicine 285(3): 1384, December 9, 1971.

(*287*) OTTENS, A.J. The effect of transcendental meditation upon modifying the cigarette smoking habit. Journal of School Health 45(10): 577-583, December 1975.

(*288*) OWEN, T.B. Tar and nicotine from U.S. cigarettes: Trends over the past twenty years. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 73-80.

(*289*) PAINTER, J.H. The Modification of Smoking Behavior in a Controlled Public Clinic. Doctoral dissertation, Arizona State University, 1972, 145 pp. Dissertation Abstracts International 32(8): 4867-B, February 1972. (University Microfilms No. 72-6256).

(*290*) PAUN, D. Zehn Jahre Gruppentherapie in der Raucherberatungs-stelle Berlin-Friedrichshain (Ten years of group therapy at the counseling service in Berlin-Friedrichshain). In: Gibel, W. Gesundheitsschaden durch Rauchen—Moeglichkeiten einer Prophylaxe. Berlin, Akademie-Verlag, 1976, pp. 162-172.

(*291*) PEABODY, H.D., JR. A practical approach to the office management of cessation of cigarette smoking. In: Richardson, R.G. (Editor). The Second World Conference on Smoking and Health. The proceedings of a conference organized by the Health Education Council, Imperial College, London, September 20-24, 1971. London, Pitman Medical, 1972, pp. 185-189.

(292) PECHACEK, T.F. An Evaluation of Cessation and Maintenance Strategies in the Modification of Smoking Behavior. Doctoral dissertation, University of Texas at Austin, 1977, 75 pp. University Microfilms, Inc., Ann Arbor, Michigan, November 1977. (University Microfilms No. 77-23,013).

(293) PECHACEK, T.F. A probabilistic model of intensive designs. Journal of Applied Behavior Analysis 11(3): 357-362, Fall 1978.

(294) PEDERSON, L.L., LEFCOE, N.M. A psychological and behavioural comparison of ex-smokers and smokers. Journal of Chronic Diseases 29(7): 431-434, 1976.

(295) PEDERSON, L.L., SCRIMGEOUR, W.G., LEFCOE, N.M. Comparison of hypnosis plus counseling, counseling alone, and hypnosis alone in a community service smoking withdrawal program. Journal of Consulting and Clinical Psychology 43(6): 920, December 1975.

(296) PERRI, M.G., RICHARDS, C.S., SCHULTHEIS, K.R. Behavioral self-control and smoking reduction: A study of self-initiated attempts to reduce smoking. Behavior Therapy 8(3): 360-365, June 1977.

(297) PERRY, C., MULLEN, G. The effects of hypnotic susceptibility on reducing smoking behavior treated by an hypnotic technique. Journal of Clinical Psychology 31(3): 498-505, July 1975.

(298) PETERSON, D.I., LONERGAN, L.H., HARDINGE, M.G., TEEL, C.W. Results of a stop-smoking program. Archives of Environmental Health 16(2): 211-214, February 1968.

(299) PETTIGREW, A.R., FELL, G.S. Microdiffusion method for estimation of cyanide in whole blood and its application to the study of conversion of cyanide to thiocyanate. Clinical Chemistry 19(5): 466-471, 1973.

(300) PETTIGREW, A.R., FELL, G.S. Simplified colorimetric determination of thiocyanate in biological fluids, and its application to investigation of the toxic amblyopias. Clinical Chemistry 18(9): 996-1000, 1972.

(301) PHILLIPS, A.J. Smoking control programs for Canadian adults. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 269-273.

(302) PINCHERLE, G., WRIGHT H.B. Smoking habits of business executives. Doctor variation in reducing cigarette consumption. Practitioner 205(1226): 209-212, August 1970.

(303) PLATT, E.S., KRASSEN, E., MAUSNER, B. Individual variation in behavioral change following role playing. Psychological Reports 24: 155-170, February 1969.

(304) POMERLEAU, O.F. Some suggestions for research in the smoking-cessation clinic. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 643-648.

(305) POMERLEAU, O.F. Strategies for maintenance: The problem of sustaining abstinence from cigarettes. Paper presented at the International Conference on Smoking-Cessation, New York, June 1978, 16 pp.

(306) POMERLEAU, O.F. Why people smoke: Current psychobiological models. In: Davidson, O. (Editors). Behavioral Medicine: Changing Health Lifestyles. New York, Bruner/Mazel, 1979, 38 pp. (to be published)

(307) POMERLEAU, O.F. You can get patients to change their habits. Medical Times 104(10): 149-158, October 1976.

(*308*) POMERLEAU, O.F., ADKINS, D.M., PERTSCHUK, M. Predictors of outcome and recidivism in smoking-cessation treatment. Addictive Behaviors 3:65-70, 1978 Meeting for the Association for The Advancement of Behavior Therapy, New York, December 1976, 7 pp.

(*309*) POMERLEAU, O., BASS, F., CROWN, V. Role of behavior modification in preventive medicine. New England Journal of Medicine 292(24): 1277-1282, June 1975.

(*310*) POMERLEAU, O.F., POMERLEAU, C.S. Break the Smoking Habit. A Behavioral Program for Giving Up Cigarettes. Champaign, Illinois, Research Press Company, 1977, 108 pp.

(*311*) POPE, J.W., MOUNT, G.R. The control of cigarette smoking through the application of a portable electronic device designed to dispense an aversive stimulus in relation to subject's smoking frequency. Behavioral Engineering 2(2): 52-56, Winter 1975.

(*312*) PORTER, A.M.W., MCCULLOUGH, D.M. Counselling against cigarette smoking. A controlled study from a general practice. Practitioner 209(1253): 686-689, November 1972.

(*313*) POWELL, J., AZRIN, N. The effects of shock as a punisher for cigarette smoking. Journal of Applied Behavior Analysis 1(1): 63-71, Spring 1968.

(*314*) PREMACK, D. Mechanisms of self-control. In: Hunt, W.A. Learning Mechanisms in Smoking. Chicago, Aldine Publishing Company, 1970, pp. 107-130.

(*315*) PRIMO, R.V. Covert Avoidance Learning: A Refined Covert Sensitization Method for the Modification of Smoking Behavior. Doctoral dissertation, University of Pittsburgh, 1972, 134 pp. Dissertation Abstracts International 33(8): 3958-B-3959-B, February 1973. (University Microfilms No. 73-4992).

(*316*) PUSKA, P., KOSKELA, K., PAKARINEN, H., PUUMALAINEN, P., SOININEN, V., TUOMILEHTO, J. The North Karelia project: A programme for community control of cardiovascular diseases. Scandinavian Journal of Social Medicine 4(2): 57-60, 1976.

(*317*) PYKE, S., AGNEW, N.M., KOPPERUD, J. Modification of an overlearned maladaptive response through a relearning program: A pilot study on smoking. Behaviour Research and Therapy 4(3): 197-203, August 1966.

(*318*) PYSZKA, R.H., RUGGELS, W.L., JANOWICZ, L.M. IR and D Report. Health Behavior Change: Smoking Cessation. Menlo Park, Stanford Research Institute, December 1973, 31 pp.

(*319*) RAW, M. Persuading people to stop smoking. Behaviour Research and Therapy 14(2): 97-101, 1976.

(*320*) REA, J.N., TYRER, P.J., KASAP, H.S., BERESFORD, S.A.A. Expired air carbon monoxide, smoking, and other variables. A community study. British Journal of Preventive and Social Medicine 27(2): 114-120, May 1973.

(*321*) REED, H.D., JR., JANIS, I.L. Effects of a new type of psychological treatment on smokers' resistance to warnings about health hazards. Journal of Consulting and Clinical Psychology 42(5): 748, October 1974.

(*322*) REED, K. Smoking control with an in-patient general hospital population. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 107-109.

(*323*) REEDER, L.G. Sociocultural factors in the etiology of smoking behavior: An assessment. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. Research on Smoking Behavior. (NIDA Research Monograph 17). U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-201.581, December 1977, pp. 186-201.

(324) REID, D.D., BRETT, G.Z., HAMILTON, P.J.S., JARRETT, R.J., KEEN, H., ROSE, G. Cardiorespiratory disease and diabetes among middle-aged male civil servants. A study of screening and intervention. Lancet 1(7856): 469-473, March 23, 1974.

(325) RELINGER, H., BORNSTEIN, P.H., BUGGE, I.D., CARMODY, T.P., ZOHN, C.J. Utilization of adverse rapid smoking in groups: Efficacy of treatment and maintenance procedures. Journal of Consulting and Clinical Psychology 45(2): 245-249, April 1977.

(326) RESNICK, J.H. The control of smoking behavior by stimulus satiation. Behaviour Research and Therapy 6(1): 113-114, February 1968.

(327) RESNICK, J.H. Effects of stimulus satiation on the overlearned maladaptive response of cigarette smoking. Journal of Consulting and Clinical Psychology 32(5-Part 1): 501-505, October 1968.

(328) RICHARDSON, F.L. The Effect of Nonspecific Factors on the Modification of Smoking Behavior in Treatment Follow-up. Doctoral dissertation, University of Southern California, 1972, 140 pp. Dissertation Abstracts International 33(4): 1804-B-1805-B, October 1972. (University Microfilms No. 72-26,050).

(329) RICHMOND, H.W. A fifteen-year prospective study of the incidence of coronary heart disease related to cigarette smoking habits in Cummins Engine Company management personnel with results of a vigorous anti-smoking education campaign. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 275-281.

(330) RINGOLD, A., GOLDSMITH, J.R., HELWIG, H.L., FINN, R., SCHUETTE, F. Estimating recent carbon monoxide exposures. A rapid method. Archives of Environmental Health 5: 308-318, October 1962.

(331) RODGERS, M.P. The Effect of Social Support on the Modification of Smoking Behavior. Doctoral dissertation, University of Michigan, 1977, 289 pp. Dissertation Abstracts International 38(3): 1448-B, September 1977. (University Microfilms No. 77-18,105).

(332) ROGERS, R.W. A protection motivation theory of fear appeals and attitude change. Journal of Psychology 91: 93-114, September 1975.

(333) ROGERS, R.W., DECKNER, C.W. Effects of fear appeals and physiological arousal upon emotion, attitudes, and cigarette smoking. Journal of Personality and Social Psychology 32(2): 222-230, 1975.

(334) ROGERS, R.W., DECKNER, C.W., MEWBORN, C.R. An expectancy-value theory approach to the long-term modification of smoking behavior. Journal of Clinical Psychology 34(2): 562-566, April 1978.

(335) RORKE, G.W. Situational analysis: Profile of women's smoking habits in Canada and the United Kingdom. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 299-307.

(336) ROSE, G. Anti-smoking programmes. In: Tibblin, G., Keys, A., Werkoe, L. (Editors). Preventive Cardiology. Proceedings of an International Symposium, Skovde, Sweden, August 21, 1971. New York, John Wiley and Sons, 1972, pp. 92-96.

(337) ROSE, G. Smoking cessation in high-risk subjects. Health Magazine 12(4): 19-22, Winter 1975/76.

(*338*) ROSE, G. Physician counseling and personal intervention. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 515-523.

(*339*) ROSEN, G.M., LICHTENSTEIN, E. An employee incentive program to reduce cigarette smoking. Journal of Consulting and Clinical Psychology 45(5): 957, October 1977.

(*340*) ROSENBERG, A. An investigation into the effect on cigarette smoking of a new anti-smoking chewing gum. Journal of International Medical Research 5(1): 68-70, 1977.

(*341*) ROSS, C.A. Smoking withdrawal research clinics. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 111-113.

(*342*) ROVNER, R.A. Effects of Contingency Contracting on Cigarette Smoking. Doctoral dissertation, University of Maryland, 1975, 80 pp. Dissertation Abstracts International 37(2): 986-B, August 1976. (University Microfilms No. 76-18,711).

(*343*) ROYAL COLLEGE OF PHYSICIANS. Smoking or Health: The Third Report from the Royal College of Physicians of London. London, Pitman Medical Publishing Co. Ltd., 1977, 128 pp.

(*344*) ROZENSKY, R.H. The effect of timing of self-monitoring behavior on reducing cigarette consumption. Journal of Behavior Therapy and Experimental Psychiatry 5(4): 301-303, December 1974.

(*345*) ROZENSKY, R., BELLACK, A. Behavior change and individual differences in self-control. Behaviour Research and Therapy 12(3): 267-268, September 1974.

(*346*) RUSSELL, M.A.H. Effect of electric aversion on cigarette smoking. British Medical Journal 1(5688): 82-86, January 10, 1970.

(*347*) RUSSELL, M.A.H. Realistic goals for smoking and health. A case for safer smoking. Lancet 1(7851): 254-258, February 16, 1974.

(*348*) RUSSELL, M.A.H. Tar, nicotine and CO yields in cigarettes. British Medical Journal 3(5982): 540, August 30, 1975.

(*349*) RUSSELL, M.A.H. Tobacco smoking and nicotine dependence. In: Gibbins, R.J., Israel, Y., Kalant, H., Popham, R.E., Schmidt, W., Smart, R.G. (Editors). Research Advances in Alcohol and Drug Problems, Volume 3. New York, John Wiley and Sons, 1976, pp. 1-47.

(*350*) RUSSELL, M.A.H., ARMSTRONG, E., PATEL, U.A. Temporal contiguity in electric aversion therapy for cigarette smoking. Behaviour Research and Therapy 14(2): 103-123, 1976.

(*351*) RUSSELL, M.A.H., COLE, P.V. Confirmation of abstinence from smoking. British Medical Journal 2(6038): 755-756, September 25, 1976. (letter)

(*352*) RUSSELL, M.A.H., WILSON, C., FEYERABEND, C., COLE, P.V. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. British Medical Journal 2(6032): 391-393, August 14, 1976.

(*353*) RYAN, F.J. Cold turkey in Greenfield, Iowa: A follow-up study. In: Dunn, W.L., Jr. (Editor). Smoking Behavior: Motives and Incentives. New York, John Wiley and Sons, 1973, pp. 231-241.

(*354*) SACHS, D.P.L., HALL, R.G., HALL, S.M. Effects of rapid smoking. Physiologic evaluation of a smoking-cessation therapy. Annals of Internal Medicine 88(5): 639-641, May 1978.

(*355*) SACHS, L.B., BEAN, H., MORROW, J.E. Comparison of smoking treatments. Behavior Therapy 1(4): 465-472, November 1970.

(*356*) ST. PIERRE, R., LAWRENCE, P.S. Reducing smoking using positive self-management. Journal of School Health 45(1): 7-9, January 1975.

(*357*) SALK, G.C. A Comparison of Two Smoking Reduction Treatments Under Conditions Designed to be Interfering or Not Interfering with the Smoking Habit. Doctoral dissertation, University of Louisville, 1975, 127 pp. Dissertation Abstracts International 36(8): 4178-B, February 1976. (University Microfilms No. 75-25,474).

(*358*) SANDERS, S. Mutual group hypnosis and smoking. American Journal of Clinical Hypnosis 20(2): 131-135, October 1977.

(*359*) SCHACHTER, S. Pharmacological and psychological determinants of smoking. Annals of Internal Medicine 88(1): 104-114, January 1978.

(*360*) SCHACHTER, S., SILVERSTEIN, B., KOZLOWSKI, L.T., PERLICK, D., HERMAN, C.P., LIEBLING, B. Studies of the interaction of psychological and pharmacological determinants of smoking. Journal of Experimental Psychology: General 106(1): 3-40, March 1977.

(*361*) SCHLEGEL, R.P., KUNETSKY, M. Immediate and delayed effects of the "five-day plan to stop smoking" including factors affecting recidivism. Preventive Medicine 6(3): 454-461, September 1977.

(*362*) SCHMAHL, D.P., LICHTENSTEIN, E., HARRIS, D.E. Successful treatment of habitual smokers with warm, smoky air and rapid smoking. Journal of Consulting and Clinical Psychology 38(1): 105-111, February 1972.

(*363*) SCHMIDT, F. Medikamentose unterstuetzung der raucherentwohnung. Bericht ueber versuche an ueber 5000 rauchern im doppelblindversuch. (Medical support of nicotine withdrawal. Report on a double blind study in over 5000 smokers.) Muenchener Medizinische Wochenschrift 166(11): 557-564, March 15, 1974.

(*364*) SCHNEIDER, N.G., POPEK, P., JARVIK, M.E., GRITZ, E.R. The use of nicotine gum during cessation of smoking. American Journal of Psychiatry 134(4): 439-440, April 1977.

(*365*) SCHOPP, R.F. The Effects of Experimenter Knowledge on Self-Monitoring and Self-Reinforcement Approaches to Control of Smoking. Doctoral dissertation, North Carolina State University at Raleigh, 1977, 91 pp. Dissertation Abstracts International 38(7): 3414-B, January 1978. (University Microfilms No. 77-29,674).

(*366*) SCHWARTZ, J.L. A critical review and evaluation of smoking control methods. Public Health Reports 84(6): 483-506, June 1969.

(*367*) SCHWARTZ, J.L. Research methodology in smoking cessation: A critique. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 649-653.

(*368*) SCHWARTZ, J.L. Smoking cures: Ways to kick an unhealthy habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17, December 1977. DHEW Publication No. (ADM) 78-581, pp. 308-337.

(*369*) SCHWARTZ, J.L. Status of cessation control programs in Europe and North America. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 869-882.

(*370*) SCHWARTZ, J.L., DUBITZKY, M. Changes in anxiety, mood, and self-esteem resulting from an attempt to stop smoking. American Journal of Psychiatry 124(11): 138-142, May 1968.

(*371*) SCHWARTZ, J.L., DUBITZKY, M. Expressed willingness of smokers to try 10 smoking withdrawal methods. Public Health Reports 82(10): 855-861, October 1967.

(*372*) SCHWARTZ, J.L., DUBITZKY, M. Maximizing success in smoking cessation methods. American Journal of Public Health 59(8): 1392-1399, August 1969.

(*373*) SCHWARTZ, J.L., DUBITZKY, M. One-year follow-up results of a smoking cessation program. Canadian Journal of Public Health 59: 161-165, April 1968.

(*374*) SCHWARTZ, J.L., DUBITZKY, M. Psycho-Social Factors Involved in Cigarette Smoking and Cessation. Final Report of the Smoking Control Research Project, Berkeley, September 1968, 680 pp.

(*375*) SCHWARTZ, J.L., DUBITZKY, M. Requisites for success in smoking withdrawal. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 231-247.

(*376*) SCHWARTZ, J.L., RIDER, G. Smoking cessation methods in the United States and Canada: 1969-1974. In: Steinfeld, J. Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 695-732.

(*377*) SHAPIRO, D., TURSKY, B., SCHWARTZ, G.E., SHNIDMAN, S.R. Smoking on cue: A behavioral approach to smoking reduction. Journal of Health and Social Behavior 12(2): 108-113, June 1971.

(*378*) SHEPHARD, R.J., RODE, A., ROSS, R. Reinforcement of a smoking withdrawal program: The role of the physiologist and the psychologist. Canadian Journal of Public Health 64(2, Supplement): S42-S51, March/April 1973.

(*379*) SHEWCHUK, L.A. Guidelines for organizing smoking withdrawal clinics. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. DHEW Publication No. (NIH) 77-1413, 1977, pp. 665-668.

(*380*) SHEWCHUK, L.A. Problems of high-risk populations and high-risk nonresponders: Smoking behavior. In: Cullen, J.W., Fox, B.H. Isom, R.N. (Editors). Cancer: The Behavioral Dimensions. New York, Raven Press, 1976, pp. 93-99.

(*381*) SHEWCHUK, L.A. Special Report. Smoking cessation programs of the American Health Foundation. Preventive Medicine 5(3): 454-474, September 1976.

(*382*) SHEWCHUK, L.A., DUBREN, R., BURTON, D., FORMAN, M., CLARK, R.R., JAFFIN, A.R. Preliminary observations on an intervention program for heavy smokers. International Journal of the Addictions 12(2-3): 323-336, 1977.

(*383*) SHEWCHUK, L.A., WYNDER, E.L. Guidelines on smoking cessation clinics. Preventive Medicine 6(1): 130-133, March 1977.

(*384*) SIPICH, J.F., RUSSELL, R.K., TOBIAS, L.L. A comparison of covert sensitization and "non-specific" treatment in the modification of smoking behavior. Journal of Behavior Therapy and Experimental Psychiatry 5(2): 201-203, September 1974.

(*385*) SLETTEN, P.M. An Experimental Study of the Effects of Training Smokers with Behavior Chains Designed to be Antagonistic to Smoking. Doctoral dissertation, University of South Dakota, 1972, 58 pp. Dissertation Abstracts International 33(6): 2823-B, December 1972. (University Microfilms No. 72-32, 737).

(*386*) SLOAN, M.D. The Effect of Self-Monitoring, Surveillance, and Verbal Contingencies on Smoking Frequency. Doctoral dissertation, University of South Carolina, 1976, 77 pp. Dissertation Abstracts International 37(10): 5378-B, April 1977. (University Microfilms No. 77-6783).

(*387*) SPIEGEL, H. A single-treatment method to stop smoking using ancillary self-hypnosis. International Journal of Clinical and Experimental Hypnosis 18(4): 235-250, October 1970.

(*388*) SPIEGEL, H. Termination of smoking by a single treatment. Archives of Environmental Health 20: 736-742, June 1970.

(*389*) SROLE, L., FISCHER, A.K. Smoking behavior 1953 and 1970: The Midtown Manhattan Study. In: Dunn, W.L. Jr. (Editor). Smoking Behavior: Motives and Incentives. New York, John Wiley and Sons, 1973, pp. 255-265.

(*390*) SROLE, L., FISCHER, A.K. The social epidemiology of smoking behavior 1953 and 1970: The Midtown Manhattan Study. Social Science and Medicine 7(5): 341-358, May 1973.

(*391*) STAMLER, J. Acute myocardial infarction—progress in primary prevention. British Heart Journal 33(Supplement): 145-164, 1971.

(*392*) STAMLER, J. Coronary risk factors and prevention of atherosclerotic coronary heart disease. Chicago Medicine 73(14): 509-518, July 4, 1970.

(*393*) STANLEY, J.C. Designing psychological experiments. In: Wolman, B.B. (Editor). Handbook of General Psychology. Englewood Cliffs, Prentice-Hall, 1973, pp. 90-106.

(*394*) STEFFY, R.A., MEICHENBAUM, D., BEST, J.A. Aversive and cognitive factors in the modification of smoking behaviour. Behaviour Research and Therapy 8(2): 115-125, May 1970.

(*395*) STERLING, T.D., WEINKAM, J.J. Smoking characteristics by type of employment. Journal of Occupational Medicine 18(11): 743-754, November 1976.

(*396*) STEVENS, S.S. Mathematics, measurement, and psychophysics. In: Stevens, S.S. Handbook of Experimental Psychology. New York, John Wiley and Sons, Inc., 1951, pp. 1-49.

(*397*) STEWART, R.D. The effect of carbon monoxide on humans. Annual Review of Pharmacology 15: 409-423, 1975.

(*398*) STRAITS, B.C. Research design and methodology in laboratory settings. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 635-641.

(*399*) STRAITS, B.C. Resume of the Chicago study of smoking behavior. In: Zagona, S.V. Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 73-78.

(*400*) STRAITS, B.C. Social and psycho-physiological correlates of smoking withdrawal. Social Science Quarterly 51(1): 81-96, June 1970.

(*401*) STRELTZER, N.E., KOCH, G.V. Influence of emotional role-playing on smoking habits and attitudes. Psychological Reports 22(3-1): 817-820, June 1968.

(*402*) STROSS, L. Practical office approaches. Diseases of the Chest 54(3): 192-195, September 1968.

(*403*) STRUBEL, K. Frage: Raucherberatungsstellen (Question: Smokers' counselling centers). Deutsche Gesundheitswesen 29(36): 1720-1721, September 1974.

(404) STURZENBERGER, E. Die hypnotische aversionsbehandlung von rauchern (Hypnotic aversion treatment of smokers). In: Gibel, W. Gesundheitsschaden durch Rauchen—Moeglichkeiten einer Prophylaxe. Berlin, Akademie-Verlag, 1976, pp. 173-181.

(405) SUEDFELD, P., BEST, J.A. Satiation and sensory deprivation combined in smoking therapy: Some case studies and unexpected side-effects. International Journal of the Addictions 12(2-3): 337-359, 1977.

(406) SUEDFELD, P., IKARD, F.F. Attitude manipulation in restricted environments: IV. Psychologically addicted smokers treated in sensory deprivation. British Journal of Addictions 68(2): 170-176, 1973.

(407) SUEDFELD, P., IKARD, F.F. Use of sensory deprivation in facilitating the reduction of cigarette smoking. Journal of Consulting and Clinical Psychology 42(5): 888-895, December 1974.

(408) SUSHINSKY, L.W. Expectation of future treatment, stimulus satiation, and smoking. Journal of Consulting and Clinical Psychology 39(2): 343, October 1972.

(409) SUTHERLAND, A., AMIT, Z., GOLDEN, M., ROSEBERGER, Z. Comparison of three behavioral techniques in the modification of smoking behavior. Journal of Consulting and Clinical Psychology 43(4): 443-447, August 1975.

(410) SYME, S.L., JACOBS, M.J. Smoking cessation activities in the Multiple Risk Factor Intervention Trial: A preliminary report. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 613-615.

(411) TAYLOR, P.W. Cigarette Smoking Behavior: Self-Managed Change. Doctoral dissertation, North Texas State University, 1977, 73 pp. Dissertation Abstracts International 38(3): 1425-B, September 1977. (University Microfilms No. 77-19,688).

(412) THOMPSON, D.S., WILSON, T.R. Discontinuance of cigarette smoking: "Natural" and with "therapy." A ten-week and ten-month follow-up study of 298 adult participants in a five-day plan to stop smoking. Journal of the American Medical Association 196(12): 1048-1052, June 20, 1966.

(413) THOMPSON, E.L. Smoking education programs 1960-1976. American Journal of Public Health 68(3): 250-257, March 1978.

(414) THORESEN, C.E., COATES, T.J. Behavioral self-control: Some clinical concerns. In: Hersen, M., Eisler, R.M., Miller, P.M. (Editors). Advances in Behavior Modification, Volume 3. New York, Academic Press, 1975, pp. 307-352.

(415) THORESEN, C.E., MAHONEY, M.J. Behavioral Self-Control. New York, Holt, Rinehart and Winston, Inc., 1974, 177 pp.

(416) TOOLEY, J.T., PRATT, S. An experimental procedure for the extinction of smoking behavior. Psychological Record 17(2): 209-218, April 1967.

(417) TORI, C.D. A smoking satiation procedure with reduced medical risk. Journal of Clinical Psychology 34(2): 574-577, April 1978.

(418) TRAHAIR, R.C.S. Giving up cigarettes: 222 case studies. Medical Journal of Australia I: 929-932, May 6, 1967.

(419) TRAHAIR, R.C.S. Motivation to give up cigarettes: Problems and solutions. Medical Journal of Australia I: 177-180, January 25, 1969.

(420) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, DHEW Publication No. (CDC) 78-8357, 1976, 657 pp.

(421) U.S. PUBLIC HEALTH SERVICE. Survey of Health Professionals: Smoking and Health, 1975. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, 1977, 33pp.

(422) U.S.PUBLIC HEALTH SERVICE. Teenage Smoking. National Patterns of Cigarette Smoking Ages 12 through 18, in 1972 and 1974. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 76-931, 123 pp.

(423) VOGT, T.M. Smoking behavioral factors as predictors of risks. In: Jarvik, M.E., Gullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 98-111.

(424) VOGT, T.M., SELVIN, S., WIDDOWSON, G., HULLEY, S.B. Expired air carbon monoxide and serum thiocyanate as objective measures of cigarette exposure. American Journal of Public Health 67(6): 545-549, June 1977.

(425) VON DEDENROTH, T.E.A. The use of hypnosis in 1000 cases of "tobaccomaniacs." American Journal of Clinical Hypnosis 10(3): 194-197, January 1968.

(426) WAGNER, M.K., BRAGG, R.A. Comparing behavior modification approaches to habit decrement-smoking. Journal of Consulting and Clinical Psychology 34(2): 258-263, April 1970.

(427) WALLACE, N.D., DAVIS, G.L., RUTLEDGE, R.B., KAHN, A. Smoking and carboxyhemoglobin in the St. Louis metropolitan population. Archives of Environmental Health 29: 136-142, September 1974.

(428) WARNER, K.E. The effects of the anti-smoking campaign on cigarette consumption. American Journal of Public Health 67(7): 645-650, July 1977.

(429) WATKINS, H.H. Hypnosis and smoking: A five-session approach. International Journal of Clinical and Experimental Hypnosis 24(4): 381-390, October 1976.

(430) WEINBLATT, E., SHAPIRO, S., FRANK, C.W. Changes in personal characteristics of men, over five years, following first diagnosis of coronary heart disease. American Journal of Public Health 61(4): 831-842, April 1971.

(431) WEIR, J.M., DUBITZKY, M., SCHWARTZ, J.L. Counselor style and group effectiveness in a smoking withdrawal study. American Journal of Psychotherapy 23(1): 106-118, January 1969.

(432) WERKO, L. Can we prevent heart disease? Annals of Internal Medicine 74(2): 278-288, February 1971.

(433) WEST, D.W., GRAHAM, S., SWANSON, M., WILKINSON, G. Five year follow-up of a smoking withdrawal clinic population. American Journal of Public Health 67(6): 536-544, June 1977.

(434) WHITMAN, T.L. Aversive control of smoking behavior in a group context. Behaviour Research and Therapy 10(2): 97-104, 1972.

(435) WHITMAN, T.L. Modification of chronic smoking behavior: A comparison of three approaches. Behaviour Research and Therapy 7(3): 257-263, September 1969.

(436) WILDE, G.J.S. Behaviour therapy for addicted cigarette smokers: A preliminary investigation. Behaviour Research and Therapy 2(2): 107-109, September 1964.

(437) WILDE, G.J.S. Correspondence. Behaviour Research and Therapy 2(5): 313, February 1965.

(438) WILHELMSEN, L. One year's experience in an anti-smoking clinic. Scandinavian Journal of Respiratory Diseases 49(4): 251-259, 1968.

(439) WILHELMSEN, L. A smoking cessation program in a field trial. In: Tibblin, G., Keys, A., Werko, L. Preventive Cardiology. Proceedings of an International Symposium, Skovde, Sweden, August 21, 1971. New York, John Wiley and Sons, 1972, pp. 97-102.

(*440*) WILHELMSEN, L. Synpunkter pa rokavvanjning. Rokavvanjningsverksamhet i Goteborg (Viewpoints on smoking withdrawal. Smoking withdrawal clinic activity in Goteborg). Social Medicinsk Tidskrifts 2(Special No.): 116-119, February 1971.

(*441*) WILHELMSEN, L., TIBBLIN, G., WERKO, L. A primary preventive study in Gothenburg, Sweden. Preventive Medicine 1(1/2): 153-160, March 1972.

(*442*) WILHELMSSON, C., VEDIN, J.A., ELMFELDT, D., TIBBLIN, G., WILHELMSEN, L. Smoking and myocardial infarction. Lancet 1(7904): 415-420, February 22, 1975.

(*443*) WILLIAMS, H.O. Routine advice against smoking. A chest clinic pilot study. Practitioner 202(1211): 672-676, May 1969.

(*444*) WILSON, J., MATTHEWS, D.M. Metabolic inter-relationships between cyanide, thiocyanate and vitamin B_{12} in smokers and non-smokers. Clinical Science 31(1): 1-7, August 1966.

(*445*) WINER, B.J. Statistical Principles in Experimental Design. New York, McGraw-Hill Book Company, 1971, pp. 203-228.

(*446*) WINETT, R.A. Parameters of deposit contracts in the modification of smoking. Psychological Record 23(1): 49-60, Winter 1973.

(*447*) WISOCKI, P.A., ROONEY, E.J. A comparison of thought stopping and covert sensitization techniques in the treatment of smoking: A brief report. Psychological Record 24(2): 191-192, Spring 1974.

(*448*) WOEBER, R., BAUERMANN, E. Raucherentwohnungslehrgang fuer abhangige Raeucher (Courses for habitual smokers to stop smoking). Rehabilitation. Sozialmedizin, Physikalische Medizin, Praeventivmedizin 28(3-4): 33-46, 1975.

(*449*) WORLD HEALTH ORGANIZATION, REGIONAL OFFICE FOR EUROPE. Working group on methodology of multifactor preventive trials in ischaemic heart disease. Community Health 5(2): 101-103, October 1973.

(*450*) WRIGHT, M.E. A single-treatment method to stop smoking using ancillary self-hypnosis: Discussion. International Journal of Clinical and Experimental Hypnosis 18(4): 261-267, October 1970.

(*451*) YATES, A.J. Theory and Practice in Behavior Therapy. New York, John Wiley and Sons, 1975, pp. 114-132.

(*452*) YOUNGGREN, J.N., PARKER, R.A. The smoking control clinic: A behavioral approach to quitting smoking. Professional Psychology 8(1): 81-87, February 1977.

PART III

EDUCATION AND PREVENTION

20. YOUTH EDUCATION.

CONTENTS

LIST OF TABLES

Introduction

In January 1964, the report on smoking and health of the Advisory Committee to the Surgeon General of the Public Health Service was released. It presented to the public incontrovertible evidence that cigarette smoking was associated with disease. Major health professional organizations had already endorsed or committed themselves to educational programs against cigarettes (*18*). Several States had passed anti-cigarette resolutions urging the adoption of public health education in regard to the hazards of smoking; the Canadian Government had already begun to pursue a strong educational program against smoking (*78*). Since then, programs in the schools have proliferated, both in this country and abroad. Many state and local ordinances have required teachers to cover the facts on the negative effects of smoking on the body, but, in the absence of detailed information, we do not know in what ways educators have complied with these regulations. In any case, this chapter does not deal with the role of the educator, which is covered in a separate chapter, but reviews and discusses those antismoking programs directed toward youth that have been reported in the literature.

While many recommendations have been made for school programs and many programs have been described in the professional literature, there must be thousands that have never been reported. It is hoped that a comprehensive review can be made of ongoing programs, with a view toward describing them and selecting for review those that show promise of being effective in changing behavior. These, we hope, can be evaluated, and recommendations made for programmatic directions that appear to be potentially effective. There are many opinions concerning the relative effectiveness of various approaches, but few programs have been evaluated systematically. Thus, many recommendations for programs in schools are based on a general philosophy of education and others are based on studies specifically in the area of youthful smoking.

In the remainder of this section, we review some of the recommendations that have been made. Many are based on the belief that the greatest deterrent to smoking is knowledge of the adverse effects on health, others are based on the belief that attitude change is more important, and still others stress the influence of adult exemplars, peers, or both. Social and psychological components are discussed by some. Some recommend that all these facets be taken into account.

The second section of this chapter, which points to school programs reported in the literature, is divided into two parts. First, past and present school programs are described briefly. Second, three noteworthy programs are singled out for particular attention. In the first part, programs are divided into general programs, those that involve young people talking to other young people, those that involve physicians, and those that have an evaluation component.

In the third section, programs outside the formal education structure are touched upon, including those sponsored by voluntary health agencies and other organizations.

There follows a summary of the state of knowledge regarding smoking programs for young people. While many programs have been reviewed and discussed, it should be remembered that, in the absence of evaluative research, no one knows which programs are most effective, which subject matter material should be covered, or which approaches are most likely to yield desirable results. The chapter ends with general conclusions and recommendations.

Current Smoking Education Approaches

Although recommendations for school smoking programs vary widely, one common goal, expressed either implicitly or explicitly, is maximal prevention of those illnesses related to cigarette smoking. It can be summed up by a statement that Secretary Califano made at the National School Health Conference in May 1977: "Effective health education early in life can help to prevent the major diseases of adulthood" (*21*). It is not surprising, then, that most recommendations emphasize the effects of smoking on health, long-term and immediate (*1, 4, 18, 24, 46, 47, 48, 50, 59, 61, 95*). However, there is increasing concern that facts alone are not sufficient to deter teenagers from becoming smokers. Some take the position that positive, favorable attitudes toward realization of the hazards of smoking are necessary. Where negative attitudes exist, efforts should be made to redirect them into positive ones and to affect behavior as well as attitudes. As Bynner pointed out at the Second World Conference on Smoking and Health, "there is good evidence from research into attitude change to suggest that an attempt to bring about change in a favorable direction on a combination of all these attitudes may be more effective than simply continuing to supply information about health risk alone" (*20*). Briney (*16*) found no significant relationship between knowledge of the effects of cigarette smoking and smoking behavior of high school seniors. Many have pointed out that youth imitates, and that one of the major influences is the example set by parents, teachers, health professionals, and other significant adults with whom the teenager is in contact. Thus, focusing attention on the exemplar is recommended (*4, 48, 57, 62, 96, 101, 104*). Closely related to the example which adults set for teenagers is the total environment, or climate, in which the adolescent finds himself. As Horn stated, "There are serious difficulties in attempting to influence young people by teaching them in the classroom to adopt behavior opposed to practices that are encouraged in the larger environment. Educators have found that smoking education programs in school meet with strong counterforces in television advertising and the smoking patterns of parents, other adults, and people youngsters admire in their own group" (*54*). A

number of people have addressed this problem and made suggestions for counteragents in the schools to cope with it (*4, 20, 57, 96, 101, 104, 109*). Although cigarette advertising no longer appears on television, it continues to be an accepted part of program content. Another area that is touched on by some is that of the social-psychological components of teenage smoking. Approaches here focus on the individual and personal behavior choices, recognizing the needs some believe cigarette smoking fulfills (*4, 12, 24, 28, 29, 48, 50, 75, 101, 105*). Many recommend taking all of these into account, as exemplified by the position statement of the American Association for Health, Physical Education, and Recreation (*4*).

School Programs

School programs have usually followed one or more of the approaches outlined above, taking into account the health threat, the influence of adult exemplars, peer influence, or combinations of these. Many are one-time campaigns, with little or no evaluation. Because of this lack, it is impossible to report on the results or on the effectiveness of these programs. Only a few are carefully planned, long-term programs, with a systematic evaluation plan.

Past and Ongoing Programs

In citing school programs, we have divided them into four categories: general, youth-to-youth, those involving physicians, and programs with strong evaluation components. General programs include both demonstration and long-term programs. Demonstration programs are those that are either one-time antismoking campaigns or innovative classroom procedures, as opposed to established programs that are or have been a part of the school curriculum. Long-term programs are those that extend over several years and include a large number of children. Youth-to-youth, physician, and evaluation component programs may also fit into these definitions, but they are discussed separately.

General Programs

Demonstration Programs

A number of original and imaginative techniques have been reported in the literature, including an experiment demonstrating to fourth-grade students the effect of tar on the lungs (*10*), use of students' questions to assist in the development of a health unit (*17*), a school survey conducted by students (*33*), construction of a model of a smoking man (*67*), construction of a train filled with empty cigarette packs (*51*), and a health fair put on by college students in an East Harlem junior high school (*58*). Other antismoking campaigns em-

ployed combinations of speeches, films, posters, and other exhibits (*35, 56, 72*).

It is difficult to assess the effectiveness of these programs since some reported no evaluation results (*10, 17, 33, 58, 70*) and others were assessed merely on the basis of students' reactions (*51, 56, 67*). Estrin, in 1965, compared responses of ninth- and tenth-grade students to a questionnaire administered before the campaign with responses to a questionnaire administered "several weeks after". There was no difference in the proportion of smokers, nor in the proportion of smokers who said they would be interested in trying to stop smoking, but there was a decrease in the number of cigarettes smoked. However, there was no control group with which to compare the results (*35*).

Long-Term Programs

Several programs that have reached a large number of children but have had no experimental-control evaluation are reported on in this section.

Surveys of smoking habits of students in grades 6 through 12 in Selah, Washington, were done in 1961, 1962, and 1964. Filmstrips were shown, literature was distributed, and an essay contest was held. After the first survey, results were reported to the students, stressing the fact that smoking students tend not to compete successfully athletically or academically, nor do they participate in extracurricular activities. Over the period of the program, the proportion of smokers at the junior high school level increased, but the proportion of smokers at the senior high school level stayed the same. The conclusion of the authors was that "an educational antismoking campaign defeats its purpose and actually increases the numbers who smoke" (*2*).

A program begun in Pennsylvania in 1962 placed emphasis on changing the social status of smoking. Much of the work was done through teachers and youth leaders. By 1967, 8,000 kits containing smoking and health information and resource materials for teachers and students and 10,000 copies of a teacher's resource unit had been distributed. A variety of pamphlets, posters, and audiovisual aids was prepared, regional meetings were held, and other activities such as school assemblies, exhibits, youth forums, and the like were planned. This effort was reported by Bohlayer (*14*).

A program initiated in 1968 in Monticello, New York, and designed to reach pupils in kindergarten through twelfth grade, featured a curriculum based on psychosocial needs of students, with emphasis on concept formation, attitude formation, and habit establishment. The program, funded for 3 years, was reported by Fleckman (*39*).

In Germany, a comprehensive campaign aimed at school children has been going on since the late 1960's. Newspaper articles, posters, and other means of conveying messages, such as badges, were tried.

Nonsmoking clubs were established and had their own newspaper. In addition, a booklet of programmed instruction for teachers was developed (*42*).

Youth-to-Youth Programs

These programs focus on peer influence; typically, high school students carry on antismoking activities with elementary or junior high school students. Although some of these programs reach relatively few elementary pupils (e.g., *22, 49, 53, 72, 85*), others are very widespread, reaching 10,000 to 20,000 students (*73, 80*). One program that includes plans for a systematic follow-up was reported by McAlister, et al. This California program is designed to help young people resist peer group and advertising pressures. At the 3-month follow-up, twice as many in the control group as in the experimental group reported smoking occasionally. The investigators plan to follow the participants for at least 2 years (*72*). In Broome County, New York, data were gathered from 10,000 fifth- and sixth-graders before the program was begun. Teams of high school students, each responsible for its own format, visited 71 elementary schools, reaching approximately 10,000 students. Favorable comments on the program were received from fifth- and sixth-graders, principals, teenagers, and community groups. No objective data, however, were reported on the effectiveness of the program (*73*). In a program that began in Philadelphia in 1968—Students Concerned with Public Health—32 low-income students created, produced, and performed puppet shows for fourth-, fifth-, and sixth-grade pupils. When this group graduated in 1971, the program continued with 130 10th-grade students who planned to spend 3 years in the program. During the 1970-71 school year alone, the program reached 20,665 pupils in 28 public and 11 parochial schools. No evaluation data were reported (*80*).

Programs Involving Physicians

Harlin has suggested that school physicians take time to work with teachers and pupils since physicians know more about the health consequences of smoking (*47*). In Israel physicians visit interested high schools, lecture on cancer and the hazards of smoking, and distribute colorful antismoking material (*12*). In Ireland, on the basis of a survey of Dublin school children, recommendations for health education were made to general practitioners who were doctor-educators. Much of the emphasis was on health hazards, including immediate effects (decrease of "prowess at games") and long-term effects (parents are at high risk if they smoke) (*86*). In Boston, a group of cancer research workers volunteers its services in the public schools. Seven years after the beginning of the program, 20 active members make about 50 talks a year and show films at school assemblies. The results of a question-

naire, filled out by approximately 3,400 seventh- and eighth-grade pupils 4 to 12 weeks after one assembly, indicate that 29 percent of current smokers had quit (*94*). One of the earliest long-term antismoking programs began in 1959 with high school freshmen in King City, California. Each year for 5 years, six 50-minute periods of instruction by two volunteer physicians were conducted during a 2-week period. Smoking increased every year from 1960 to 1964. It was thought that these teenagers were simply reflecting a nationwide trend of increased smoking among teenagers. Also, the authors felt that efforts would be better directed toward a younger group (*9*).

Approximately 10,000 secondary and grammar school children in four areas of southeast England were divided into experimental and control groups. Each of the experimental classes received a visit from a team of the Central Council of Health Education who used posters, flannelgraphs, and discussions. The authors concluded that the "scheme had disappointingly little effect on the smoking habits of children" (*52*).

Several field studies have been conducted with relatively few subjects. Examples are: Sadler's 1969 study of 130 pupils in sixth-grade classes, where, in the experimental condition, physicians visited classes twice within a 4-week period (*97*); Estrin's 2-week project in 1965 that used experiments, films, posters, and exhibits (*35*); and the work of Jefferys and Westaway in 1961 with six classes in the third form (average age, 13 years and 9 months), using exhibits, talks, and films (*63*). In general, little or no differences were found between the experimental and control groups.

Programs with Evaluation Components

The programs described in this section differ from those above in that they have strong evaluation components, with control groups as well as experimental groups.

In most of these programs, a simple comparison is made between experimental schools with antismoking programs and control schools without such programs. A notable exception is Horn's early study (1959) in the Portland schools (*55*). Schools were assigned to take part in one of five experimental conditions or in a control condition. The five experimental approaches involved mass communication messages emphasizing: (1) the remote effects (health hazards) of smoking, (2) the current meaning of smoking, (3) the two sides of the smoking issue, (4) authoritative stands on the issue, and (5) the assuming of an adult role and trying to dissuade parents from smoking. Evaluation was based on questionnaire responses at the beginning of the school year compared with those at the end of the school year. In the remote effects (or health hazards) group there was a reduction in recruitment rate compared with that of the control group. Recruitment rate was obtained by subtracting the percentage of smokers in the pretest from

the percentage of smokers in the post-test and dividing by the percentage of nonsmokers in the pretest. No other experimental condition showed a significant difference when compared with the control condition (*66*). This study was replicated as a part of the University of Illinois smoking studies (see below).

The pattern of testing several hypotheses against a control group has not been repeated in most field studies, but several studies have attempted to test a single hypothesis. For example, Botvin, et al. are presently testing a model with 8th-, 9th-, and 10th-graders based on "Life Skills Training" (LST); this includes information on smoking knowledge, self-image, dating skills, and so on. Comparisons between pretest and post-test findings "indicate substantial differences between experimental and control groups." The LST strategy apparently reduced the incidence of new smoking, but the absence of follow-up data leaves the results inconclusive (*15*).

In 1971 Fodor and Glass tested a sixth-grade curriculum based on the immediate effects of smoking, and found differences in knowledge between experimental and control groups. Few of the sixth-graders were smokers (*40*).

A health program conducted with approximately 3,000 school children aged 11 to 14 in Westchester County, New York, and New York City involves a medical screening program with feedback. The "Know Your Body" program consists of (1) health screening, (2) return of results, and (3) education. The health program "seeks to capitalize on students' personal knowledge of their own risk factors." Students, teachers, and parents are involved in the program. Results of the effectiveness of the program have not been reported, but plans are indicated for follow-up "over the next several years" (*107*). Pupils in grades 7 through 9, in 36 randomly selected classes, were administered questionnaires prior to and 6 months after the completion of a smoking education program in half the schools. The content of the course and the methods used are not described, except that "after a comprehensive orientation meeting, teachers were provided throughout the project's course with guidance from consultants and resource persons and computerized documentation sources and planning aids." Changes in knowledge and attitudes, but not in smoking behavior, were greater for the experimental than for the control group (*90*). A study of the teachers and parents showed significant changes in smoking behavior (*91*).

The Saskatoon Smoking Study, started in the fall of 1968, is a student-directed program in smoking education in the Saskatoon Rural Health Region of Canada. Eighth-grade opinion leaders in each of the test schools were identified by a sociometric questionnaire, and two from each school were invited to attend a seminar on smoking and health at the University of Saskatchewan. They were charged with the responsibility for taking information back to their schools, particularly

to students in the lower grades. The participants were introduced to educational aids and encouraged to use ingenuity in planning programs. Although it was found that projects varied in scope and complexity, all delegates reported back to their schools. One school completed 12 different projects; the average for all study schools was 5. The program was repeated the following year. Questionnaire data were gathered from 7th- and 8th-grade students in 22 study schools and 12 control schools immediately before the seminar and again in the 5th month after the seminar. The questionnaire measured the students' (1) awareness of the threat of cigarette smoking, (2) perception of its importance, and (3) perception of its personal relevance. It also sought information on smoking behavior and a number of demographic variables. During the first year of the study, the proportion of students in the highest awareness and importance categories increased significantly in both seventh- and eighth-grade classes, in both study and control groups. There was no significant change in the proportion of students in the highest relevance category in either study or control schools. Both eighth-grade boys and eighth-grade girls in the study schools showed a significant decrease in the proportion of current smokers; in the control schools there was no significant change in smoking behavior. By the fall of 1969, one year after the first administration of the questionnaires, the proportion of current smokers increased sharply; the increase was greater in the study group than in the control group. When these pupils were tested for the third time in March 1970, the proportion of boys' smoking increased in the control group but decreased in the study group. Among girls, there was a slight (nonsignificant) decrease in the control group and a slight (nonsignificant) increase in the study group. The changes in eighth-grade students in the second year were similar to those of eighth-grade students in the first year of the study (*64, 71, 87, 88, 89*).

In 1968 in Portland, Oregon, some aspect of the cigarette smoking problem was introduced in the experimental condition in each grade from kindergarten through twelfth grade. The goal was to incorporate and integrate educational material about the cigarette-smoking problem into the existing school curriculum wherever possible, with the individual teacher deciding what material, if any, to introduce into a given learning unit. The two major hypotheses were: (1) application of the educational program by teachers as they see fit will affect knowledge, attitudes, and smoking behavior; and (2) certain attitudes, beliefs, and knowledge, relevant to cigarette smoking and possessed by school children, are predictive of later actual smoking behavior. Baseline data have been reported; unfortunately, the follow-up was not completed (*43*).

An educational program in Maine beginning in the fall of 1961, with high school students in 26 experimental schools and 26 control schools, used all five of Horn's communication messages in one program. The

program consisted of five educational exposures spaced throughout the school year, including an audiovisual component, a discussion, and a pamphlet or piece of literature the pupil could take home and read. Questionnaires were administered in the fall of 1961, the spring of 1962, and the fall of 1962. Attitude changes were apparent by the end of the school year, but changes in smoking behavior were not seen until the beginning of the next year, when the original ninth-grade group contained significantly fewer smokers in the experimental than in the control group (*11, 69*).

The smoking habits of Winnipeg students, grades 5 through 12, were surveyed before (fall 1960) and after (spring 1963) a 3-year program on the hazards of smoking, directed to 8,300 out of 48,000 students. Two high schools were selected for the trial program; all elementary and junior high schools that normally sent students to these high schools were included. It was decided that the program in the elementary schools should be casual and informal and that it should focus on the teachers and parents. The main direct approach was in the junior high schools, with the program continued in high school. The nature of the programs in these schools was left up to the principals and teachers in the schools in the program. Resource materials were provided, student participation and discussion groups were encouraged, and conferences were held between health professionals, students, and teachers. Attempts were made to interest parents, community club organizers, and some sports coaches, but all except one of these attempts met with failure. In one of the two high schools, the program was enthusiastically received and student participation was very active, compared with the other high school. This difference was reflected in the results. There was a slight decrease in the proportion of smokers in this high school at the end of 3 years, while there were increases in smoking in the other experimental high school and in the control group of all other high schools in Winnipeg (*78, 79*).

In Baltimore, two comparable male senior high schools with approximately 3,000 students each were selected as control and experimental schools in an antismoking study. Questionnaires were administered in September 1963 and again in May 1964. Students in the experimental school had 26 exposures in the antismoking project over a period of 7 months, primarily concentrated on smoking and lung cancer. Activities included school assemblies, posters, letters from the commissioner of health sent to students' homes, articles in the school newpaper, distribution of leaflets, and a large exhibit. The follow-up questionnaire was supplemented by interviews with 95 students in the experimental school. It was found that the proportion of smokers increased in the 10th grade and decreased in the 11th and 12th grades in both schools. For all three grades combined, there was no change in either school. Of four attitudes measured, a significant change was found in one—"Smoking is dangerous to health." There was an

increase in the percentage agreeing with this statement in the experimental group and a small decrease in the control group (*77*).

Descriptions of Selected Programs

Three programs deserve special attention: The San Diego program, because it is part of an 8-year comprehensive community program; the University of Illinois Antismoking Education Study, because of the experimental nature of its components; and the School Health Curriculum Project, because of its innovative nature and rate of its proliferation.

San Diego Program (3, 30, 31, 32, 98, 99)

Background

In February 1966, the National Clearinghouse for Smoking and Health established the San Diego Community Laboratory to develop a comprehensive smoking control program. The San Diego County Council on Smoking and Health, with 18 member agencies, provided the organizational basis for the school and community programs. The Council established four program commissions encompassing health professions, mass media, schools and colleges, and community programs. The membership of the commission responsible for school programs—Educational Programs for Youth Commission—included classroom teachers at all grade levels, administrators, school nurses, voluntary and official agency members, and representatives from youth-serving agencies outside school. The commissions worked together in a comprehensive community effort to attack the smoking problem.

Program Content

During the 8 years of the program, from 1966 to 1974, a wide variety of programs was undertaken, and resource materials were developed to support them. The focus was primarily on working through classroom teachers. Among the first activities were a teacher workshop and development of a curriculum guide in smoking education for grades 1 through 12. Throughout the program, teacher workshops and inservice education programs were held. Source material for teachers (and others) included: (1) "What's New," a publication mailed five times a year to teachers, nurses, librarians, and youth leaders which reports on the newest teaching methods as well as on material available in the area of smoking education; (2) a list of available materials; (3) "Up in Smoke," a workbook in Spanish and English for primary grade children; (4) a kit of reference and source material; (5) a science teacher kit; (6) "Smoking Sam" and "Nicoteena" dolls that smoke cigarettes, with a device that allows tar and nicotine to be deposited visibly on filter paper; (7) bumper stickers; (8) a checklist of key facts

related to smoking and health; (9) a smoking and health vocabulary; (10) a guide for follow-up activities; and (11) a special health unit for junior high school girls, "Health and Appearance Program for a Prettier You," which covers such topics as diet, grooming, use of alcohol, skin and hair care, and the like, as well as smoking.

Despite an emphasis on working through teachers, the tremendous number of requests for "experts" to work directly with children in the classroom resulted in the hiring of a full-time staff member. The emphasis was on the classroom visit as a demonstration for the teacher's future use. Typically, the visit, in grades five through nine, included a demonstration of "Smoking Sam." To keep this visit from being merely a one-shot effort, a guide was developed for the teacher to use in preparing the class for the visit and continuing the teaching after the visit. During the first 3 years of the program, 884 such school visits were conducted.

A youth-to-youth program involved high school Key Club members who talked with fifth- and sixth-graders in schools that served as "feeder" schools to their high schools. (Key Club is sponsored by the Kiwanis Club.) In a 3-year period, 1971 to 1974, a total of 728 students, trained to conduct peer-training programs, conducted 1,010 such programs and talked with a total of 35,445 students.

Other activities included working with science fairs, workshops, youth-serving conferences, and the like.

Evaluation

In January 1967, a baseline survey was conducted with a random sample of 25 percent of all students in grades 7 through 12. A second survey was conducted in January 1971. During this period, a decrease in the proportion of smokers among boys was found at every grade level, a finding not consistent with experience nationwide, in which boys' smoking increased slightly (*44*). Although increases were seen among girls in grades 7 through 10 (see Table 1), the results were not considered discouraging because increases in girls' smoking were observed nationwide during this period (*44*). A decrease in the proportion of students who predicted they would be smokers in later life was considered encouraging.

University of Illinois Antismoking Education Study

The University of Illinois study comprised several related studies using varied approaches to the problem of smoking prevention. The initial survey, in October 1966, included 23,724 public and parochial school pupils in grades 7 through 12 in the Rockford-Winnebago County area of northern Illinois. Follow-up surveys were carried out in May 1967 and October 1968. Data were obtained on measures of smoking knowledge, attitudes, and behavior, adapted from instruments used by

TABLE 1.—Percentage who smoke either "...just about every day" or "...once in a while, but not every day"

	Grade					
	7	8	9	10	11	12
Boys						
1967	16.9	17.5	25.2	31.8	32.4	34.7
1971	10.2	14.0	17.4	19.7	24.7	28.8
Girls						
1967	10.0	11.0	18.5	20.6	31.1	29.3
1971	12.7	19.2	22.4	22.8	25.4	25.3

SOURCE: San Diego County Council on Smoking and Health (*98*).

Horn, et al. in the 1958 Portland study (see above). The classroom experiments are described briefly below.

1. The Horn study was replicated, using the same five mass communication messages previously cited. Groups were matched according to the proportion of smokers, then were randomly assigned to either the control group or to one of the experimental groups using the five different message themes. The five messages were presented in the form of pamphlets, fliers, and posters. Three distributions were made between February and April 1967 with a 3-week interval between each distribution. The survey was repeated in May 1967 to assess the relative effects of the different message themes on attitudes and smoking behavior.

Three criterion measures were used: (a) net recruitment rate, which was obtained by subtracting the percentage of smokers in the pretest from the percentage of smokers in the post-test and dividing by the percentage of nonsmokers in the pretest; (b) changes in the proportion of smokers; and (c) changes in scores on the attitude scale.

The effect of the five message themes on smoking behavior was assessed by comparing the changes in proportion of smokers in each of the experimental groups with each other and with the change in the proportion of smokers in the control group from pretest to post-test. Only the group that received the contemporary message theme was different from the control group on this criterion. Among the experimental groups, the significant differences in change in proportion of smoking were as follows: the contemporary approach was more effective than the remote approach or the approach in which both sides of the cigarette smoking question were presented; the authoritarian theme was more effective than either the remote or both-sided approach; and the adult-role-taking theme was more effective than either the remote or both-sided approach. In the Portland study, the remote message was found to be most effective (*25, 26, 27, 55*).

2. A student-centered approach was tested with 8th- and 11th-grade pupils in 12 junior and 5 senior high schools in the rural areas of

Winnebago County. This included 18 classrooms at each level. Four experimental groups and one control group, randomly assigned, at both the 8th- and 11th-grade levels were established. The four experimental conditions were (a) student-centered, remote message, (b) student-centered, contemporary message, (c) mass communication, remote message, and (d) mass communication, contemporary message. The mass communication approach was carried out in the same way as it was in the replication of the Horn study described above. (Pamphlets, fliers, and posters were distributed three times at 3-week intervals.) The student-centered method employed a symposium consisting of four students for each class who were nominated by school administrators, counselors, and English and speech teachers. Three symposia were presented in each class, with a 3-week interval separating each meeting.

The differences in rates of increase, between pretest and post-test, in the proportion of smokers in each group were used as the criterion for measuring effect on smoking behavior. No significant differences were found between the groups with respect to smoking practices.

At the eighth-grade level, significant differences in attitude change were found, with the student-centered approach proving more effective. No significant differences were found between the experimental groups at the 11th grade level (*25*, *74*).

3. An experiment designed to test the role of materials in changing attitudes and beliefs was conducted with seventh-grade pupils. Important elements of this study involved the use of student-selected materials and the sequencing of these materials according to the steps in the health-behavior change model. Experimental and control groups were pretested and post-tested over a 5-week period. Results showed that students exposed to the materials achieved significantly more favorable changes toward nonsmoking attitudes and beliefs (*25*).

4. A final study, based on findings of the first 2 years, was designed to test the effects of a teacher preparation and classroom approach or method on students' attitudes, beliefs, and knowledge about smoking. Teacher preparation compared the effect of a regular classroom teacher with that of a teacher who had been trained in nonsmoking education. The classroom approaches or methods were: (a) the individual approach, depending upon the student's own study and interpretation of curriculum materials; (b) the peer-led approach, emphasizing classroom discussions led by class members; and (c) the teacher-led approach, combining individual study with class discussions and the teacher's direction. The same curriculum materials were used in all three approaches.

The subjects of the study were 575 seventh-grade students in four junior high schools. The criterion was changes in the students' attitude-belief scores and knowledge scores.

The results on the attitude-belief criterion show that significantly higher scores were achieved (a) in the regular classroom rather than with the specially trained teacher, (b) by students in the individual group rather than in the peer-led group, and (c) by more girls than boys.

On the knowledge test, students in the individual study and teacher-led approaches had higher scores than did students taught by the peer-led approach.

Attitude-belief scores for all approaches combined showed approximately 130 percent increase in mean score. The increase in mean knowledge score was approximately 15 percent (*60*).

In addition to the classroom experiments, a number of other studies were carried out, including development and studies of the instruments, prospective studies of changes in smoking behavior, and a participant-observation study in one school (*25, 65, 82, 83, 93*). These, however, are not properly within the purview of this chapter.

School Health Curriculum Project (19)

Background

In an effort to meet the need for a school health program that would prove both exciting and stimulating to pupils, a health curriculum model and a teacher-training model were initially developed in the San Ramon Unified School District in California and later transferred to the Berkeley Unified School District in California. The first curricula to be introduced into the schools consisted of three units. Each unit was organized around a body system: lungs and respiratory system for the fifth grade, heart and circulatory system for the sixth grade, and brain and nervous system for the seventh grade. A fourth-grade unit on the digestive system, a third-grade unit on the eye and vision, and a second-grade unit on the ear and hearing were developed later.

Curriculum Model

Each unit runs from 8 to 10 weeks during the school year and covers (1) the physiology of the body system being studied; (2) how the body system can be affected by man's abuse of the environment; (3) how it is possible to abuse the body by individual actions such as smoking cigarettes, taking drugs, and overindulging in certain foods and alcohol; and (4) how to take care of the body for maximum health. A wide variety of classroom techniques and resources is used, including tapes, filmstrips, and models, and also animal hearts, lungs, brains, etc. All units are specifically correlated with other subjects in the curriculum, such as art, music, mathematics, social studies, and basic language skills.

Teacher Training Model

A 2-week training session for each unit is held before the program is introduced into a school system. Each school sends a team which includes two classroom teachers, their principal, and one or two general support staff members such as school nurses, health educators, or curriculum specialists. It is their responsibility to disseminate the training model within their local school systems.

Evaluation

The rapid growth of the project attests to the acceptance with which it has been met. In addition, several systematic studies have been conducted, the more comprehensive of which are described below.

One evaluation study, which took into account the seven school districts in which the project was initially introduced in 1969, was begun in 1973, when those who had the first unit (lung) in the fifth grade had reached the ninth grade. They were followed up the next year, when they were in 10th grade, and, at the same time, 9th- and 11th-grade students served as additional control groups. Two of the school districts were unable to participate because of extremely high mobility out of their areas, making it impossible to locate many of the students. The experimental group consisted of those pupils who had been exposed to one or more of the units. Controls had never participated in any one of the units. The data collection instruments used were (1) Health Knowledge Test, (2) Health Behavior Inventory, (3) Teenage Self Test (*14*), (4) School Related Behavior Inventory, and (5) Smoking Behavior Classification. All except the Teenage Self Test were constructed specifically for this study. The findings were as follows: (1) Health Knowledge Test scores obtained 2 to 5 years later do relate to the kind and number of curriculum units students were exposed to—the greater the curriculum exposure, the higher the scores on the Health Knowledge Test. (2) A significant relationship was found between curriculum exposure and Health Behavior Inventory scores for the 9th grade, but not for the 10th. (3) There was no relationship between exposure to the curriculum and scores on the Teenage Self Test. (4) Smoking behavior was found to be significantly related to exposure to the curriculum for 9th-graders, with fewer smokers in the experimental than in the control groups, but this did not hold true for the 10th-graders. (5) The School Behavior Inventory failed to differentiate on the basis of whether or not a student had been enrolled in the curriculum (*76*).

An evaluation of the fifth-grade unit was conducted with approximately 280 students in three selected school districts (*23*). Control groups were selected by school district coordinators. Instruments used were (1) a knowledge test which had been previously developed for this unit of study, (2) the University of Illinois smoking attitude items (*25*),

(3) items "based on the Teenage Self Test," and (4) items eliciting demographic information. Data were collected prior to the beginning of instruction and immediately following the instructional program. The findings were: (1) the curriculum project positively influences health knowledge and attitudes, and (2) significant correlations were found between students' health knowledge and attitudes toward cigarette smoking and the smoking behavior of their parents, their older siblings, and their peers. Very few smokers were found among the fifth-grade pupils (*23*).

A study conducted in 1974-1975 in the Wichita Public Schools evaluated three curriculum units (lung, heart, brain) through a pretest and post-test control group design. A stratified random sample of the project schools was selected for evaluation purposes and was based on two variables: socioeconomic level of the school, and type of class in which the health unit was taught (i.e., self-contained or combination, etc.). Control schools were selected to match the project schools on relevant variables. Data were available for 512 project pupils and 206 control pupils. Each of three knowledge tests (lung, heart, brain) was used in the appropriate unit. These tests were developed by the School Health Curriculum Project regional office at Champaign, Illinois. The Teenage Self Test was used as the attitude measure. Scores on the Lung Unit Knowledge Test improved significantly from pretest to post-test for both the project pupils and control pupils. There was no significant difference between pretest scores of the project and control groups, nor between their post-test scores. On the Heart Unit Knowledge Test, the control group achieved a higher mean score on the pretest than the project group, but the project group improved significantly from pretest to post-test while the control group decreased significantly. On the Brain Unit Knowledge Test, the project and control groups started out with essentially the same mean score; the project group improved significantly but the control group made significantly lower scores on the post-test than on the pretest. The Heart and Brain Unit Tests, then, were shown to have a substantial impact on knowledge; this was not shown for the Lung Unit Test. Only in the Brain Unit group was a significant difference found on the Attitude Test. It is difficult to understand how a total score was calculated on the Teenage Self Test, which is made up of eight relatively independent factors designed to obtain eight scores. Since a total score might well be meaningless, it is not surprising that no differences were found (*75*). Another aspect of the Wichita evaluation was the analysis of scores of pupils of "first generation teachers," that is, those who attended the National Training Workshop, and pupils of "second generation teachers," those trained locally by first generation teachers. For both the Heart and Lung Units, mean post-test knowledge scores were higher for the pupils of first generation teachers than for those of second generation teachers. This difference

may well disappear, of course, as the second generation teachers gain more experience with the project. Responses to both student and parent questionnaires showed generally favorable attitudes toward the project (*106*).

An evaluation of the Heart Unit in lower socioeconomic classes of sixth-grade black students was carried out in two elementary schools in an East coast village and one inner-city school in the Midwest. A total of 144 students participated in the study. In the East coast sample, two experimental classes—one which completed the pretest and one which did not—and a control class were used. The two experimental classes were taught by sixth-grade teachers trained in the School Health Curriculum Project. In the Midwest school, the one experimental class was taught by the researcher, who is a health education specialist. The high incidence of hypertension among blacks motivated the study of the Heart Unit in black schools. Instruments used were the Health Knowledge Test (Heart Unit) developed by Cook at the University of Illinois, the Teenage Self Test, and the reading comprehension and vocabulary sections of the Iowa Test of Basic Skills. On the knowledge test, significant differences between post-test means, adjusted by analysis of covariance on the basis of pretest scores, and between the experimental and control groups were observed. No difference between post-test mean scores of the two experimental East groups was seen, indicating that the use of a pretest had no observable effect. Adjusted post-test means on the attitude measure were significantly higher for experimental than for control groups.[1] No difference between control and experimental groups was found on the reading comprehension test, but a significant difference was observed between post-test means on the vocabulary test. (Reading comprehension and vocabulary tests were not administered to the East coast classes.) No differences between the Midwest class, taught by the researcher, and the East coast classes, taught by the classroom teacher, were found on either knowledge or attitude measures (*92*).

During the 1975-1976 school year, 635 5th-grade students representing 33 intact groups from 12 Albuquerque public schools participated in an evaluation of the Lung Unit. Emphasis was placed on perceptions and attitudes rather than on knowledge. Measures of the following variables were included: locus of control, perceived vulnerability, semantic differential for health concepts, semantic differential for self-esteem, and two scores from the Teenage Self Test combined. The population included 24 intact groups in the experimental condition, 5

[1]In this study, the total score on the Teenage Self Test was obtained as follows: "The attitude section response categories were assigned scores ranging from one to five. A score of five for a response category indicated a very favorable health attitude toward the statement and a score of one indicated a very negative attitude toward the item in question... The highest obtainable score was 200." Since, in the development of the Teenage Self Test the items were not constructed to test either "favorable" or "negative" attitudes toward smoking, it is not known what criterion was used to assign scores to each of the statements.

groups in a control condition with a pretest and post-test, and 4 groups in a post-test-only control condition. No differences were found between the two control groups' scores on any of the measures; they were combined into one control group for further analysis. The only significant differences between post-test means of the experimental and control groups were on the semantic differential for health concepts and the health effects and rationalization scores combined on the Teenage Self Test. The differences were in the desired direction for the experimental group. Secondary analyses examined the differences between subgroups of the treatment group. Sex differences were found on the perceived vulnerability measure (girls higher than boys) and on the Self Test measure (boys higher than girls). Anglos scored higher on perceived vulnerability than Spanish Americans; Spanish Americans scored higher on the Self Test. Those reading below grade level scored higher on locus of control and Teenage Self Test measures than those reading at or above grade level. (A low score on the Teenage Self Test measure indicated attitudes in favor of not smoking.) In general, changes in the treatment group were favorable in the direction of the objectives of the program (*10*).

The prevalence of smoking behavior is negligible at the grade levels covered by the project, so it cannot be used as a criterion measure on immediate follow-up.

Nonschool Programs

Voluntary Health Agencies

The three major voluntary agencies concerned with cigarette smoking have recognized a responsibility to discourage young people from smoking, but they have approached the problem in different ways.

The American Cancer Society conducted 172,628 programs for young people aged 10 to 18 during fiscal year September 1, 1976 to August 31, 1977. In addition, they conducted 55,740 health education programs which promoted life styles oriented toward nonsmoking. In September 1977, they added a teaching kit aimed at the 5 to 9 age group. Over 25,000 of these units have been distributed, representing 33 percent of the potential schools (*68*).

The American Heart Association is supporting five local demonstration projects designed to test hypotheses in decision making, health education, and behavior modification of adolescent smoking behavior (*13*).

The American Lung Association has approached the problem in a completely different way. It has supported, in cooperation with the Bureau of Health Education, the development and field-test evaluation of curriculum models for kindergarten through third grade. The four units were designed to lead into the four units of the School Health Curriculum Project now being used in grades four through seven. The

kindergarten unit, "Happiness is Being Healthy," focuses on individual differences, helping children to discover their own unique qualities. "Super Me," the first-grade unit, helps pupils to understand that each person is very important and unique, yet shares common needs with others. The second-grade curriculum, "Sights and Sounds," is a study of the five senses; children learn how emotion is communicated. In the third-grade unit, "The Body—Its Framework and Movement," children learn about the muscular and skeletal systems. One of the goals throughout is to help children decide to begin or continue health-related behaviors that are likely to contribute to optimal health (*6, 100*).

This curriculum was written and tested in Seattle, Washington. Further testing was done in El Cajon, California; Fort Myers, Florida; and North Belmore (Long Island), New York. The finished model was completed in June 1977, and the first training workshops were held that summer. By mid-1978, 39 school districts in 14 states were implementing the model.

The field-testing of the model was carried out in five school districts in the United States. Experimental and control groups were tested before and after the unit was taught. The variables investigated were: (1) changes in children's attitudes toward smoking and good health, (2) changes in knowledge about body systems and the effect of smoking on health, (3) social networks of classrooms, (4) teacher attitudes toward teaching, and (5) reported changes in family health practices. Analysis of covariance was used to assess post-test differences, controlling on pretest scores. Findings were: (1) There were significant changes in attitudes of kindergarten and third-grade treatment groups compared with controls. The changes in the first- and second-grade attitudes were in the desired direction but not significantly greater in the treatment groups than in the control groups. (2) Knowledge gains at all four levels were significantly greater in the treatment groups than in the control groups. (3) Social networks in the experimental classrooms became more cohesive, efficient, and effective during the experiment. (4) There was no difference between attitudes of experimental teachers and those of control teachers at the end of the experiment. (5) Parents reported positive changes in children's health habits, and some changes in the habits of other members of the family (*7*). A plan for a longitudinal study has been developed (*8*).

Other Efforts

The American Dental Association has developed school programs on oral health for four levels: Level I, Grades Kindergarten through 3; Level II, Grades 4 through 6; Level III, Grades 7 through 9; and Level IV, Grades 10 through 12. All include material on smoking. It is not known how widely this material is used, or what effect it has (*5*).

The National Interagency Council on Smoking and Health, an organization composed of more than 30 member agencies, funded eight antismoking projects during the 1977-78 school year. Four of the projects were cosponsored by local lung associations. Others were sponsored by the Indiana School of Medicine, the Chicago Heart Association, The Door (a center for adolescents in New York City), and the State University of New York at Buffalo. All programs were student-centered; students were involved in the planning and carrying out of the programs. One program concerns itself with assertiveness training, another with biofeedback machines that allow students to monitor the immediate effects of smoking on their bodies. Three of the projects use youth-to-youth approaches. One program simulated an advertising campaign; in another, "rap" groups and individual counseling were used. At another school, a committee of students was given a $500 bank account to use in any way it liked to promote a nonsmoking attitude in the school. Results of the evaluation are not yet available (*37, 81*).

The YMCA has two programs that include antismoking information. The first, "Feelin' Good," is a cardiovascular/fitness program for children, grades kindergarten through nine. Besides being designed for use by YMCA's (Saturday morning gym programs, Indian Guides, leaders' clubs, and so forth), it can be used by schools and churches. It was field-tested on more than 5,000 children and more than 100 teachers and administrators nationwide. Critical comments were furnished by students, teachers, and educational consultants (*111*).

The other program, "Activetics," is a program for all age groups from high school through senior citizen. "The materials were critiqued by a group of professionals including health educators, exercise physiologists, and valuing educators" (*110*).

Training programs are available for both "Feelin' Good" and "Activetics."

Summary

For many years a wide variety of antismoking programs have been conducted in schools. These programs have been reported on, reviewed (*36, 37, 78, 82, 101, 103, 108*), and discussed (*41*) many times. Undoubtedly, for every school program reported in the literature, there are many underway that have not been reported. Yet, even with this vast proliferation of programs, we still do not know what kinds of educational experiences are effective in keeping young people from moving from merely experimenting with cigarettes to becoming habitual smokers.

Most of the programs are not based on any sound theoretical model, but rather on what people *think* might work—on what seems reasonable to them at the time. For example, it is logical to assume

that young people who know about the harmful effects of cigarettes on health will not take up the habit. Thus, many school programs have used the health threat as one basis for instruction, and many have used it as the only basis. We know that 94 percent of teenagers say that smoking is harmful to health and that 90 percent of teenage smokers are aware of the health threat (*44*). But it appears people cannot be expected to behave rationally in the face of strong social and psychological pressures to the contrary.

The assumption that young people are more influenced by their peers than by adults has resulted in widespread use of a variety of youth-to-youth programs. Some appear to be more effective than others, but no one knows what particular elements of the program are responsible for the differences. For example, no one has investigated which special qualifications of high school students are most desirable for an effective program. The peer leaders are often selected by the principal (*73*) on the basis of ability to speak before a group (*22*), excellent academic record (*53*), participation in extracurricular activities (*53*), or ability to perform laboratory experiments (*22*). Often stress is placed on selecting leaders who are mature, "cool," independent (*38*), and attractive (*38, 72*). Whether these are the teenagers most likely to influence younger peers is not known. In fact Newman observed that "hoods," who smoked the most, did not want to emulate the "popular" teenagers. As one girl put it, "I wouldn't want to be rich or nothing like that; they are stuck up—they won't talk to you. I wouldn't want to be like that in a million years" (*84*). So there is reasonable doubt that those being chosen as peer leaders are actually the most influential.

Another reason for lack of knowledge about what works is that there has been no assessment of the effect of programs on the smoking behavior of children after they become adults. Even data on smoking behavior in the 9th and 10th grades, 3 to 5 years after the program (*76*), are not sufficient evidence for a comprehensive evaluation.

Changes in health knowledge and changes in attitudes have been measured when pretest scores are compared with post-test scores soon after the program. Are these changes lasting? And if they are, to what extent do they have a significant effect on behavior?

Findings from one study to another have been inconsistent, partly due to lack of comparability of programs, use of varied definitions, and failure to use common evaluation instruments. Even in the School Health Curriculum Project, where classroom procedures are probably similar from one school to another, and where several researchers have used a common instrument (the Teenage Self Test), each changed the scoring procedure in such a way that results were not comparable to each other or to national norms (*23, 92, 102, 106*).

The greatest gap in knowledge results from paucity of experiments that compare several treatments with one another. Programs that do have an evaluation component usually compare a program in which

something takes place with one where nothing takes place—or, more likely, where nothing is known about what takes place.

Recommendations and Conclusions

Recommendations:

1. Research on program *content* is needed. Should the course content emphasize physiology and the effects of personal choice and of the environment on the body, as in the School Health Curriculum Project (*30*)? Should lifestyle be the focus, as it is in the American Health Foundation program (*15*)? Only if the experimental design includes several treatments with different content can we determine what kinds of information are most effective.

2. The most effective *methods* or *approaches* must be determined. What is the best way of getting information to students? Should it come from teachers or other pupils? What other pupils? What learning experiences are most effective? Any experimental design that will answer some of these questions must include several approaches.

3. Which combinations of methods and content work best with various *subgroups* of the student population? At what grade levels are the various techniques effective? With which socioeconomic groups? Studies must be replicated in varied settings and with different kinds of groups.

4. *Evaluation* must include *long-term follow-up.* We do not know if the information and antismoking attitudes of a fifth- or sixth-grader will influence his behavior as a senior in high school.

5. *Standard definitions and common evaluation instruments* are essential if we are to compare experimental programs with one another.

Conclusions:

Much is known about adolescents in general, and about their taking up smoking in particular. This knowledge must be used as a basis for developing sound experimental programs, with theoretical models rooted in established educational and psychological principles. Evaluation literature is rife with descriptions of appropriate procedures. Once goals have been defined in specific, objective, and measureable terms, instruments can be developed to assess the extent to which goals of programs are being met. Whether the purpose of a given instrument is to measure knowledge, attitudes, beliefs, or behavior, it should use sound psychometric procedures. It should, for example, meet criteria for acceptable reliability and validity. Such research should begin immediately. It is hoped that in another 15 years we will not have to say "We still don't know what works!"

Youth Education: References

(1) AARFLOT, A. National Association on Smoking and Health in Norway: Scope and activities of a voluntary organization. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 943-947.

(2) ALLEN, A.R., ALLEN, L.M. The case against anti-smoking campaigns in the public schools. South Dakota Journal of Medicine 20(4): 41-46, 51, April 1967.

(3) ALTHAFER, C.A. The San Diego story: An adventure in smoking education. Bulletin of the National Tuberculosis and Respiratory Disease Association 36(10): 13-16, November 1970.

(4) AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION, AND RECREATION. Position statement. Smoking education: The school's responsibility. Journal of School Health 41(8): 444-445, October 1971.

(5) AMERICAN DENTAL ASSOCIATION. Oral health curriculum. Chicago, American Dental Association, 1977, 166 pp. (Materials packet)

(6) AMERICAN LUNG ASSOCIATION. American Lung Association—Bureau of Health Education's primary grades health curriculum project. U. S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, Community Program Development Division. New York, American Lung Association. March 1978. 28 pp.

(7) ANDREWS, R.L. Evaluation report: Seattle school health curriculum project. Field test phase. New York, American Lung Association, May 11, 1977, 19 pp.

(8) ANDREWS, R.L. Longitudinal evaluation design. Seattle primary health curriculum project. New York, American Lung Association, July 17, 1977, pp. 3-4.

(9) ANDRUS, L.H., HYDE, D.F., FISCHER, E. Smoking by high school students: Failure of a campaign to persuade adolescents not to smoke. California Medicine 101(4): 246-247, October 1964.

(10) BARNES, S.E. The smoking classroom. Health Education 7(2): 37-38, March/April 1976.

(11) BECKERMAN, S.C. Report of an educational program regarding cigarette smoking among high school students. Journal of the Maine Medical Association 54(3): 60-63,74, March 1963.

(12) BEN-MEIR, D. Fighting smoking habits in a country at war. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health. National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 937-941.

(13) BENNETT, G. Personal communication. Dallas, American Heart Association, April 1978.

(14) BOHLAYER, S.K. Pennsylvania—Toward a generation of nonsmokers. Journal of School Health 36(10): 515-517, December 1966.

(15) BOTVIN, G.J., ENG, A., WILLIAMS, C.L. Life skills training: A psychosocial approach to the prevention of cigarette smoking. Paper presented at 106th Annual Meeting of the American Public Health Association and Related Organizations, Los Angeles, California, October 15-19, 1978. Washington, D.C., American Public Health Association, 1978, pp. 143. (Abstract)

(16) BRINEY, K.L. Relation of knowledge of effects of cigarette smoking to the practice of smoking among high school seniors. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 53-55.

(17) BROOKS, R.W. The use of student questions as a partial format for instruction regarding smoking and health. Journal of School Health 40(10): 542-544, December 1970.

(18) BROWN, R.L. Where there's smoking there's trouble. Journal of School Health 36(10): 493-497, December 1966.

(19) BUREAU OF HEALTH EDUCATION. The school health curriculum project. U. S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, HEW Publication No. (CDC) 78-8359, December 1977.

(20) BYNNER, J.M. The dilemma facing health educators. In: Richardson, R.G. (Editor). The Second World Conference on Smoking and Health: Proceedings of a Conference Organized by the Health Education Council at Imperial College, London, September 20-24, 1971. London, Pittman Medical, 1971, pp. 81-84.

(21) CALIFANO, J.A., JR. School health message. Journal of School Health 47(7): 395-396, September 1977.

(22) CAMPBELL, L.P. Modifying attitudes of upper elementary students toward smoking. Journal of School Health 44(2): 97-98, February 1974.

(23) CARAMANICA, V.P., FEILER, E.G., OLSEN, L.K. Evaluation of the effects of performance based teacher education on the health knowledge and attitudes of fifth grade students. Journal of School Health 44(8): 449-454, October 1974.

(24) CRAIL, J.W. The big count. Journal of School Health 36(10): 517-518, December 1966.

(25) CRESWELL, J.M., CRESWELL, W.H., JR. Youth Smoking Behavior Characteristics and Their Educational Implications. A Report of the University of Illinois Anti-Smoking Education Study. Champaign, University of Illinois, June 30, 1970, 164 pp.

(26) CRESWELL, W.H., JR., HUFFMAN, W.J., STONE, D.B., MERKI, D.J., NEWMAN, I.M. University of Illinois anti-smoking education study. Illinois Journal of Education. 60(3): 27-37, March 1969.

(27) CRESWELL, W.H., JR., STONE, D.B., HUFFMAN, W.J., NEWMAN, I.M. Antismoking education study at the University of Illinois. HSMHA Health Reports 86(6): 565-576, June 1971.

(28) DALZELL-WARD, A.J. The new frontier of preventive medicine. Public Health 90(3): 101-109, March 1976.

(29) DALZELL-WARD, A. J. The role of the Health Education Council (The United Kingdom). In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 911-919.

(30) DAVIS, R.L. Making health education relevant and exciting in elementary and junior high school. Health Services Reports 88(2): 99-105, February 1973.

(31) DAVIS, R.L. Positive smoking education programs for the school-age child. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 237-244.

(*32*) DAVIS, R.L. Status of smoking education research. Journal of School Health 38(6): 323-332, June 1968.

(*33*) DIPPO, J.P. Health class project: Smoking survey. Journal of School Health 38(3): 169-176, March 1968.

(*34*) DIVISION OF LUNG DISEASES, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE. Respiratory Diseases. Task Force report on prevention, control, and education. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 78-1248, March 1977, 137 pp.

(*35*) ESTRIN, E.R., QUERRY, D.L. A "no smoking" project for ninth and tenth grades. Journal of School Health 35: 381-382, October 1965.

(*36*) EVANS, R.I. Smoking in children: Developing a social psychological strategy of deterrence. Preventive Medicine 5: 122-127, 1976.

(*37*) EVANS, R.I., HENDERSON, A.H., HILL, P.C., RAINES, B.E. Current psychological, social, and educational programs in control and prevention of smoking: A critical methodological review. Atherosclerosis Reviews. (In press)

(*38*) FISHER, L. These students helped design their own smoking education programs. American Lung Association Bulletin 63(5): 2-6, June 1977.

(*39*) FLECKMAN, B. The tables are turned. Journal of School Health 39(4): 239-241, April 1969.

(*40*) FODOR, J.T., GLASS, L.H. Curriculum development and implementation of smoking research—A longitudinal study. Journal of School Health 41: 199-202, April 1971.

(*41*) FODOR, J.T., GLASS, L.H. Education programs influencing youth. In: National Conference on Smoking and Health. A Summary of Proceedings, San Diego, September 9-11, 1970. New York, National Interagency Council on Smoking and Health, 1970, pp. 157-186.

(*42*) FRITSCHE, W.E.P. An antismoking campaign among school children in Germany. In: Richardson, R.G. (Editor). The Second World Conference on Smoking and Health: Proceedings of a Conference Organized by the Health Education Council at Imperial College, London, September 20-24, 1971. London, Pittman Medical, 1971, pp. 77-80.

(*43*) GRANT, R.L., WEITMAN, M. Cigarette smoking and school children: A longitudinal study. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Company, 1968, pp. 189-205.

(*44*) GREEN, D.E. Teenage cigarette smoking in the United States—1968, 1970, 1972, and 1974. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 375-380.

(*45*) GRITZ, E. R. Smoking: The prevention of onset. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, (ADM) 78-581, December 1977, pp. 290-307.

(*46*) HAMBURG, M.V. What can schools do? Bulletin of the New York Academy of Medicine 44(12): 1526-1535, December 1968.

(*47*) HARLIN, V.K. An editorial: The soil is ready, let's sow the seeds. Journal of School Health 43(5): 277-278, May 1973.

(*48*) HASENFUS, J.L. Cigarettes and health education among young people. Journal of School Health 41(7): 372-376, September 1971.

(*49*) HENKE, L.J. Student-to-student teaching about tobacco smoking. School Health Review 5(1): 17-18, January/February 1973.

(50) HOCHBAUM, G.M. How can we teach adolescents about smoking, drinking, and drug abuse? Journal of Health, Physical Education, Recreation 39(8): 34-38, October 1968.

(51) HOFFMAN, W. The short life line. Journal of School Health 46(1): 48, January 1976.

(52) HOLLAND, W.W., ELLIOTT, A. Cigarette smoking, respiratory symptoms, and anti-smoking propaganda. An experiment. Lancet 1(532): 41-43, January 6, 1968.

(53) HORINE, L.E. Elementary school anti-smoking project involving high school students. Journal of School Health 39(1): 43-45, January 1969.

(54) HORN, D. The cigarette smoking picture—bright spots and shadows. Bulletin of the National Tuberculosis and Respiratory Disease Association 36(10): 7-9, November 1970.

(55) HORN, D., COURTS, F.A., TAYLOR, R.M., SOLOMON, E.S. Cigarette smoking among high school students. American Journal of Public Health 49(11): 1497-1511, November 1959.

(56) HORNE, T. Smoking and health: The activities of a high school student committee. Journal of School Health 33: 451-456, 1963.

(57) HOROWITZ, M.J. Psychological aspects of education related to smoking. Journal of School Health 36(6): 281-288, June 1966.

(58) HURSTER, M., AMERLING, G., MYERSON, N., PEDRAZA, A. A health fair. Journal of School Health 40(10): 539-541, December 1970.

(59) INTELLECT. Nation fails to arouse teenagers against cigarette risks. Intellect 105(2382): 298-299, March 1977.

(60) IRWIN, R.P., CRESWELL, W.H., JR., STAUFFER, D.J. The effect of the teacher and three different classroom approaches on seventh grade students' knowledge, attitudes, and beliefs about smoking. Journal of School Health 40(7): 355-359, September 1970.

(61) JAMES, W.G. For a healthy tomorrow. Journal of School Health 47(3): 180-183, March 1977.

(62) JAMES, W.G. Smoking and youth education. In: Richardson, R.G. (Editor). The Second World Conference on Smoking and Health: Proceedings of a Conference Organized by the Health Education Council at Imperial College, London, September 20-24, 1971. London, Pittman Medical, 1971, pp. 85-89.

(63) JEFFERYS, M., WESTAWAY, W.R. Catch them before they start. A report on an attempt to influence children's smoking habits. Health Education Journal 19: 3-17, 1961.

(64) JONES, J.A., PIPER, G.W., MATTHEWS, V.L. A student-directed program in smoking education. Canadian Journal of Public Health 61(3): 253-256, May/June 1970.

(65) LAOYE, J.A., CRESWELL, W.H., JR., STONE, D.B. A cohort study of 1,205 secondary school smokers. Journal of School Health 42(1): 47-52, January 1972.

(66) LEVENTHAL, H. Experimental studies of anti-smoking communications. In: Borgatta, E.F., Evans, R.R. (Editors). Smoking, Health, and Behavior. Chicago, Aldine Publishing Co., 1968, pp. 95-121.

(67) LOY, B. Smoking—A representational and experimental model. School Science Review 53(185): 497-502, June 1972.

(68) MABURN, G.J. Personal communication. American Cancer Society, Inc., New York, June 5, 1978.

(69) MAINE STATE DEPARTMENT OF HEALTH AND WELFARE. The impact of an educational program on teen-age smoking habits. Journal of the Maine Medical Association 54: 108-112, May 1963.

(70) MARTIN, F.M., STANLEY, G.R. Experiments in dissuasion: An assessment of two anti-smoking campaigns. Part I. Health Bulletin 23(4): 1-7, October 1965.

(71) MATTHEWS, V.L. The Saskatoon Smoking Study: Habits and beliefs of children in grades seven and eight about smoking. Saskatoon, University of Saskatchewan, College of Medicine, Department of Social and Preventive Medicine, May 1974, 63 pp.

(72) MCALISTER, A.L., PERRY, C., MACCOBY, N. Systematic peer leadership to discourage onset of tobacco dependency. A paper presented at the 86th Annual Convention of the American Psychological Association, Toronto, Ontario, Canada. 1978, 22 pp.

(73) MCRAE, C.F., NELSON, D.M., Youth-to-youth communication on smoking and health. Journal of School Health 41: 445-447, October 1971.

(74) MERKI, D.J. The effects of two educational methods and message themes on rural youth smoking behavior. Journal of School Health 38(7): 238-239.

(75) MILNE, A.M., COLMEN, J.G. Development of a teenagers' self-testing kit (cigarette smoking). Washington, D.C., Education and Public Affairs, July 1973, 100 pp.

(76) MILNE, A.M., MARSHALL-MIES, J., COLMEN, J.G. A study of impact of the school health curriculum project on knowledge, attitude, and behavior of teenage students. Washington, D.C., Education and Public Affairs, November 8, 1975, 41 pp.

(77) MONK, M., TAYBACK, M., GORDON, J. Evaluation of an antismoking program among high school students. In: Schulberg, H.C., Sheldon, A., Baker, F. (Editors). Program Evaluation in the Health Fields. New York, Behavioral Publications, 1970, pp. 345-359.

(78) MORISON, J.B. Cigarette smoking: Surveys and a health education program in Winnepeg, Manitoba. Canadian Journal of Public Health 55(1): 16-22, January 1964.

(79) MORISON, J.B., MEDOVY, H., MACDONELL, G.T. Health education and cigarette smoking. A report on a three-year program in the Winnipeg school division, 1960-1963. Canadian Medical Association Journal 91(2): 49-56, July 11, 1964.

(80) MURPHY, B. Pupils and puppets teach about health. Opportunity 2(4): 10-15, May 1972.

(81) NATIONAL INTERAGENCY COUNCIL ON SMOKING AND HEALTH. Teenage cigarette smoking; a national health problem. Washington, Conference of National Interagency Council on Smoking and Health, January 11-12, 1978, 19 pp.

(82) NEEMAN, R.L., NEEMAN, M. Complexities of smoking education. Journal of School Health 45(1): 17-23, January 1975.

(83) NEWMAN, I.M. Peer pressure hypothesis for adolescent cigarette smoking. School Health Review 1(2): 15-18, 1969.

(84) NEWMAN, I.M. Status configurations and cigarette smoking in a junior high school. Journal of School Health 40(1): 28-31, January 1970.

(85) O'KANE, W.H. Peer group presents value-oriented concepts. Science Teacher 37(9): 17-18, December 1970.

(86) O'ROURKE, A., WILSON-DAVIS, K. Smoking and school children. Journal of the Royal College of General Practitioners 20(101): 354-360, December 1970.

(87) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking project—The model. Canadian Journal of Public Health 61: 503-508, November/December 1970.

(88) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study—Results of the first year. Canadian Journal of Public Health 62: 432-441, September/October 1971.

(89) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study: Results of the second year. Canadian Journal of Public Health 65: 127-129, March/April 1974.

(90) RABINOWITZ, H.S., ZIMMERLI, W.H. Effects of a health education program on junior high school students' knowledge, attitudes, and behavior concerning tobacco use. Journal of School Health 44(6): 324-330, June 1974.

(91) RABINOWITZ, H.S., ZIMMERLI, W.H. Teaching-learning mechanisms in consumer health education. Public Health Reports 91(3): 211-217, May/June 1976.

(92) REDICAN, K.J. Analyzing the effects of a special health program on lower socioeconomic sixth grade students. Doctoral dissertation. Champaign-Urbana, University of Illinois. 1976, 139 pp.

(93) REID, E.L., STONE, D.B. Smoking behavior change among junior high school youth. Journal of Drug Education 1(3): 223-234, September 1971.

(94) REIF, A.E. Public information on smoking: An urgent responsibility for cancer research workers. Journal of the National Cancer Institute 57(6): 1207-1210, December 1976.

(95) REYNOLDS, J.C., JR. The drug education gap. Clearing House 50(1): 10-11, September 1976.

(96) RORKE, G.W. Situational analysis: Profile of women's smoking habits in Canada and the United Kingdom. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 299-307.

(97) SADLER, M. A pilot program in health education related to the hazards of cigarette smoking. Rhode Island Medical Journal 52(1): 36-38, January 1969.

(98) SAN DIEGO COUNTY COUNCIL ON SMOKING AND HEALTH. Final Report. U.S. Department of Health, Education, and Welfare, Public Health Service, Regional Medical Program Services, National Clearinghouse for Smoking and Health, April 1972, 224 pp.

(99) SAN DIEGO COUNTY COUNCIL ON SMOKING AND HEALTH. Final Report. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Clearinghouse for Smoking and Health, September 30, 1974, 92 pp.

(100) SCHMIDT, R.W. These kids are excited about their health. Imagine! American Lung Association Bulletin 62(6): 2-6, July-August 1976.

(101) SCHWARTZ, J.L., DUBITZKY, M. Research in student smoking habits and smoking control. Journal of School Health 37(4): 177-182, April 1967.

(102) STONE, E.J. The effects of a health education curriculum on locus of control, perceived vulnerability, and health attitudes of fifth grade students. Doctoral dissertation. Albuquerque, The Graduate School of the University of New Mexico, December 1976.

(103) THOMPSON, E.L. Smoking education programs 1960-1976. American Journal of Public Health 68(3): 250-257, March 1978.

(104) WAKE, F.R. Antismoking—Where do we go? Canadian Journal of Public Health 64(5): 493-496, September/October 1973.

(105) WAKE, F.R., THOMAS, E., BERGIN, J. Nurses, smoking, and school children. Canadian Nurse: 19-22, July 1973.

(106) WICHITA PUBLIC SCHOOLS UNIFIED SCHOOL DISTRICT 259, RESEARCH AND EVALUATION SERVICES DIVISION. A Report of the School Health Education Curriculum Project, Wichita Model 1974-1975. Wichita, Kansas, Wichita Public Schools, July 1975, 17 pp.

(107) WILLIAMS, C.L., ARNOLD, C.B., WYNDER, E.L. Primary prevention of chronic disease beginning in childhood. The "know your body" program: Design of study. Preventive Medicine 6: 344-357, 1977.

(*108*) WILLIAMS, T.M. Summary and implications of review of literature related to adolescent smoking. U.S. Department of Health, Education, and Welfare, Health Services and Mental Health Administration, Center for Disease Control, National Clearinghouse for Smoking and Health, September 1971, 59 pp.

(*109*) YACENDA, J.A. Smoking behavior and young people. The need for new directions. Clinical Pediatrics 12(1): 13A, 17A, January 1973.

(*110*) YMCA. Activetics. National Council of YMCAs, New York, 2 pp.

(*111*) YMCA. Feelin' Good. National Council of YMCAs, New York, 4 pp.

21. ADULT EDUCATION.

CONTENTS

LIST OF TABLES

Introduction

Public concern and pressure for adult education and lifelong learning continue to increase in the United States. It is estimated that 15.5 million Americans 17 years of age and older have participated in formal adult education programs. Table 1 indicates participation of males and females by instructional source in structured adult education activities. Approximately 11 million additional students were also enrolled in adult and continuing education programs offered by various community organizations in 1972, as indicated in Table 2.

TABLE 1.—Total adult (17 and older) participation in instructional sources of adult education, United States, May, 1969

Instructional source	Number of men	Number of women	Total number
Public or private school	1,557,000	2,081,000	3,638,000
College or university part-time	1,853,000	1,459,000	3,312,000
Job training	2,558,000	1,056,000	3,614,000
Correspondence courses	736,000	315,000	1,051,000
Community organizations	573,000	1,191,000	1,764,000
Tutor or private instructor	266,000	492,000	758,000
Miscellaneous activities	701,000	647,000	1,348,000
Totals	8,244,000	7,241,000	15,485,000

SOURCE: Okes, I.E. (*62*).

The tables do not fully account for the millions of Americans involved in community education programs sponsored by such organizations as State Cooperative Extension Services, official and voluntary health organizations, hospitals, the armed forces, community development agencies, community action agencies, and other related organizations. According to Grabowski (*26*), adult participation in educational programs ranges from 25 million to 60 million, depending upon the assessment criteria. It appears that since 1975 more adults were engaged in vocational and adult educational activities than young people attending the formal educational system at all levels (*82*). Accordingly, formal and informal adult education offers a tremendous potential for health and educational professionals to influence lifestyles and prevent illness and injury.

Hiemstra (*30*) identified several forces that have played a major role in creating an interest in and a need for lifelong learning. Social and technological advances, as well as changes in lifestyle and value systems, have tended to exert pressures on adults to seek continuing education as a means to obtain the skills and knowledge necessary to cope with social problems.

TABLE 2.—Adult and continuing education in community organizations: 1972 data

Type of organization	Number with adult education programs[a]	Number of people involved	% of total
Churches	50,480	3,614,000	32.9
Other religious groups[b]	3,310	474,000	4.3
Y's and Red Cross	3,360	3,050,000	27.8
Civic organizations[c]	3,730	1,175,000	10.7
Social service groups[d]	4,350	2,285,000	20.9
Cultural and other groups[e]	1,540	370,000	3.4
Totals	66,770	10,968,000	100.0

[a]Adult education programs included those aimed at skill, knowledge, and attitude building. They included organized instructional efforts, primarily on a part-time basis, and did not include credit classes, in-service training efforts, and recreational activities.

[b]Church headquarters, council of churches, Salvation Army, youth centers, related homes for the aged, etc.

[c]Neighborhood centers, senior citizen groups, civil liberties groups, and others concerned with community issues and betterment.

[d]Social welfare groups, American Cancer Society, vocational rehabilitation, alcohol groups, etc.

[e]Social and literary societies, civic theater groups, symphony organizations, etc.

SOURCE: Kay, E.R. (*36*).

Vivian and Wesley (*94*) point out that "education is the key to continuing lifelong growth and action, a means by which one can see what more he or she can learn and do, regardless of age or circumstance."

Various educational researchers have commented upon the high level of adult interest and participation in learning activities outside the institutional framework of education. Tough (*89*), for example, discovered that many adults spend 700 to 800 hours each year in learning activities, but that a large part of this learning is self-planned and separate from the typical formal classroom-related activity. As a result, educators are increasingly interested in nontraditional activities, alternative learning programs, innovative educational ideas, and new teaching strategies based on the concept and need for lifelong adult learning (*30*).

Bergevin (*6*) lists five basic goals for adult and continuing education: (1) to help the learner achieve a degree of happiness and meaning in life; (2) to help the learner understand himself, his talents and limitations, and his relationship with other persons; (3) to help adults recognize and understand the need for lifelong learning; (4) to provide conditions and opportunities to help the adult mature spiritually, culturally, physically, politically, and vocationally; and (5) to provide, where needed, education for survival in literacy, vocational skills, and health measures. Thus, as Wallace (*95*) indicates, health education should be considered for lifelong development of individuals. Health education ought to continue throughout life to help individuals to maintain their health.

Each section of this chapter will discuss adult education opportunities related to cigarette smoking and the implications for educational agencies, professional and voluntary organizations, and the federal government.

Health Competency Development and Smoking Education

The major purpose of the Adult Education Act, Public Law 89-750 (*91*) and its amendments through 1974, including Public Law 93-380 (*92*), is the establishment and expansion of adult public education programs to enable all adults to continue their basic education at least to the termination of secondary school and to receive training enabling them to become productive and responsible citizens. The Adult Education Act has provided the necessary financing for establishing Adult Basic Education (ABE) programs that stress certain teaching skills necessary for maintaining daily life and fulfilling adult responsibilities. Section 306 of the Act (*91*) makes provisions for cooperative arrangements between State educational agencies and State health authorities to provide health information and services that may be necessary to enable adults to benefit from such instruction. However, Mezirow, et al. (*49*) indicate that most teachers of ABE stress reading, writing, and arithmetic skills and make some effort to apply these basic skills to practical daily life.

The Adult Performance Level (APL) Study (*2*), conducted under the direction of Northcutt from 1972 to 1976, aroused Federal, State, and local concern for the teaching of life skills. The study staff identified 65 objectives which comprise functional literacy and grouped them into five general knowledge areas: occupational knowledge, consumer economics, health, community resources, and government and law. Thus, APL theory implies that basic skills be taught to provide adults with the knowledge and ability to participate effectively in society.

Flaherty (*22*) recently completed a systematic study of the self-perceived needs of students enrolled in ABE programs in New Jersey. A sample of 204 students showed that 72 percent indicated interest in occupational knowledge, 58 percent in consumer economics, 56 percent in health, 74 percent in government and law, and 50 percent in community resources. In the ranking of competencies in the health areas, 67.6 percent indicated they wanted to learn more about what practices are dangerous to health.

More recently, the Texas Department of Education developed an APL test designed to evaluate competencies needed for adult living, and the American College Testing Corporation established national norms for the competency-based examination (*20*). Eight test items to assess content area of community resources, occupational knowledge, consumer economics, mental and physical health, and government and

TABLE 3.—Adult performance level — goals and objectives for the content area of mental and physical health

APL Content Area - Mental and Physical Health

Goal: To understand the principles and practices that lead to good mental and physical health.

Major Objectives:

I. People should know where, when, and why to seek medical help. This means that they should:

- A. Recognize obvious signs of illness and know which require professional attention.
- B. Know the various types of medical facilities typically available in a community.
- C. Know how and why to follow medical instructions.
- D. Know how and why to communicate information about health problems to others.

II. Individuals should know what personal habits promote good health. This means that they should:

- A. Know the basic principle of health maintenance.
- B. Know the basic principles of nutrition.
- C. Understand the relationship between drugs and health.

III. Individuals should know how to apply principles of health to planning and raising a family. This means that they should:

- A. Understand the physical and psychological influences of pregnancy and the need for proper prenatal care.
- B. Understand the importance of family planning and the effectiveness of various birth control practices.
- C. Know basic child-rearing practices.
- D. Understand the special health needs and concerns of adolescents.

IV. People should know how to deal with potential hazards and accidents. This means that they should:

- A. Recognize potential hazards.
- B. Know where and when to apply basic safety measures.
- C. Know when and how to apply first aid.
- D. Know how and whom to ask for help in emergencies.

SOURCE: Fagerberg, S. (*20*).

law are included in the final instrument along with six to nine items designed to assess living skills.

Fagerberg and Holyoak (*20*) identified objectives that have major program implications for health and safety education (See Table 3). Several objectives relate indirectly to the health hazards associated with cigarette smoking; however, the APL program does not include objectives directly relating to smoking education. Thus, there appears to be a serious void in the content material of this program.

Recommendations

1. Adult Basic Education programs should incorporate more effective health education activities, including smoking education. Adults should receive information on the health hazards of smoking, benefits derived from cessation, the effect of smoke pollution on nonsmokers, the influence of peer groups and significant others, the economic factors involved, and the community services and self-help techniques available to modify or change destructive lifestyle patterns.

2. The Adult Performance Level Program that defines skills and knowledge necessary for successful functioning in society should provide more emphasis on health maintenance measures, including smoking education.

3. Teacher training institutions must better prepare adult and continuing education students for a significant role as change agents. Consideration should be given to the concept of the teacher as a facilitator and resource person who assists adult learners to determine their needs and to assess the resources that effectively promote positive lifestyles.

4. State and local educational agencies should provide more teacher training programs in health education, including study of risk-taking behavior, not limited solely to smoking education.

5. Professional and voluntary health agencies need to provide consultative and resource services to local ABE programs to help strengthen their health education components.

6. Federal agencies should encourage adult education programs to place more emphasis on preventive health education programs and to develop model programs in health education that could be replicated elsewhere.

Accessibility to Instruction

Formal health education classes are now offered in most colleges and universities in the United States as evidenced by current college catalogs. College students generally are exposed to introductory courses in personal health on an elective basis or as part of the general requirements for the baccalaureate degree. Major units in introductory courses usually include instruction on smoking and health and cover such topics as the use of tobacco, the consequences of smoking, reasons for smoking or not smoking, cessation techniques, risk reduction, economic consequences, and social approaches to combat the problem.

A recent study, conducted by Goodrow (*25*) to determine current health areas of high interest and concern to college students at Western Kentucky University, reveals that smoking and disease ranked fourth in interest out of 50 topics and received a relatively high weight with respect to degree of concern. Another important finding is that major student health interests and concerns changed little over a

6-year period when compared to previous studies at the University of Oregon and the University of Tennessee.

Worden, et al. (*99*) studied audience interest in 25 potential message concepts that were to be employed in a mass media campaign designed to influence knowledge, attitudes, and behavior concerning lung disease. The investigators found that individuals aged 50 and older were most interested in messages that suggested ways to deal with symptoms of lung disease and that smokers expressed highest interest in messages that offered advice on how to quit smoking.

A study by DeRoos and Coder (*16*), into the health concerns of a low-income, multiethnic female population, indicated that the subjects gave high priority to heart disease, cancer, and drug problems and low priority to such health concerns as overweight, long-range effects of alcohol, and smoking and health. Respondents failed to see the relationship between smoking and heart disease and cancer.

Adult educational campaigns against cigarette smoking have used many combinations of methods and materials, including advertising through mass media, pamphlets, exhibits, films, group discussion, counseling, public lectures, smoking-withdrawal clinics, and other assorted techniques (*88*). However, few of these programs have produced significant changes in the smoking behavior of adults (*3*, *19*, *67*).

Although studies indicate concern and interest on the part of many adults for adult education programs concerning smoking, in terms of their impact on smoking behavior, such programs have not been particularly successful. College students have more access to formal educational programs involving smoking education. Other adults are much more likely to receive less intensive antismoking education via the mass media, pamphlets, posters, or single lectures. At the same time, they receive many advertising and other messages which encourage smoking.

Many health educators say that individuals have significant responsibility for their own health (*42*, *50*, *68*, *84*, *85*). The report of the Task Force on Consumer Health Education (*84*) emphasizes that individual behavior and lifestyle play a major role in health, illness, disability, and premature death and that behavior and lifestyle are influenced by many internal, external, environmental, and societal factors. As one of its major goals, the National Consumer Health Information Act of 1976 (Public Law 94-317) advocates an increase in the individual's capacity and incentive to take major responsibility for his own health maintenance.

Recommendations

1. Colleges and universities should seek to maintain and strengthen their existing health education courses while maintaining a positive focus on smoking education.

2. Teacher training institutions need to consider that all students majoring in education, and in elementary education in particular, should be required to enroll in basic health education courses that include our major societal health problems. Method courses should provide future teachers with innovative teaching strategies and materials concerning smoking education. State and local educational agencies should give strong consideration to requiring for certification, as a minimum, a methods and a content course in health education.

3. Professional and voluntary organizations and federal health agencies need to provide technical and logistical support based on sound behavioral science principles to all levels of adult education programs.

4. New model adult educational programs need to be developed in concert with all agencies and institutions concerned with the smoking problem. The coordination of program efforts is essential for the development of successful model community programs. Also, a strong financial commitment to smoking education by federal health agencies, as well as by professional and voluntary agencies, is necessary to support sound research and demonstration projects.

Influence of Adult Role Models

Among the most powerful determinants of teenage cigarette smoking are the smoking practices of significant others (*27*). This section describes some published research reports concerning the influence on smoking behavior by health professionals, teachers, coaches, parents, and peers. Glover (*24*) claims that "in terms of promoting health behavior and life styles, modeling exists as a powerful tool that may either greatly enhance or destroy the verbal message of human health."

Health Professionals

Surveys conducted in Switzerland by Abelin (*1*) indicate that physicians were generally regarded as the most likely persons from whom advice on smoking would be accepted by smokers and nonsmokers. Most nonsmokers, but only a minority of smokers, were willing to accept similar advice from dentists.

A nationwide survey of American teenagers conducted by the American Cancer Society (*66*) indicated that 72 percent of the nonsmokers identified physicians as the one group that could influence them not to start smoking. Correspondingly, 42 percent of the smokers felt that the physician's advice would influence their decision to stop smoking.

Klonglan, et al. (*39*) undertook a study to determine how the general public perceives physicians as nonsmoking exemplars. Approximately 88 percent of the sample indicated that teachers, parents, and health

professionals (physicians in particular) should act as exemplars by not smoking cigarettes. In addition, physicians were perceived as educators in conveying the hazards of smoking to their patients. Also, 20 percent of the subjects felt that dental associations should be more actively involved in smoking education programs.

While several studies (*10, 43, 60, 81*) have indicated that cigarette smoking is less common among physicians than in the general public, certain medical specialists, psychiatrists in particular, tend to have higher smoking rates than other specialists. Low smoking rates were observed among internists, cardiologists, and physicians who were more apt to be exposed to patients with pathological states related to smoking. Accordingly, Purvis and Smith (*70*) suggested that increased emphasis on the health consequences of smoking be included in the medical curriculum. Further, Aronow (*4*) suggested that the medical profession assume leadership in educating the public about the health hazards of smoking and vigorously promote smoking-cessation programs.

Numerous studies (*5, 39, 65, 75, 90*) indicate specific strategies that physicians should use in assisting patients to stop smoking. Among the techniques mentioned are conveying the idea that smoking is hazardous, giving simple, firm instructions to stop, and suggesting attendance at smoking withdrawal clinics. Burke (*12*) also advocated that physicians serve as role models and support the rights of nonsmokers.

Several studies (*11, 23*), which found that a relatively high percentage of nurses smoke, expressed concern about nurses serving as exemplars and educators. A recent study by Burk and Nilson (*11*) indicated that the majority of both smoking and nonsmoking nurses felt that they had an important role in educating patients about the health consequences of smoking.

Teachers

Newman (*58*) surveyed 653 elementary and secondary teachers to determine their perceptions of the exemplar role, whether they believed they could influence student smoking behavior, and if they would be willing to change their smoking behavior if they felt it would benefit their students. Sixty-two percent of the smokers and 73 percent of the nonsmoking teachers felt that their behavior influenced the smoking habits of their students. The teachers also expressed a willingness to restrict their smoking as an example to their students, and 80 percent of the total sample indicated that teachers should not smoke when student smoking is prohibited. Thus, Newman (*58*) concluded that teachers "display a readiness to assume the exemplar role in smoking."

The smoking behavior and attitudes of 162 elementary, junior high, and secondary school teachers were studied by Chen and Rakip (*13*) to

ascertain if the teachers' smoking behavior was related to their attitudes and behavior toward students' smoking practices and smoking education in schools. Results indicated that the teachers' attitudes and behavior toward smoking education *were* related to their smoking practices. Also, ex-smokers were more active in attempting to change student smoking behavior than were present smokers. The authors concluded that teachers need more inservice and preservice teacher-training programs involving smoking education.

Rabinowitz and Zimmerli (*71*), using a limited sample, studied the effects of a smoking education program on students, teachers, and parents and concluded that the students had significantly more behavior-modification influence on the teachers and parents than vice versa.

An American Cancer Society study (*34*) to determine public school teachers' cigarette smoking attitudes and practices indicated that 21 percent of the teachers sampled currently smoked cigarettes and 22 percent were ex-cigarette smokers. Thus, cigarette smoking appears to be lower among teachers than the general adult population and has shown a general declining trend over the past 10 years. Smoking was observed to be higher among guidance counselors than among health education or science teachers, and the teachers indicated that smoking and health education needed to be introduced in elementary schools rather than in junior or senior high schools.

Coaches

Morris and Tichy (*51*) surveyed the smoking habits and attitudes of Oregon secondary school coaches and found that 84.5 percent believed that smoking constituted a moderate or severe health hazard. The vast majority of coaches (92 percent) indicated that smoking adversely affected athletic performance and fitness. The study showed that only 29.2 percent of the coaches were current regular cigarette smokers and that 44.4 percent had smoked previously. Approximately 75 percent of the coaches believed that their own attitudes concerning smoking influenced their athletes and students. The authors concluded that coaches, teachers, physicians, and parents "represent important examples to teenagers and thus education programs should be vigorously directed toward these groups as well as the students if maximum benefit is to result" (*51*).

Parents and Peers

Numerous studies (*8, 31, 32, 56, 86, 98*) indicated that parents and siblings, particularly at earlier ages, played an important role in determining the smoking habits of children. And, in terms of whether their children would or would not smoke, parental smoking behavior appeared to be a more important predictor than parental attitude (*37, 87*). As the child matured and matriculated at higher grade levels in

school, peer influences tended to become the predominant factor in determining smoking behavior (*41, 59, 73, 76*). As students entered the college environment, parental influence decreased significantly while peer influence became the major force in influencing smoking behavior (*47, 48, 69*).

Recommendations

1. The American Medical Association and State and local medical associations need to intensify efforts to convince physicians of the importance of informing their patients of the negative consequences of smoking. Physicians should point out the potentially harmful effect of passive smoking on infants. Furthermore, the importance of the exemplar role of the physician and all health professionals should be stressed.
2. The National League of Nursing and other professional nursing organizations should stress the role that nurses can play in influencing patients to stop smoking, and nurses should be aware of their important role as educators and exemplars.
3. State and local education agencies and Parent-Teacher Associations, as well as professional and voluntary health organizations, should continue their adult education efforts. Teachers and coaches also need to be kept informed of new developments with respect to smoking and health and their perceived influence as role models.
4. Health and educational agencies must work to reduce teenage and adult smoking "simultaneously and with equally vigorous efforts since they strongly influence each other" (*32*).
5. More research is needed to assess fully the impact of the adult and professional exemplar role.
6. Support should be given to movements that advocate the rights of nonsmokers because they have great potential for changing the social climate from acceptance to rejection of cigarette smoking.

Smoking Education and Cessation Programs

In 1969, Schwartz (*77*) examined 62 studies of smoking-cessation programs in the United States, Canada, Australia, England, Scandinavia, and other parts of Europe during 1957–68. The programs, primarily aimed at adults, employed a wide variety of methods including withdrawal clinics, lobeline and other nicotine substitutes, medication (such as tranquilizers, stimulants, amphetamines, anticholinergics, astringents, and local anesthetics), the "five-day plan", conditioning techniques, physician counseling, role playing, and hypnosis. The author concluded that few techniques were shown to have high success rates, that the most commonly used cessation methods were those which were least acceptable to smokers who desired to stop, and that most methods had high recidivism rates (*79*).

However, Schwartz commented that "the action of voluntary and governmental agencies, increased efforts by physicians to counsel patients in their offices, and the application of research findings about the psychological factors involved in smoking cessation, are helping to create the environmental conditions which will aid smokers to quit permanently" (*77*).

Schwartz and Rider (*80*), in 1975, reviewed the literature on smoking-cessation programs conducted in Canada and the United States during the years 1969 to 1974. They reported that although most methods obtained excellent end-of-treatment results, in that 70 to 80 percent of the subjects quit smoking, follow-up evaluations reduced the percentage of abstainers by 20 to 35 percent. In conclusion, the authors felt that major conditions necessary to program success were the use of multiple cessation methods to accommodate different types of individuals, monetary payment to intensify personal commitment, and the presence of illness or risk factors which motivate abstention. Two major ways that helped individuals stop smoking were found to be self-care techniques and extrinsic measures (*78*).

Self-care techniques involve using tools or guides to quitting (such as books, records, filters, or other gimmicks and devices), developing one's own way of quitting, and receiving advice on how to abstain. (The National Clearinghouse has developed a Smoker's Self-Testing Kit (*52*) and a Teenage Self-Test: Cigarette Smoking (*55*) as self-testing "insight development" procedures for educational use with adolescents and adults (*33*).) Schwartz (*78*) reported that self-devised methods contributed to a 13.5 percent reduction in cigarette smoking among adult males from 1964 to 1975.

Extrinsic measures include public information about the health consequences of smoking via newspapers, radio, and television, or through scientific reports, posters, pamphlets, films, and seminars sponsored by heart, cancer, and lung associations, or by governmental, educational, and professional agencies and organizations.

Educational approaches to help adults stop smoking generally are programs conducted in schools or institutional settings and in groups that use the lecture approach (*78*). In The Seventh Day Adventists' Five-Day Plan, perhaps the most popular type of program, a physician-clergyman team usually conducts five consecutive 2-hour sessions and several weekly follow-up meetings. During this period participants are exposed to films, lectures, models, and discussion; a buddy system is also employed. Participants are encouraged to engage in a physical fitness program, to eat a balanced diet, to drink a lot of fluids, and to abstain from caffeine products and alcohol. Similar plans are widely used by other professional organizations and lay groups. The program has been offered on commuter trains, on television, in prisons, hospitals, and factories, and by physicians, health-related agencies and organizations, and the armed forces. It is estimated that over 11

million cigarette smokers throughout the world have participated in this program (*80*). Follow-up reports indicate abstinence rates ranging from 14 to 33 percent after 1 year (*46, 80*).

Voluntary organizations, such as the American Heart Association, the American Cancer Society, and the American Lung Association, have sponsored smoking-withdrawal clinics in the United States and Canada. Several manuals have been developed for training volunteers to conduct smoking-cessation programs. Health departments, hospitals, medical group prepaid health plans such as the Kaiser-Permanente Health Plan, and interagency councils on smoking and health have also conducted group withdrawal clinics. Abstention rates after 1 year varied from 18 to 48 percent (*80*).

The American Health Foundation (AHF) based in New York City also conducts cessation programs using individualized approaches, positive orientation, individual responsibility, and continuous contact during treatment and maintenance procedures. Participants in the AHF program showed an abstention rate of 30 percent after 1 year (*80*).

A variety of commercial organizations such as Smoke Watchers, SmokEnders, and Schick offer withdrawal programs to the public. Smoke Watchers charges a relatively small fee for participation in a program based on gradual withdrawal. SmokEnders, using a highly structured format employing positive reinforcement techniques, charged fees ranging from $120 to $175 in 1974. Schick Smoking Control Centers, which employ aversive conditioning involving smoke satiation, rapid smoking and shock treatments, charged $450 in 1975 (*80*).

Reported success rates for Smoke Watchers varied from 25.4 to 36.8 percent. Those who attended more sessions were reported to have had higher abstention rates, and men had higher success rates than women (*80*). Schwartz and Rider (*80*) estimated the abstinence rate for SmokEnders at approximately 27 percent and said that twice as many men as women continued abstinence from cigarettes. The success rate claimed by Schick indicated that 53 percent of the participants had quit after the first year (*80*).

Schwartz and Rider (*80*) indicated that experimental research on smoking withdrawal techniques and cessation clinics suffers from major deficiencies, including reports based on inadequate numbers of subjects, inappropriate ways of measuring success, and poorly conducted follow-up procedures.

The Second and Third World Conferences on Smoking and Health recognized the need for standardizing research and evaluation techniques, and the National Interagency Council on Smoking and Health has recommended that basic guidelines be employed in research on the effectiveness of smoking-control programs (*57*). The Council

suggested that research reports on smoking-control programs cover the following areas:

1. Comprehensive description of the treatment program or references to where such information may be obtained.
2. Description of the data collection procedures and (where applicable) the experimental design.
3. Complete presentation of response rates and reasons for nonresponse at each point in time.
4. Presentation of results including: (a) descriptive data regarding the characteristics of the participants; and (b) analytic data on factors related to success/failure or other aspects measured.

Specific data to be collected, definition of terms, and recommendations that follow-up should be conducted at 1 week, 4 months, and 1 year after treatment, are also contained in the guidelines.

Recommendations

1. Research investigators should be encouraged to follow the recommended guidelines established by the National Interagency Council on Smoking and Health to increase the comparability and replicability of research in the smoking field (*88*).
2. Educational agencies, professional and voluntary organizations, colleges and universities, and Federal agencies should recommend the use of these guidelines in any smoking research project they sponsor.
3. More research needs to be encouraged to devise new techniques and methods for improving smoking-abstinence rates.
4. Successful programs should be replicated and disseminated to local, State, and Federal agencies concerned with the smoking problem.

Laws, Regulations, and Policies Affecting Adult Smoking

Educational campaigns by professional and voluntary health agencies, the mass media, and others have increased public awareness of the potentially harmful effects of "second-hand smoke." For example, lung associations point out that (1) nonsmokers exposed to smoke in enclosed areas experience physiological changes, such as increased carbon monoxide levels, faster heart beat, and rise in blood pressure; (2) people with respiratory or heart conditions are affected by second-hand smoke; and that (3) second-hand smoke may affect the unborn and infants during the first year of life (*93*). An increased interest in legislative action was noted by two recent reports (*53, 54*) summarizing state legislation on smoking and health.

Table 4 summarizes major legislative efforts of the States. In the table, "limitations on smoking" refers to laws and ordinances restricting smoking in public areas, buildings, elevators, schools, drug

TABLE 4.—State legislation on smoking and health for 1976 and 1977

Type of legislation	1976 introduced	Passed	1977 introduced	Passed
Limitations on smoking	68	4	133	12
Commerce	125	16	219	29
Smoking and schools	7	1	16	1
Advertising of tobacco products	3	0	7	0
Sales to minors	4	0	5	1
Insurance and other	8	2	12	1
Totals	215	23	392	44

SOURCE: National Clearinghouse for Smoking and Health (*53, 54*).

and department stores, hospitals, buses, airplanes, theaters, sports arenas, and certain government buildings. "Commerce" refers to bills and laws regarding taxation and the distribution of cigarette tax revenue, control of sales, licensing of vendors, wholesalers, distributors and retailers, and the control of transportation of tobacco products.

As indicated in Table 4, almost twice as many bills were introduced in 1977 as in 1976 with respect to limitations on smoking, commerce, smoking and schools, advertising, and total legislation. Major legislative efforts appear to be focused primarily on economic factors rather than on health factors. Rozovsky (*74*) indicates that most of the legislation is not designed for the benefit of nonsmokers (even though it may have some impact) but for purposes of fire safety.

Many communities, as a result of pressure from nonsmokers who are the majority of the adult population, have enacted ordinances restricting second-hand smoke in public places, but as Vanderslice (*93*) and Rozovsky (*74*) indicated, enforcement is quite difficult since there are many loopholes and a large percentage of the population may simply choose to ignore the ordinances.

Curran (*14*) indicates that smoking control is indeed a very difficult, complex, and frustrating aspect of public health preventive campaigns. He stresses the need for better relationships in public health between legal counsel and health personnel in order that more imaginative legal approaches can be developed to combat smoking problems.

A World Health Organization report (*100*) describes some of the major obstacles preventing legislation from becoming law. Most of the opposition comes not only from tobacco producers and manufacturers, but also from advertising interests since this represents a major source of revenue. In addition, the taxes generated from tobacco sources serve as an important source of revenue for governments, thus creating a real dilemma.

Recommendations

1. More studies should be undertaken to determine the impact of legislation on the prevention and cessation of cigarette smoking.
2. Educators should inform students of the potential impact of second-hand smoke on the health of adults, the unborn, and infants.
3. Communities should be encouraged by health, educational, and civic groups to emphasize the health consequences of smoking, including the rights of nonsmokers.

Influence of School-Based Programs on Parents

This section reports on selected published health education programs and curricula units involving smoking education with emphasis on those designed to involve parents in the educational process.

The School Health Curriculum Project (SHCP) (*9*), originated nearly a decade ago by educators who envisioned the need for children to assume personal responsibility for their own health decisions, particularly as they relate to cigarette smoking, has become much broader in scope and is now considered as a curriculum, method, and training program that focuses on the human body and on health maintenance. Recently, the National Center for Health Education received a contract award from the Bureau of Health Education, Center for Disease Control, for the management, further development, and nationwide dissemination of the School Health Curriculum Project.

The model employs a core curriculum that uses specific body systems as a central unifying thread. For each grade level, a particular body system is examined in relation to all body systems, enabling students to understand how complex systems interact in one's own body. Each instructional unit begins with an introduction that attempts to increase motivation and to arouse curiosity for learning on the part of the students. Awareness, appreciation, structure and function, desire and disorders, prevention, and a culmination activity represent the other educational phases of SHCP. The project attempts not only to affect the health behaviors of children but also to have impact on peers, teachers, family, and the community.

Basically the model uses a multimedia approach employing models, movies, filmstrips, tape recorders, slides, records, transparencies, newspaper articles, individual work sheets, pamphlets, and textbooks. In addition, learning stations in classrooms present students with the opportunity to teach their own peers (*63*).

Schools joining the program for the first year are required to send a training team consisting of classroom teachers, a principal, and one or two other school personnel (such as the school nurse, health educator, or a curriculum coordinator) to a designated training center. Broad-based logistic, resource, and financial support for the trainees and the program have been secured from a variety of voluntary health

agencies, educational agencies, civic groups, health departments, as well as Federal agencies. By 1977, SHCP had been implemented in more than 300 school districts involving more than 2,000 schools in the United States (*9*).

To date, 20 or more evaluation studies concerning SHCP have been conducted with some encouraging evidence indicating that the project holds promise for increasing knowledge and changing lifestyles (*9*). However, more longitudinal prospective studies are selected to assess more adequately the potential of the project to change lifestyles not only of students but also of teachers and parents.

A unique program, "Know Your Body" (KYB), has been developed and implemented by the American Health Foundation under a grant from the National Cancer Institute (*97*). This program combines a screening process, to detect risk factors for heart disease, cancer, and cerebral hemorrhage, with school-related projects and activities involving units on personal risk factors, antismoking campaigns, newsletters, and informational meetings with parents to reinforce the concept that individuals are primarily responsible for their own health. The program emphasizes the identification of risk factors, personal decisionmaking, and individualized health education. Each child's height, weight, blood pressure, blood sugar, cholesterol, hematocrit, pulse recovery index, smoking habits, and health knowledge of selected topics are recorded in the student's personal health "passport" which is relayed to the parents and the family physician.

Long-term evaluative studies are needed to determine the effectiveness of KYB programs, their influence on the adoption of healthy lifestyles by children, and their impact on teachers and parents.

Another example is the Health Activities Project (HAP) supported by the Robert Wood Johnson Foundation (*28*). Student-centered modules have been developed relating to the concept of fitness and various ways by which individuals interact and obtain information from their environment. The modules enable students to measure their own levels of performance and to learn how their bodies function, how they can improve their health and fitness, and how they can make their own health decisions.

Preliminary results from the 1976–77 national trials of experimental materials indicated that HAP activities were effective in aiding children to understand certain health concepts relating to scientific reasoning, decision-making, and the complex interactions of body systems. The evaluative report also emphasized the importance of parents as a source of health information (*29*).

Extensive field testing of the HAP materials is being conducted in 15 States and it is anticipated that some materials will be revised, as feedback is obtained.

Further research activities should determine the importance of HAP's role in behavior change as well as in community awareness of health education practices.

A professional volunteer committee of the Georgia Heart Association developed a program entitled "Today It's the 3 R's and HBP" that is designed to give students practical information concerning hypertension, as well as to have them serve as health educators to their families and peers (*64*). Other objectives of the project focus on developing decision-making skills and enhancing school-community relationships.

Science or health teachers are trained by professional local volunteers to understand hypertension and to learn blood pressure measurement techniques. The teachers are provided with copies of the instructional unit and resource materials, films, tapes, and handouts for use in classrooms.

After the training phase, teachers conduct the educational phase of the program involving the heart and circulatory system. Students are trained to take blood pressure and pulse measurements and, upon completing the unit, they take home blood pressure cuffs to take measurements of their parents and siblings. Measurements are recorded on a prepared form, returned to the schools, and subsequently forwarded to the local Heart Association. Persons with elevated blood pressure readings are encouraged to see their physicians for rescreening (*44*).

To date, this program has reached thousands of children and their parents. However, more research needs to be conducted to determine the potential for altering lifestyles of parents as well as children.

The National Parent-Teacher Association is currently sponsoring six innovative health education projects that actively involve students, parents, and the community (*35*). These projects are discussed in the section involving the identification and replication of demonstration models.

Recommendations

1. Further research should be conducted into school-based programs designed to influence parental lifestyles, including an assessment of the influence of such programs on smoking behavior.
2. Continued support should be provided for school-community programs that show promise in attempts to change destructive lifestyles of parents.
3. Evaluative studies should be made of school-community-based programs that focus on altering lifestyles of parents and children; those that appear to show promise should be replicated and further evaluated to determine their impact on behavioral change.

Dissemination of Smoking-Prevention Methods and Stop-Smoking Programs

Adult education has a "philosophy of teaching that provides a solid basis for the development of health education as a process of lifelong learning" (*21*). Research has shown that in student-centered programs the preferred and often the most effective method in adult education is that in which the teacher serves as a facilitator of learning rather than simply as a knowledge transmitter. Evidence also implies that for learning to occur, participants should be involved in the planning of the process and that learning is more effective if the participant's experience is utilized in the educational process (*30*). Adult education is based on the beliefs that adults are capable of self-direction, possess unlimited learning potential, and acquire new learning needs as they move through the various stages of life (*40*).

The involvement of local community residents in attempting to solve social problems is crucial to the adult education process. Common elements of the self-help process generally include the following:

1. Analysis of the problem situation either by concerned citizens or by a change agent.
2. The setting of goals, objectives, and priorities aimed at a solution of the problem or problems.
3. An assessment of the commitment to proceed.
4. Planning and organizing the activities necessary to meet established goals.
5. Carrying out the planned activities.
6. Evaluating the activities in light of the goals and the initial problem assessment (*30*).

At the county level, health and social organizations have for many years utilized local citizens in planning for the solution of human problems. The Cooperative Extension Service, the American Heart Association, the American Lung Association, the American Cancer Society, and other agencies and institutions have played major leadership roles in involving community residents. The results of research on methods of prevention of smoking by adults and successful techniques to promote stop-smoking programs can be disseminated through community services and the mass media.

The Cooperative Extension Service (CES) offers great potential for disseminating health information to the public because of its nationwide scope and affiliates in every state. Established in 1914, the Cooperative Extension Service was developed to communicate research findings to the public and, according to Yep (*101*), through its 4-H Youth and Home Economics programs, has become heavily involved in health education programs. Further, Yep feels that CES has the ability to become a highly significant force in improving the nation's health because it is assuming a major leadership role in assisting consumers to accept greater individual responsibility for their own health.

Boone (*7*) mentions three major methods by which extension educators can provide means to disseminate information: *Individual contact* in which educator and learner interact in relation to a particular problem; *group methods*, such as lectures, panel forums, demonstrations, and workshops; and *mass media methods* to communicate with large segments of the population. One drawback, however, is the fact that few extension services have professional health educators on the program staff.

Major educational, professional, and voluntary health organizations, such as the American Cancer Society, the American Heart Association, the American Lung Association, the American Public Health Association, the American School Health Association, and others, have attempted to mobilize public support in nonsmoking efforts. In addition, 35 State interagency councils and 64 metropolitan councils have conducted nonsmoking projects (*17*). All of these organizations, acting in concert with the National Interagency Council on Smoking and Health and the National Clearinghouse on Smoking and Health, have the potential to effectively disseminate research results to the general public. In addition, universities, community colleges, and public adult education programs can play a role in such program efforts.

The influence of mass media on smoking behavior remains relatively unclear at this point. For example, O'Keefe (*61*) questions the effectiveness of antismoking TV-radio educational messages on cigarette consumption, while Warner's findings (*96*) support their effectiveness. According to the Task Force Report on Prevention, Control and Education in Respiratory Disease (*17*), the mass media appear to have been useful in stimulating action in persons already motivated to stop smoking and in recruiting individuals for smoking-cessation programs. Worden, et al. (*99*) found that adults showed greater interest in media messages that offered positive advice on how to quit smoking than in those which used approaches that were negative or satirical. A study by Maccoby (*45*) indicated that mass media techniques led to a significant reduction in smoking by subjects exposed to community programs that focused on reduction or risk.

Dubren (*18*) evaluated a sample of 310 viewers who participated in a televised "stop smoking clinic" in New York City. Participants were exposed over a 4-week period to 30- to 90-second daily televised segments designed to assist them in a step-by-step approach to stop smoking. On a mailback questionnaire, 10 percent of the subjects indicated they had stopped smoking at the conclusion of the program. However, evaluations of this nature may be somewhat suspect because self-reports were used.

Public education involving smoking cessation has emphasized mass communication techniques. Ramstrom (*72*) indicates the relative amount of face-to-face communication needs to be increased by

enlisting health professionals and others who can do such work and by organizing special training for health personnel, educators, and community leaders to establish a network of key persons to promote cessation.

Recommendations

1. To achieve effective community adult health education programs, health professionals should possess adult education skills and understand strategies. Hence, health agencies, institutions, and organizations should offer preservice and inservice programs to provide the necessary skills for working effectively with adults.
2. Comprehensive programs should be developed and implemented to improve and change health-related lifestyles, and results of successful programs should be disseminated.
3. The use of the mass media as a change agent should be more adequately assessed through well-designed research.

Identification and Replication of Demonstration Models

Several projects that appear to have potential for adult education in relation to prevention of cigarette smoking or cessation are reviewed in this section. However, several reports (*57*, *80*) note that there are serious limitations in terms of data collection, research design, failure to account for interaction effects, methodology, and follow-up, which may make difficult full assessment of the impact of a specific program on a community.

In 1972, a group of researchers from Stanford University conducted a 3-year longitudinal field study of modification of cardiovascular risk factors through community education (*45*). The study was concerned with the creation and evaluation of methods for achieving behavior changes in smoking, exercise, and diet that could apply to other large population groups and also be cost-effective. The study was conducted in three northern California communities. One community received only mass media messages, another mass media combined with face-to-face interpersonal communication, and the third served as a control group for comparison purposes.

To determine effects, the experimenters collected baseline and yearly follow-up data from surveys based on interviews and medical examinations of a random sample of thirty-five 59-year-old males and females in each of the three communities. The results indicated a slight decline in cigarette smoking in the second year of the study among residents in the control group, a greater decline using only mass media, and the greatest decrease in smoking among the residents of the community exposed to the mass media and interpersonal communications.

The Stanford experiment tends to offer evidence that behavior change can be accomplished through sustained community health education efforts. To more fully understand methods of inducing changes in lifestyles, however, more research needs to be undertaken concerning the potential of mass media and individualized face-to-face instruction for reducing risk factors in populations.

An intensive community-organized antismoking education program conducted in San Diego, California, utilized mass media techniques, pamphlets, exhibits, films, public lectures, school lectures, counseling, cessation groups, and loudspeaker vans (*3*). Kelson, et al. (*38*) in their analysis indicate an impressive reduction in smoking among boys in grades 7 through 12; however, smoking by girls had increased, except in 11th and 12th grade. A forthcoming report from the Bureau of Health Education describing an evaluation of the San Diego experiment may shed some light on the impact of a comprehensive antismoking community program.

The National Parent-Teacher Association is currently sponsoring several projects in six States designed to create public awareness of the need for health education (*35*). The pilot projects focus on such diverse adult activities as the development of school/community health education councils to provide for community awareness and planning of workshops, the use of multimedia programs involving PTA members to generate support for comprehensive health education programs, the development of programs that encourage parents and teachers as role models for student health behavior, and the fostering of health education resource centers. Through the mass media, communities are being stimulated to develop programs to identify health problems at the local level. These programs would appear, philosophically, to affect adult behavior; however, evaluative reports have not been completed.

Smith (*83*) describes an attempt to persuade an entire community to stop smoking for a single day. Monticello, Minnesota, a town of approximately 1,700 people, received State and national media attention in its attempts to persuade its citizenry to quit smoking on January 7, 1974. The Cancer Society, the Lung Association, the Heart Association, and the State departments of public health and education all played active roles.

Posters, pledge cards, fact sheets, and the mass media dramatized the health hazards of smoking in an attempt to convince residents to stop smoking on 'D-Day' as well as to consider total abstinence from cigarettes. A random survey of pledge card signers indicated that 7 percent of those surveyed may have quit entirely; however, evaluation by self-reported behavior is extremely unreliable.

While community programs such as the Stanford University Project appear to offer promise for changing lifestyles, in the final analysis, present ongoing programs need to be evaluated more fully to determine their relative effectiveness in the adult population.

In addition, Davis (*15*) feels that, because of the inherent difficulties in getting communities to attempt total community antismoking programs, maximum effort probably should be placed on key adult groups, such as parents, teachers, and health professionals, as examples for youth.

Recommendations

1. More innovative long-term, longitudinal projects, such as the Stanford University Project, should be replicated with other populations to determine their influence in changing lifestyles and their cost-effectiveness.
2. More research is needed to develop model programs designed to aid adults to stop smoking and to prevent the start of smoking in children.
3. Demonstration and model antismoking projects should be supported and encouraged by local and State educational agencies, professional and voluntary organizations, and the Federal Government.

Adult Education: References

(1) ABELIN, T. Working with professional groups to increase priorities in smoking education. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 443-451.

(2) THE ADULT PERFORMANCE LEVEL PROJECT. Adult Functional Competency: A Summary. Austin, University of Texas at Austin, 1975, 24 pp.

(3) ALTHAFER, C.A. The San Diego story, an adventure in smoking education. Bulletin of the National Tuberculosis and Respiratory Disease Association 55(10): 13-16, November 1970.

(4) ARONOW, W.S. Smoking, carbon monoxide, and coronary heart disease. Circulation 48(6): 1169-1172, December 1973.

(5) BALL, K.P. Cigarette diseases: The most preventable epidemic. Royal Society of Health Journal 90(1): 40-42, January/February 1970.

(6) BERGEVIN, P. Philosophy for Adult Education. New York, Seabury Press, 1967, pp. 29-49.

(7) BOONE, E.J. The cooperative extension service. In: Smith, R.M., Aker, G.F., Kidd, J.R. (Editors). Handbook of Adult Education. New York, Macmillan, 1970, pp. 265-281.

(8) BORLAND, B.L., RUDOLPH, J.P. Relative effects of low socioeconomic status, parental smoking and poor scholastic performance on smoking among high school students. Social Service and Medicine 9(1): 27-30, January 1975.

(9) BUREAU OF HEALTH EDUCATION. The School Health Curriculum Project. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, HEW Publication No. (CDC) 78-8359, December 1977, 52 pp.

(10) BURGESS, A.M., JR., CASEY, D.B., TIERNEY, J.T. Cigarette smoking by Rhode Island physicians, 1963-1973: Comparison with lawyers and other adult males. American Journal of Public Health 68(1): 63-65, January 1978.

(11) BURK, M.F., NILSON, G.T. Student nurses and smoking. A survey. Journal of the Maine Medical Association 66(10): 271-273, October 1975.

(12) BURKE, F.G. Stopping smoking is a family affair. Medical Opinion 3(1): 57, 59-60, 62, January 1974.

(13) CHEN, T.L., RAKIP, W.R. The effect of the teachers' smoking behavior on their involvement in smoking education in the schools. Journal of School Health 45(8): 455-461, October 1975.

(14) CURRAN, W.J. Legal imagination and education in smoking control. American Journal of Public Health 66(12): 1206-1207, December 1976.

(15) DAVIS, J.M. Exemplarmanship. Pennsylvania School Journal 118(2): 133-135, December 1969.

(16) DEROOS, K.K., CODER, R. Assessing low income health concepts. Health Education 8(3): 29-31, May/June 1977.

(17) DIVISION OF LUNG DISEASES, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE. Respiratory Diseases. Task Force Report on Prevention, Control, Education. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publication No. (NIH) 77-1248, March 1977, 137 pp.

(18) DUBREN, R. Evaluation of a televised stop-smoking clinic. Public Health Reports 92(1): 81-84, January/February 1977.

(19) EVANS, M.W. The Avdel smoking project. Health Education Journal 32(3): 76-81, 1973.

(20) FAGERBERG, S., HOLYOAK, O.J. The APL program in health and safety education. Health Education 9(2): 8-9, March/April 1978.
(21) FISHER, D.W. Adult education theory necessary in health education practice. International Journal of Health Education 19(2): 129-135, 1976.
(22) FLAHERTY, J.F. An Assessment of the Functional Education Needs of Adult Basic Education Students. Paper presented at the American Educational Research Association Conference, Toronto, March 28, 1978. 13 pp.
(23) GARRETT, N. Smoking: Now and then. Canadian Nurse 69(11): 22-26. November 1973.
(24) GLOVER, E.D. Modeling—A powerful change agent. Journal of School Health 48(3): 175-176, March 1978.
(25) GOODROW, B. Does time change the health concerns of college students? Health Education 8(3): 34-35, May/June 1977.
(26) GRABOWSKI, S.M. Training Teachers of Adults: Models and Innovative Programs. Publications in Continuing Education, Syracuse University, National Association for Public Continuing and Adult Education, Eric Clearinghouse in Career Education, Occasional Papers, Number 46, 1976, 4 pp.
(27) GREEN, L.W., GREEN, P.F. Intervening in social systems to make smoking education more effective. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 393-401.
(28) HEALTH ACTIVITIES PROJECT NEWSLETTER. Berkeley, University of California, May 1976, 4 pp.
(29) HEALTH ACTIVITIES PROJECT NEWSLETTER. Berkeley, University of California, October 1977, 4 pp.
(30) HIEMSTRA, R. Lifelong Learning. Lincoln, Nebraska, Professional Educators Publications, Inc., 1976, 114 pp.
(31) HORN, D. The cigarette smoking picture — Bright spots and shadows. Bulletin of the National Tuberculosis and Respiratory Disease Association 36(10): 7-9, November 1970.
(32) HORN, D. Current smoking among teenagers. Public Health Reports 83(6): 458-460, June 1968.
(33) HORN, D. A model for the study of personal choice health behaviour. International Journal of Health Education 19(2): 89-98, 1976.
(34) JAMES, W.G. For a healthy tomorrow. Journal of School Health 47(3): 180-183, March 1977.
(35) JERRICK, S.J. From challenge to action. PTA promotes health education at national conference in Chicago. Journal of School Health 48(4): 243-244, April 1978.
(36) KAY, E.R. Adult Education in Community Organizations. U.S. Department of Health, Education, and Welfare, Office of Education, National Center for Educational Statistics, 1974, 80 pp.
(37) KEEVE, J.P. Smoking habits and attitudes of 3,057 public school students and their families (Newburgh, New York). Journal of School Health 35(10): 458-459, December 1965.
(38) KELSON, S.R., PULLELLA, J.L., OTTERLAND, A. The growing epidemic: A survey of smoking habits and attitudes toward smoking among students in grades 7 through 12 in Toledo and Lucas County (Ohio) public schools—1964 and 1971. American Journal of Public Health 65(9): 923-938, September 1975.
(39) KLONGLAN, G.E., WARREN, R.D., WINKELPLECK, J.M. Cigarette smoking and the role of dentists. Iowa Dental Journal 58: 43-44, February 1972.

(40) KNOWLES, M.S. What do we know about the field of adult education? Adult Education 14(2): 67-79, Winter 1964.

(41) LANESE, R.R., BANKS, F.R., KELLER, M.D. Smoking behavior in a teenage population: A multivariate conceptual approach. American Journal of Public Health 62(6): 807-813, June 1972.

(42) LENTZ, J.C., JR. The road ahead—Challenges for cooperative action. Health Education Monographs 3(1): 115-119, Spring 1975.

(43) LEVITT, E.E., DEWITT, K.N. A survey of smoking behavior and attitudes of Indiana physicians. Journal of the Indiana State Medical Association 63(4): 336-339, April 1970.

(44) LEWIS, J. Today It's the 3 R's and HBP: A description of the Georgia Heart Association's high blood pressure education program for schools. Atlanta, Georgia Heart Association, Inc., 1976, 36 pp.

(45) MACCOBY, N. The Stanford heart disease prevention program. In: Newman, I. M. (Editor). Consumer Behavior in the Health Marketplace. A Symposium Proceedings, 1976. Lincoln, University of Nebraska, 1976, pp. 31-44.

(46) MCFARLAND, J.W., BERGLUND, E.-L., ALBRECHT, C.E. Present status of 5 day plans to stop smoking. In: A Summary of Proceedings, National Conference on Smoking and Health, San Diego, September 9-11, 1970. New York, National Interagency Council on Smoking and Health, 1970, pp. 82-93.

(47) METTLIN, C. Peer and other influences on smoking behavior. Journal of School Health 46(9): 529-536, November 1976.

(48) METTLIN, C. Smoking as behavior: Applying a social psychological theory. Journal of Health and Social Behavior 14(2): 144-152, June 1973.

(49) MEZIROW, J., DARKENWALD, G.G., KNOX, A.B. Last Gamble on Education: Dynamics of Adult Basic Education. Washington, D.C., Adult Education Association of the U.S.A., 1975, 206 pp.

(50) MICO, P. R. An introduction to policy for health educators. Health Education Monographs 6 (Supplement 1): 7-17, 1978.

(51) MORRIS, J.F., TICHY, M.W. Smoking habits and attitudes of Oregon secondary school coaches. American Journal of Public Health 60(7): 1271-1277, July 1970.

(52) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Smokers' Self-Testing Kit. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, DHEW Publication No. (CDC) 74-8716, December, 1973, 11 pp.

(53) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. State Legislation on Smoking and Health, 1976. U.S. Department of Health, Education, and Welfare, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, December 1976, 73 pp.

(54) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. State Legislation on Smoking and Health, 1977. U.S. Department of Health, Education and Welfare, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, HEW Publication No. (CDC) 78-8331, January 1978, 79 pp.

(55) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Teenage Self Test: Cigarette Smoking. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Clearinghouse for Smoking and Health, DHEW Publication No. (CDC) 76-8723, 1975, 15 pp.

(56) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Teenage Smoking: National Patterns of Cigarette Smoking, Ages 12 Through 18, in 1968 and 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration, DHEW Publication No. (HSM) 72-7508, 1972. 140 pp.

(57) NATIONAL INTERAGENCY COUNCIL ON SMOKING AND HEALTH. A Committee Report. Guidelines for Research on the Effectiveness of Smoking Cessation Programs. National Interagency Council on Smoking and Health. October 1974, 46 pp.

(58) NEWMAN, A.N. How teachers see themselves in the exemplar role in smoking education as evidenced by their attitudes and practices. Journal of School Health 41(5): 275-279, May 1971.

(59) NEWMAN, I.M. Peer pressure hypothesis for adolescent cigarette smoking. School Health Review 1(2): 15-18, April 1970.

(60) NOLL, C.E. Health Professionals and the Problems of Smoking and Health. Report 3. Physicians' Behavior, Beliefs and Attitudes Toward Smoking and Health. Report on NORC Survey 4001. Chicago, University of Chicago, National Opinion Research Center, November 1969, 105 pp.

(61) O'KEEFE, M.T. The anti-smoking commercials: A study of television's impact on behavior. Public Opinion Quarterly 35(2): 242-248, Summer 1971.

(62) OKES, I.E. Participation in Adult Education, Initial Report. U.S. Department of Health, Education, and Welfare, Office of Education, National Center for Educational Statistics, 1971, 151 pp.

(63) OLSEN, L.K., STONE, D.B., SAUNDERS, J.A. Inservice training for elementary school health education. Health Education 7(2): 27-29, March/April 1976.

(64) OWEN, S.L. The three R's and HBP: A unique approach to school health and high blood pressure education. Image 8(1): 13-19, February 1976.

(65) PARKE, D.W. This doctor is firm: I advise my patients not to smoke. American Lung Association Bulletin 61(4): 7-9, May 1975.

(66) PEDIATRIC NEWS. Doctors could dissuade youths from smoking. Pediatric News 4(2): 24, February 1970.

(67) PORTER, F.T.H. Assessing public reaction to an anti-smoking campaign. Ontario Medical Review 48(5): 217-221, 224, May 1969.

(68) PRENDERGAST, T. J. Consumer behavior: An epidemiological perspective. In: Newman, I.M. (Editor). Consumer Behavior in the Health Marketplace. Lincoln, University of Nebraska, 1976, pp. 94-104.

(69) PRICE, J.L., COLLINS, J.R. Smoking among baccalaureate nursing students. Nursing Research 22(4): 347-350, July/August 1973.

(70) PURVIS, J.M., SMITH, D.L. Smoking among medical students. Southern Medical Journal 69(4): 413-416, April 1976.

(71) RABINOWITZ, H.S., ZIMMERLI, W.H. Teacher-learning mechanisms in consumer health education. Public Health Reports 91(3): 211-217, May/June 1976.

(72) RAMSTROM, L.M. Public education—Its role in smoking cessation. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 525-532.

(73) READ, C.R. The teenager looks at cigarette smoking. In: UICC Technical Report Series. Volume 6. Public Education About Cancer. Recent Research and Current Programmes, 1969. Geneva, Union Internationale Contre Le Cancer, pp. 97-104.

(74) ROZOVSKY, L.E. Smoking and the law. Dimensions in Health Service 52 (10): 58-60, October 1975.

(75) RUSSELL, M.A.H. Cigarette dependence: II. Doctor's role in management. British Medical Journal 2(5758): 393-395, May 15, 1971.

(76) SALBER, E.J., WELSH, B., TAYLOR, S.V. Reasons for smoking given by secondary school children. Journal of Health and Human Behavior 4(2): 118-129, Summer 1963.

(77) SCHWARTZ, J.L. A critical review and evaluation of smoking control methods. Public Health Reports 84(6): 483-506, June 1969.

(78) SCHWARTZ, J.L. Smoking cures: Ways to kick an unhealthy habit. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph 17. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute on Drug Abuse, DHEW Publication No. (ADM) 78-581, December 1977, pp. 308-337.

(79) SCHWARTZ, J.L., DUBITZKY, M. Expressed willingness of smokers to try 10 smoking withdrawal methods. Public Health Reports 82(10): 855-861, October 1967.

(80) SCHWARTZ, J.L., RIDER, G. Smoking cessation methods in the United States and Canada: 1969-1974. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 695-732.

(81) SCOTT, B.T. Physicians' attitude survey: Doctor's smoking and drinking habits. Medical Opinion 3(1): 49, 51, 54, January 1974.

(82) SHEATS, P.H. Introduction. In: Smith, R.M., Aker, G.F., Kidd, J.R. (Editors). Handbook of Adult Education. New York, Macmillan, 1970, pp. XXV-XXX.

(83) SMITH, L. The D-day story. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R. (Editors). Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 409-413.

(84) SOMERS, A.R. (Editor). Promoting Health: Consumer Education and National Policy. Germantown, Maryland, Aspen Systems Corporation, 1976, 264 pp.

(85) SOMERS, A.R., HAYDEN, M.C. Rights and responsibilities in prevention. Health Education 9(1): 37-39, January/February 1978.

(86) STONE, D.B., HUFFMAN, W.J. A replication of the Horn study on youth smoking in 1967. In: Creswell, J.M., Creswell, W.H., Jr. (Editors). Youth Smoking Behavior Characteristics and Their Educational Implications. A report of The University of Illinois Anti-Smoking Education Study. Champaign, University of Illinois, June 30, 1970, pp. 11-24.

(87) TANDY, R.E. Smoking among teenagers: Effects of programmed instruction on attitudes, behaviour and knowledge. International Journal of Health Education 15(2): 106-112, 1972.

(88) THOMPSON, E.L. Smoking Education Programs 1960-1976. American Journal of Public Health 68(3): 250-257, March 1978.

(89) TOUGH, A. The Adult's Learning Projects. A Fresh Approach to Theory and Practice in Adult Learning. Research in Education Series No. 1. Toronto, The Ontario Institute for Studies in Education, 1971, 191 pp.

(90) TUCKER, A.H., JR. New goals in smoking and health education for youth. Pennsylvania's Health 33(2): 7-9, Summer 1972.

(91) U.S. CONGRESS, Public Law 91-750, November 3, 1966, Title III, 80 Stat. 1191.

(92) U.S. CONGRESS, Public Law 93-380, August 21, 1974, Title VI, Part A, 88 Stat. 576.

(93) VANDERSLICE, J. State laws on smoking in public places. American Lung Association Bulletin 62(1): 8-10, January/February 1976.

(94) VIVIAN, V., WESLEY, W.A. Report from the Congress on the quality of life—The later years. Health Education 6(4): 16-18, July/August 1975.

(95) WALLACE, B.C. Aging: Health education's responsibility. Health Education 6(4): 8-10, July/August, 1975.

(96) WARNER, K.E. The effects of the anti-smoking campaign on cigarette consumption. American Journal of Public Health 67(7): 645-650, July 1977.

(97) WILLIAMS, C.L., WYNDER, E.L. A blind spot in preventive medicine. Journal of the American Medical Association 236(19): 2196-2197, November 8, 1976.

(98) WINDSOR, R.A. Smoking habits and attitudes of 4-H youth in Illinois, Ages 9-12. Journal of School Health 42(9): 558-560, November 1972.

(99) WORDEN, J.K., SWEENEY, R.R., WALLER, J.A. Audience interest in mass media messages about lung disease in Vermont. American Journal of Public Health 68(4): 378-382, April 1978.

(100) WORLD HEALTH ORGANIZATION. Legislative action to combat smoking around the world. A survey of existing legislation. International Digest of Health Legislation 27(3): 493-517, 1976.

(101) YEP, B. A framework for the study of the role of cooperative extension service in the health field. Health Education Monographs 3(1): 31-40, Spring 1975.

22. THE ROLE OF HEALTH CARE PROVIDERS.

CONTENTS

LIST OF TABLES

Introduction

Health professionals and the public have reciprocal expectations that health professionals should be authorities on good health practices and should be perceived as such. This interdependent relationship puts health professionals in a strategic position to influence the public's smoking habits.

The public's attitude toward health professionals may extend to those who are not themselves professionals but who work with health professionals or in health care settings or health-oriented occupations. These persons, therefore, may also be in a position to have a more than ordinary influence on the smoking habits of others. For these reasons, this chapter extends beyond the role of health professionals to all health care providers in preventing the hazards of smoking.

Definition of Health Care Providers

For the purposes of this chapter, a health care provider is defined as anyone who (1) provides health care directly (e.g., doctors in active practice, nurses, podiatrists, dentists, midwives); (2) provides a service related to health care (e.g., pharmacists, X-ray technicians); (3) works in a health care setting (e.g., maids in hospitals, dietitians in nursing homes, receptionists in doctors' offices); or (4) works for a health-related agency or institution (e.g., employees of a State health department, teaching staff in a medical school, staff of a voluntary health agency).

In 1976, about 4.3 million of the work force of 87.5 million people were employed in health-related occupations, approximately 5 percent of employees in all occupations (*67*). Distribution of employment among health occupations was as follows: health practitioners, 13 percent; nursing occupations, 57 percent; health technologists, technicians, and assistants, 20 percent; therapy and rehabilitation, 2 percent; and other health occupations, 8 percent. Hospitals employ about half of all workers in the health field; the other half work in clinics, laboratories, pharmacies, mental health centers, private offices, and patients' homes.

Possible Roles of Health Care Providers

Health care providers may affect the smoking habits of the public in several ways:

1. They may act as exemplars in their own smoking habits.
2. They may act as health educators by informing individuals of the hazards of smoking and by advising them to stop smoking.
3. They may, as managers, control smoking practices in health care settings.

The remainder of this chapter describes the results of a search of the literature pertaining to health care providers in each of these three

roles. Based on these findings, recommendations are made for appropriate ways in which health care providers may help prevent the hazards of smoking.

Health Care Providers as Exemplars

Attitudes Toward The Role of Exemplar

The importance of the exemplar role of health care providers was recognized in a 1972 agreement between the Danish Ministry of the Interior and the Danish tobacco industry. That agreement prohibited cigarette advertisements showing "persons who are or appear to be physicians,[1] dentists, nurses, midwives, or as belonging to other categories within the hospital or health services" (*75*).

A U.S. survey for the National Clearinghouse for Smoking and Health in 1970 found that most of the public expects persons in the health professions to act as exemplars (*41*): 72 percent of adult males and 79 percent of adult females agreed with a statement that persons in the health professions should set a good example by not smoking cigarettes. A similar survey of adults in 1975 found that about the same proportions (76 percent of males, 82 percent of females) agreed with this statement (*42*).

The same surveys (*41*, *42*) gathered data on how respondents perceived the smoking habits of their family doctors and those of 20 adults they knew. Of adults with a family doctor, 73 percent in each survey responded when asked if their doctor smoked cigarettes and, of these, the proportion who said their doctor smoked cigarettes decreased from 32 percent in 1970 to 27 percent in 1975. In both years, the respondents perceived as cigarette smokers about half of 20 adults they knew (the mean number of cigarette smokers estimated among 20 adults was 11.2 in 1970 and 10.8 in 1975). Respondents in the two surveys apparently perceived their family doctors as setting a better example in their smoking habits than the 20 other adults they knew.

That an adult's perception of a doctor's smoking habits may be influenced by his own was indicated in the surveys discussed above (*41*, *42*): they found that cigarette smokers were more likely than nonsmokers to report that their family doctor smoked cigarettes. It may be that some cigarette smokers, in order to feel less anxious about their own smoking, believe that their doctors also smoke. Another explanation for this trend in the data may be that if doctors who smoke are less likely to advise patients not to smoke, or be less successful in getting them to stop smoking, then smoking doctors may accumulate a larger proportion of smoking patients than do nonsmoking doctors.

[1]Throughout this chapter the terms "physician" and "doctor" are used synonymously. This is in contrast to the term "physician" as it is used in some British Commonwealth countries to distinguish between surgeons and other doctors.

On the other hand, public perceptions of how well health care providers act as exemplars may be influenced by expectations. A 1969 nationwide sample of teenagers placed doctors and nurses among the four types of persons they considered least likely to smoke (*57*). During that period a much lower proportion of physicians smoked cigarettes than adult males in general (*41*, *49*), but nurses had a higher rate of cigarette smoking than adult females in the general population (*41*, *51*).

Even those in a position to observe the smoking practices of health providers may not estimate them accurately. Baric, et al. (*6*) reported in 1976 that there was no difference between medical and other students at the University of Manchester in their perception of the smoking habits of doctors. More than half of both groups, in estimating the proportion of doctors who smoke, gave a figure that would have been correct for the general adult population, but was an overestimation for doctors. The smoking habits of the students were not related to their estimates of the doctors' smoking practices. The authors do not speculate on the cause of the medical students' overestimation, but they do report that the medical students were more likely than the others to agree with a statement that doctors should not smoke. Perhaps the medical students, having high standards for doctors, tended to be more aware of doctors who smoked than of doctors who did not and thus overestimated the proportion of doctors who smoke; other students, having lower standards for doctors, may have assumed doctors were like everyone else and thus also overestimated the proportion who smoked.

Although a 1972 national survey in Sweden (*72*) found that only 34 percent of physicians surveyed believed that public smoking habits would be affected if physicians were to stop smoking, other studies indicate that a majority of health care providers agree with the public that they should act as exemplars by not smoking. The National Clearinghouse for Smoking and Health sponsored a series of surveys of doctors, dentists, pharmacists, and nurses in the late 1960's (48–51), which were repeated in 1975 (*46*). The percentage of the respondents agreeing that their profession should set a good example by not smoking is shown in Table 1.

The National Clearinghouse for Smoking and Health also supported a 1972 survey of a random sample of the membership of the American Public Health Association which asked the same question (*1*). Matthews, et al. (*33*) carried out a similar survey of the entire membership of the Canadian Public Health Association in 1974. The percentages of the members of these two associations of health professionals with a positive attitude toward their responsibility to set a good example are presented in Table 2.

The data shown in Tables 1 and 2 indicate that a major proportion of health professionals in the early 1970's felt that members of their

TABLE 1.—Percentage of persons in four health professions who agreed that persons in their profession should set a good example by not smoking, 1967–1969 and 1975

Professional group	Year of survey	
	1967–1969[1]	1975[2]
Doctors	78	91
Dentists	72	88
Pharmacists	62	73
Nurses	82	87

[1]SOURCE: Noll, C.E. (*48–51*).
[2]SOURCE: National Clearinghouse for Smoking and Health (*46*).

TABLE 2.—Percentage of the membership of two public health associations who agreed their membership had a responsibility to set a good example by not smoking

Association	Percent agreeing
American Public Health Association	
All members	85[1]
Female members of public health nursing section	81.3[2]
Female members of other section	73.9[2]
Canadian Public Health Association	89.6[3]

[1]SOURCE: Atwater, J.B. (*5*).
[2]SOURCE: Eyres, S.J. (*20*).
[3]SOURCE: Matthews, V.L. (*55*).

profession should act as exemplars, and that this attitude toward the exemplar role gained support between 1967 and 1975. Pharmacists and female members of sections other than the Public Health Nursing Section of the American Public Health Association had the lowest proportion of members who felt it was a responsibility of their respective professions to set a good example by not smoking; even so, almost three-fourths of these believed they should act as exemplars.

In 1967, Coe and Brehm (*13*) studied a nationwide stratified sample of 1,591 general practitioners and internists interviewed about the routine preventive health services they provided their patients. In the area of smoking, the interviewers asked many of the questions used in the national surveys sponsored by the National Clearinghouse for Smoking and Health. On the question of the physician's responsibility to set a good example, they found that 80 percent of the doctors agreed that physicians did have a responsibility to set a good example by not smoking. This finding agrees with the 1967 survey reported by Noll (*49*) and shown in Table 1, above.

Pharmacists have considered the conflict between their exemplar role as health professionals and their sale of cigarettes as businessmen. The American Pharmaceutical Association's House of Delegates recommended in 1971 that tobacco products not be sold in pharmacies (*61*). Some State associations, however, had already passed such resolutions. For example, the Iowa Pharmaceutical Association passed a resolution in 1969 that pharmacists discontinue selling cigarettes (*69*). When Vlassis (*69*) surveyed the Iowa state membership shortly afterward, however, he found that 51 percent of those responding believed the State association should not take a position on the sale of cigarettes. Fifty-two percent also said that ethics should not enter into the sale of cigarettes, and an additional 15 percent expressed uncertainty on this point.

Actions as Exemplar

Many studies have examined the smoking habits of health care providers, but one problem with these studies is the inconsistency in the definitions of smoking behavior. Because the data reported by different researchers are not entirely comparable, findings reported here should be examined with that limitation in mind.

Smoking Habits of Doctors

Researchers have paid a great deal of attention to the smoking habits of doctors, and their studies indicate that there have indeed been changes in the smoking practices of physicians during the past 20 years. Table 3 presents some of the data from these studies, some of which is discussed in the following pages.

Vaillant, et al. (*68*) reported a longitudinal study which periodically questioned a group of 258 men who were first studied as sophomores at a liberal arts college. Part of the information gathered was about their smoking habits. The authors compared the smoking habits of the 45 men who became medical doctors with those of their classmates. Their data cover the period from the early 1940's until 1967. It thus fortuitously provides prospective data on changes in the smoking habits of a group of doctors during the period when a major change in attitudes toward smoking took place in the United States.

The study found that, initially, there was a lower proportion of smokers among students who later became doctors than among their classmates; when the men were about 28 years of age, however, a much higher percentage of the doctors (65 percent) were smoking cigarettes in contrast to 45 percent of the other men, and a somewhat higher proportion of the doctors were smokers of all tobacco products (almost 70 percent as compared with about 60 percent). During the 1950's, the proportion of smokers of all tobacco products in both groups

TABLE 3.—Smoking habits of doctors as reported in studies carried out between the years 1949 and 1975; data in percentages

Year and author of survey	Smokers		Former smokers	Nonsmokers	
	Cigarette	All forms		All	Never smoked
1949					
Vaillant, G.E. (*68*)	60	60			
1954					
Snegireff, L.S. (*62*)	51.1			32.9	16.4
1959					
Snegireff, L.S. (*63*)	38.5			44.5	
Garfinkel, L. (*24*)	39.6				
1961					
Garfinkel, L. (*24*)	38.3				
1963					
Burgess, A.M., Jr. (*9*)	38				
Garfinkel, L. (24)	32.6				
1964					
Modern Medicine (36)	22.5	47.8	31.8	52.2	20.4
Tate, C.I. (*65*)	30		45[a]	70[a]	25[a]
Vaillant, G.E. (*68*)	35[b]	60[b]			
Weitman, M. (*70*)		39.2	27.2	60.8	33.6
1966					
Modern Medicine (*35*)		41.2		58.8	
1967					
Coe, R.M. (*13*)	26.8-32.6		33.4-39.3		33.9-34.0
Garfinkel, L. (24)	29				
Noll, C.E. (*49*)	30		36[a]		35[a]
Vaillant, G.E. (*68*)	32[b]	60[b]			
1968					
Monson, R.R. (*39*)	24		37.8[a]		14.2[a]
Burgess, A.M. Jr. (*9*)	25.5				
Westling-Wikstrand, H. (*71*)	35.8[c]		13.6[a,c]		42.0[a,c]
1969					
Greenwald, P. (*26*)		24	40		30
Levitt, E.E. (*31*)	16.8[a]			83.2[a]	
1970					
Modern Medicine (37)		36.9		63.1	
1971					
Lipp, M.R. (*32*)	21		40[a]		39[a]
1972					
Fulghum, J.E. (*22*)	18		45[a]		37[a]
Garfinkel, L. (25)	19.5				
1975					
National Clearinghouse for Smoking and Health (*46*)	21		37[a]	79[a]	42[a]

[a]Of cigarettes only.
[b]Approximately.
[c]Women only.

was about 60 percent and of cigarette smokers about 45 percent; the doctors, however, had a lower proportion of heavy cigarette smokers.

During the 1960's, neither group gave up smoking in large numbers, with the proportion of doctors who smoked any tobacco product remaining at about 60 percent and the smokers among their former classmates dropping to somewhat less than 50 percent. The proportion of cigarette smokers in both groups, however, did decrease sharply: in 1967 only about half the smokers in each group smoked cigarettes. The number of cigarettes smoked also reflected the pattern set in the 1950's: in 1967 less than 15 percent of the doctors smoked more than 10 cigarettes a day while 20 percent of their former classmates were smoking more than a pack a day.

The American Cancer Society's prospective study (*25*) of a cohort of 5,000 physicians in 25 States found that, of those 2,899 doctors who were in all four surveys, the percentage who were cigarette smokers declined from 38.6 percent in 1959 to 19.5 percent in 1972.

Three separate studies of Massachusetts physicians found that cigarette smokers made up 51.8 percent of the state's doctors in 1954 (*62*), 38.5 percent in 1959 (*63*), and only 24 percent in 1968 (*39*).

The 1960's produced a flurry of studies and polls on the smoking habits of physicians that may well have reflected concern about their role as exemplars.

Modern Medicine carried out three surveys of physicians in the United States (*35, 36, 37*). In 1964, when questionnaires were sent to all physicians in active practice, 47.8 percent of the physicians responding said they smoked tobacco in some form and 22.5 percent said they were cigarette smokers (*36*). (As can be seen in Table 3, the latter figure seems very much out of line with other surveys at that time and may underestimate the proportion of cigarette smokers among practicing physicians.) In 1966, when only a small sample of physicians was polled, 41.2 percent of the doctors said they smoked (*35*). All active physicians were again questioned in 1970, and only 36.9 percent of those responding said they smoked (*37*).

The response rates for the two large surveys by *Modern Medicine* were only 31.4 percent in 1964 and 16.6 percent in 1970, and the data they reported may therefore be particularly susceptible to a tendency reported by Burgess and Tierney (*9*) for cigarette smokers to be underrepresented among physicians who respond to mailed questionnaires. When these authors contacted a sample of the 13.3 percent of physicians in Rhode Island who had not responded to two mailed questionnaires, they found that, although only 22.6 percent of those responding by mail said they smoked cigarettes, 45.5 percent of their sample of nonrespondents were cigarette smokers. The authors applied their finding to data they had already reported (*10, 40*) on the smoking habits of Rhode Island physicians and estimated the correct percentages of cigarette smokers to have been 38 percent in 1963 and 25.5 percent in 1968 (*9*).

The data in the national surveys of physicians carried out for the National Clearinghouse for Smoking and Health were based on responses to questionnaires mailed to two different samples of 5,000 medical doctors and on responses obtained in a telephone survey of samples of nonrespondents (*46*, *49*) to the mailed questionnaire. These surveys indicated that the proportion of physicians smoking cigarettes decreased from 30 percent in 1967 to 21 percent in 1975. The latter figure agrees with the finding of Lipp and Benson in 1971 (*32*) that 21 percent of 1,314 physicians chosen at random from four geographical areas smoked cigarettes.

Smoking Habits of Dentists

Two major studies on the smoking habits of dentists have been carried out for the National Clearinghouse for Smoking and Health. A 1967 study by Noll (*48*) reported that 34 percent of dentists were currently smoking cigarettes; in a similar survey in 1975 the proportion of dentists smoking cigarettes had decreased to 23 percent (*46*).

Smoking Habits of Nurses

A 1969 national survey of a sample of 6,003 nurses for the National Clearinghouse for Smoking and Health found that 36.9 percent of the nurses smoked cigarettes (*51*).

Phillips (*52*), on the other hand, reported that a 1970 survey of Canadian nurses found that only 28.7 percent were smokers. This finding may underestimate the true percentage of smokers among Canadian nurses, however, because only 53 percent of the sample responded and there was no follow-up of nonrespondents. Noll (*51*) reported that, in his U.S. survey, the proportion of nurses who said they smoked increased from 31 percent of those who responded to a first mailing of the questionnaire to 42 percent of those who, having failed to respond to four mailed questionnaires, were reached by telephone.

A national survey of nurses carried out for the National Clearinghouse for Smoking and Health (*46*) reported that 39 percent were smokers in 1975.

Smoking Habits of Pharmacists

Two national surveys carried out for the National Clearinghouse for Smoking and Health reported that, of the pharmacists sampled, 34.5 percent in 1969 (*50*) and 28 percent in 1975 (*46*) were cigarette smokers. A study in Iowa of a smaller number of pharmacists reported that 32 percent smoked cigarettes in 1969 (*69*).

TABLE 4.—Proportion of cigarette-smoking health professionals who said they never smoked in front of patients, students, or patrons, 1967–1969 and 1975

Professional group	Year of survey	
	1967–1969[1]	1975[2]
Doctors	39	54
Dentists	50	65
Pharmacists	22	41
Nurses	75	89

[1]SOURCE: Noll C.E. (*48–51*).
[2]SOURCE: National Clearinghouse for Smoking and Health (*46*).

Smoking Habits of Other Health Care Providers

There are few studies of the smoking habits of other health care providers. However, there was a 1972 survey of nursing home administrators and 34 percent smoked (*38*).

In summary, as of 1975, proportionately more doctors and dentists than other health care providers are setting a good example by not smoking cigarettes. By contrast, nurses as a group in 1975 have proportionately more smokers (39 percent) than the general female population (29 percent) and equal the proportion of smokers among adult males (39 percent) (*42, 46*). Since persons in the nursing occupations make up more than half the employees in health occupations (*67*), this failure on the part of the nursing profession to act as nonsmoking exemplars has potentially great impact.

Smoking in the Presence of Patients or Customers

Those health care providers who smoke may still act as exemplars if they do not smoke in the presence of patients or customers. In the several national surveys conducted for the National Clearinghouse for Smoking and Health (*46, 48-51*), the respondents were asked if they smoked in front of patients, students, or patrons (customers). Table 4 summarizes the findings of these surveys on this question.

From Table 4 it appears that, of health professionals who smoke, nurses are much better than doctors at not smoking in front of the public when they are functioning as health care providers. Whether this is due to their desire to set a good example or to the nature of their job and work setting is not clear. The 1969 survey (*51*), however, found a smaller proportion of smokers among nurses who worked in the community, in nursing education, in schools, or in doctors' offices. The author hypothesized that the low rates of cigarette smoking (24 to 28 percent) among nurses who work in these settings might be due to their awareness of their exemplar role.

Eisinger (*19*) compared pediatricians with the other physicians in the 1967 national survey of doctors (*49*) and reported that 30 percent of the pediatricians and 44 percent of the other doctors who smoked cigarettes did so in front of patients. Apparently pediatricians were more aware of their exemplar role; their actions in this regard, however, were not as likely to extend to their own smoking habits as were those of other doctors: 36 percent of pediatricians and 30 percent of all doctors smoked cigarettes in 1967 (*49*).

In the surveys described above (*46*, *48–51*), the question on smoking in front of students was asked only of nurses. Although the exemplar role of health professionals in medical, dental, and other schools in which future health professionals are being trained would appear to be an important one, little research has been done on the role of the faculty of these institutions as exemplars.

In Ireland, Herity, et al. (*27*) surveyed the smoking behavior of the faculty of University College, Dublin. They did not ask about smoking in front of students but did report a much lower percentage of smokers among both the medical (45 percent) and nonmedical (42 percent) staff than existed in the general population of Ireland (68 percent) in 1971. Although a slightly higher proportion of the medical faculty smoked compared to the nonmedical faculty, the medical faculty also had a higher proportion of former smokers (35 percent as compared with 24 percent). The authors report that these differences between the medical and nonmedical staff were not statistically significant.

At the 1967 World Conference on Smoking and Health, Ravenholt (*56*) reported on a survey he had made of the faculty of the University of Washington Medical School. He found that more than 25 percent of the medical faculty, more than 25 percent of the dental faculty, and 50 percent of the nursing faculty were cigarette smokers. These figures for medical and dental faculties are lower than those of doctors and dentists in general at that time, but the figure for faculty nurses is higher than that of nurses in general.

Health Care Providers as Health Educators

Attitudes Toward the Role of Health Educator

In 1967, the Committee on Youth of the Council on Child Health of the American Academy of Pediatrics issued a statement emphasizing the importance of pediatricians as educators. That statement said that the physician had an obligation to prevent patients from beginning to smoke and recommended that physicians give parents information on the harmful effects of smoking when their first child is born (*14*).

A number of surveys have asked health professionals about their attitudes toward several kinds of health education activities. The national surveys sponsored by the National Clearinghouse for Smoking and Health during the late 1960's and in 1975 (*46*, *48–51*) asked the

TABLE 5.—Percentages of health professionals who agreed with statements about their responsibilities in the role of teacher, 1967–1969[1] and 1975[2]

Statements of health professionals' responsibilities	Professional group and year of survey							
	Doctors		Dentists		Pharmacists		Nurses	
	1967	1975	1967	1975	1967	1975	1967	1975
Should be more active than they have been in speaking to lay groups about cigarette smoking.	74	82	57	68	56	68	62	74
Should help patients (patrons) who wish to stop smoking to accomplish this.	92	—	72	—	77	—	85	—
Should convince patients (patrons) to stop smoking.	84	74	59	61	46	51	66	77

[1]SOURCE: Noll, C.E. (*48–51*).
[2]SOURCE: National Clearinghouse for Smoking and Health (*46*).

TABLE 6.—Percentages of the membership of the American Public Health Association and the Canadian Public Health Association agreeing with statements about their role of teacher, 1972 and 1974

Statements on health professionals' responsibilities	[1]Proportion of APHA members in agreement	[2]Proportion of CPHA members in agreement
Should be more active than they have been in speaking to lay groups about cigarette smoking.	80	90
Should convince people to stop smoking.	85	93

[1]SOURCE: Atwater, J.B. (*3*).
[2]SOURCE: Matthews, V.L. (*33*).

respondents if they agreed with three statements that are pertinent to an educational role. Table 5 shows the proportions of doctors, dentists, pharmacists, and nurses who agreed with each statement.

Two of the above statements were used in surveys of the American and the Canadian Public Health Associations (*3*, *33*). Table 6 compares the proportion of their members who agreed with each statement.

Coe and Brehm (*13*) also asked their large sample of general practitioners about their attitudes toward their responsibilities in

getting their patients to stop smoking. They found that 92 percent agreed they should help persons who wanted to stop smoking to do so, and that 83 percent believed they should convince their patients to stop smoking.

Actions as Health Educators

Somewhat fewer health care providers act as health educators than believe they should do so. Surveys in 1967 and 1970 found that about two-thirds of doctors (*13, 37, 49*) but only one-third of dentists (*48*) inquired about their adult patients' smoking habits as a routine procedure. As for teenage patients, in 1967 only about half of doctors who treated teenagers said they routinely asked if they smoked (*49*).

Two 1967 studies that asked about doctors' routine advice to patients concerning smoking reported, in one case, that 29 percent (*49*) and, in the other, 62 percent (*13*) of doctors said they routinely advised all patients against smoking. Differences in the composition of the groups surveyed have affected the surveys' findings on this question. The first survey (*49*) used a simple random sample of the membership (excluding certain classes of members) of the American Medical Association, and the second (*13*) used a nationwide sample of internists and general practioners, stratified for several variables. Also, differences in the context in which the question was asked may have elicited different responses. The first survey (*49*) asked about the advice on smoking in the context of whether the advice was given when the patients had specific health problems, with the alternative "any condition" being given as the final condition in the list. The second survey (*13*) did not report the question exactly as asked but said that it "sought information on how often the physician advised the patient who smoked to give up cigarettes even though the condition being treated was unrelated to smoking."

Proportionately fewer pediatricians than physicians in general advised parents not to smoke in 1967 (*19*). This may reflect the relatively high rates of smokers among pediatricians (*19*). As has been reported in several studies (*8, 13, 49*), physicians who were smokers were less likely than nonsmokers to advise their patients not to smoke.

More than half of the doctors in the 1967 national survey reported by Noll (*49*) said they warned all patients with lung, respiratory, or heart conditions, peripheral vascular disease, peptic ulcers, or mouth or lip lesions against smoking. Less than one-third routinely advised pregnant women not to smoke. This latter finding may reflect the more recent recognition of the hazards of smoking during pregnancy (see the Chapter on Pregnancy and Infant Health).

Stamler, et al. (*64*) studied industrial workers who were referred to their physicians in a coronary heart disease detection project. They interviewed both the workers and their physicians about 6 months after the referral and found that 80 percent of the referred smokers

had seen their doctors. Of those who did so, 70 percent had been advised to stop smoking.

Among dentists in 1967 (*48*), 75 percent said they warned patients with leukoplakia against smoking, but only 36 percent gave that warning to patients with any soft tissue lesion. Some dentists have taken action to help their patients stop smoking. In 1970, for instance, the directorate of dental services at Wilford Hall USAF Medical Center, Lackland Air Force Base, Texas, instituted a cessation program for interested patients (*12*).

When Noll (*51*) asked nurses in 1969 if they had discussed smoking and health with patients and students, only 30 percent said they had discussed it with more than one-third of the patients and students with whom they had contact. As with physicians, nurses who smoked were less likely than those who did not smoke to advise patients and students against smoking. About 65 percent of nonsmokers, but only 50 percent of smokers, had suggested to at least 5 percent of their patients or students that they should stop.

In Noll's 1969 survey of pharmacists (*50*), only 17 percent said they had discussed smoking and health with more than one-third of their patrons (customers), and only 50 percent of nonsmokers and 39 percent of smokers had warned at least 5 percent of their patrons against smoking. Vlassis (*69*) found that, although more than half of Iowa pharmacists surveyed did not believe the state Pharmaceutical Association should take a position on the sale of cigarettes, almost 90 percent were in agreement with the Association's actions in distributing educational material on the harmful effects of tobacco.

Health professionals who train others have an extended opportunity to influence the smoking habits of others; not only may they influence those persons and students they see themselves, but they may also indirectly influence the patients who will be treated by the students they teach. It appears, however, that this opportunity has been frequently neglected by medical schools. In 1969, Anderson (*2*) surveyed the 28 medical schools in the United Kingdom and reported that less than one-third advised entering medical students who smoked that they should stop, and less than one-fourth taught all students during their first year of clinical training about the medical effects of smoking. Knopf (*29*) reported that about one-fourth of medical students at the University of Manchester said in 1972 that they had been advised that smoking was inappropriate for a doctor, and almost two-fifths mentioned antismoking attitudes of the staff. However, about 10 percent mentioned that the staff smoked while teaching and about the same number had heard a teacher justify smoking. At least one medical school has taken steps to provide all its students with information on the hazards of smoking; the Middlesex Hospital Medical School, London, began a policy in 1970 of giving all preclinical

students information and an opportunity to discuss smoking and health on the day they enter the school (*5*).

Effectiveness as Health Educators

Knopf and Wakefield (*30*) interviewed 99 percent of the medical students at the University of Manchester in 1972 and reported that the students were more likely to begin smoking during their training than to give it up and, if they already smoked upon entering school, were more likely to smoke more rather than less during the course of their study. Even so, less than one-third of the medical students smoked, and more than 80 percent considered smoking a major health risk. Knopf (*29*) reported that only 9 percent of a sample of these students said that some aspect of their medical training was relevant to their deciding to stop or to cut down on smoking.

Purvis and Smith (*55*) surveyed the medical and basic science graduate students at the University of Mississippi Medical Center and reported in 1976 that significantly more of the graduate students than medical students smoked (19 percent as compared with 11 percent). They also found that of the former smokers among the medical students, one-third had quit smoking during the preceding year; of these, almost half gave their future profession as a significant reason for stopping.

When the results of physicians' advising patients to stop smoking are measured, generally fewer than one-fourth of the patients do so for any length of time; however, patients who are ill with a disease affected by smoking may respond in proportionately greater numbers. For example, Baric, et al. (*7*) counseled some women at a prenatal clinic about the hazards of smoking and did not counsel others. Eleven weeks later they found that only 14 percent of the group who had been counseled had stopped smoking. Only 4 percent of the women who had not been counseled had stopped.

Williams (*73*) reported that a somewhat higher proportion of patients being treated for chest conditions quit or cut down on smoking after being given routine advice to do so; after 3 to 5 months, 37 percent of patients who had formerly smoked at least 10 cigarettes a day had stopped smoking, and 24 percent had reduced their smoking by at least one half.

Rose and Udechuku (*58*) reported that many patients tended to forget within a few weeks that they had been advised against smoking. In a study of patients under 70 years old who had been discharged from a hospital after being treated for atherosclerotic disease, chronic bronchitis, or hypertension, they found that, when asked less than 4 weeks after discharge, about three-fourths recalled being advised against smoking, but when asked more than 8 weeks after discharge, a little more than half remembered being advised. They also reported

that 34 percent of the patients who recalled the advice had stopped smoking at the time of the survey.

Mausner (*34*) compared respiratory-disease patients' recollection of being advised against smoking with their physicians' notation of advice in medical records. At least 1 year after they had been cautioned not to smoke, almost all remembered the advice and more than half had stopped smoking.

Pincherle and Wright (*53*) studied the effectiveness of advice against smoking given to business executives during routine physical examinations. They reported that at the next routine examination about one-fourth of the executives had stopped smoking cigarettes or had reduced their cigarette smoking by 30 percent. They compared the effectiveness of the physicians' advice with the smoking habits of the physicians and found that, of 10 doctors, the 3 who had never smoked or who had smoked no more than five cigarettes a day tended to have more patients who gave up or cut down on smoking (24 to 37 percent of their patients did so) than did doctors who had previously been heavy cigarette smokers (17 to 23 percent of their patients stopped or cut down on smoking). Apparently, these findings are not a product of individual differences in persuasiveness among the doctors, because those doctors who were most successful in influencing patients against smoking were least successful in dealing with patients' weight problems.

The study by Stamler, et al. (*64*) of industrial workers who were referred to their physicians in a coronary heart disease detection project found that 20 percent of the workers who had been advised to quit smoking by their doctors had stopped 6 months later.

In summary, these studies tend to show that, if doctors advise their patients not to smoke, about 10 to 25 percent may quit or reduce the amount they smoke.

Health Care Providers as Managers in the Control of Smoking in Health Care Settings

Smoking in health care facilities is being increasingly limited by law, and health care providers in administrative positions will be involved in this implementation. This trend toward limiting smoking in public places and medical care facilities is evident in several recent state legislative reports from the National Clearinghouse for Smoking and Health (*4, 43-45*).

Some health care providers in administrative positions have acted to control smoking in health care facilities, regardless of legal requirements, for a variety of reasons other than fire prevention: insuring that employees set a nonsmoking example, protecting nonsmokers from tobacco smoke, reinforcing advice not to smoke, and providing an opportunity for smokers to stop smoking.

Attitudes Toward Controlling Smoking

In 1967, Schnitzer reported on an informal survey he had made of health professionals concerning the question of controlling smoking in hospitals. The consensus of this group of health professionals was that "absolute nonsmoking hospitals would be ideal, but it is not possible at this time" (*60*).

Since 1970, health care providers have begun to move toward greater control of smoking in health care settings, as indicated by resolutions calling for the control of smoking in these facilities by various professional groups. In 1975, for example, the Canadian Hospital Association passed a resolution requesting the prohibition of smoking in patient areas and for the establishment of nonsmoking sections in public and general use areas of hospitals (*11*). The resolution also recommended that hospitals ban the sale of cigarettes on their premises. In 1976, the same group resolved to adopt a policy of actively discouraging the sale and use of tobacco products in Canadian health facilities as an example for the public and to emphasize the hazards of smoking. Even earlier than these resolutions, the American Cancer Society was conducting a nationwide campaign against the sale of cigarettes in hospitals (*18*). And in Britain, in 1977, the Social Services Secretary announced a new antismoking drive which included guidelines to hospitals on restricting smoking (*66*).

Actions to Control Smoking

Willingness on the part of health care providers to act to control smoking in health care settings has developed more slowly than their willingness to assume the roles of exemplars and health educators. In a 1963 letter to *The New England Journal of Medicine*, Gage (*23*) reported that the general staff of the Cooley Dickenson Hospital, Northampton, Massachusetts, had passed a resolution recommending that the sale of cigarettes in the hospital be stopped. The hospital trustees voted to deny their request, however, and agreed only to place signs which indicated the hazards of smoking. Nevertheless, there were hospitals even at that early date that were willing to ban the sale of cigarettes. Another 1963 letter (*28*) to *The New England Journal of Medicine* reported that the Emerson Hospital in Concord, Massachusetts, had banned the sale of cigarettes in December 1962 and had banned smoking by visitors earlier in the same year.

In 1973 the Connecticut Lung Association (*17*) carried out a statewide survey of hospital smoking policies. The findings are shown in Table 7.

A survey in 1972 of 222 nursing homes (*38*) reported that 2 percent had no restrictions on smoking by patients, 4 percent did not permit patients to smoke, and the remainder had some restrictions. Of those permitting smoking by patients, 68 percent did not permit smoking in

TABLE 7.—Smoking regulations reported by Connecticut hospitals in 1973

Type of regulation	1973 survey (Percent of 41 hospitals)
Written smoking policies	78
No tobacco products sold on premises	71
Visitor smoking regulated	71
Employee smoking at duty stations, offices, desks, prohibited	36.5

SOURCE: Davis, K.M. (*17*).

patients' rooms. The most frequent reason given for restricting patients' smoking was the danger of fire, and 2 percent of those that permitted smoking issued fire-resistant clothing to patients who smoked. Also, 18 percent of the institutions reported they had had fires caused by smoking. Finally, this survey reported that 7 percent did not permit visitors to smoke, and in 33 percent, employees were not allowed to smoke in front of the public.

A study of Canadian hospitals (*11*), reported in 1976, found that 66 percent had some form of smoking policy. Smoking was prohibited on 47 percent of psychiatric wards, 45 percent of maternity wards, 37 percent of general wards, and 60 percent of out-patient departments. Depending on the type of hospital, 85 to 90 percent of heart and chest wards prohibited smoking. In 63 percent of the hospitals, physicians and nurses on the wards were responsible for enforcing the smoking regulations; in 25 percent this was the fire marshal's responsibility. Fifty-six percent of the hospitals said the regulations were partially enforced. Forty-nine percent of the hospitals did not sell cigarettes.

In 1977, Crofton (*15*) reported that 36 percent of Scottish hospitals sold cigarettes in some way; 28 percent sold them on the wards through the ward trolley service, and in some cases the trolley service to maternity wards sold cigarettes.

Another study of Scottish hospitals (*16*) in 1977 found that they were more likely to ban smoking by visitors (67 percent) than by patients (12 percent) or nursing staff (44 percent).

In a 1976 survey of 37 hospitals in the Washington, D.C., metropolitan area to determine smoking policies of hospitals (*21*), 21 (57 percent) returned completed questionnaires. Nine of the twenty-one (43 percent) hospitals consistently provided for a nonsmoker's preference for a nonsmoking room; 10 hospitals did not sell cigarettes; and 17 hospitals did not permit staff to smoke in patients' rooms.

Sangster in 1967 (*59*) had reported that a no-smoking ward in an Australian repatriation general hospital was met with enthusiasm by patients and with cooperation by the staff. Of the first 100 patients

discharged from the ward, one-fourth said they had stopped smoking permanently and two staff members also stopped smoking.

Efforts to control smoking in health care settings are not always met with enthusiasm. A hospital that removed vending machines and prohibited the sale of cigarettes in the hospital gift shop shortly after publication of the 1964 Surgeon General's Report on the effects of smoking found that the work of hospital employees was interrupted by trips away from the hospital to buy cigarettes, for themselves and for patients (*60*). Some employees were also charging patients highly inflated prices for cigarettes. As a result, the hospital staff reconsidered their decision not to sell cigarettes.

A more recent study reports on a Massachusetts hospital (*74*) that attempted to influence established smokers to change to low "tar," low nicotine cigarettes by selling only those types. The hypothesis was that smoking behavior could be modified in a limited supply situation. Some employees did try the low "tar", low nicotine cigarettes, but there was no indication of any permanent change in their smoking habits. Many employees expressed resentment at this control of their smoking habits, although there was no indication that employees were leaving the hospital to purchase other types of cigarettes.

A number of specific recommendations have been made by health care providers for the control of smoking in health care settings. The National Forum on Office Management of Smoking Problems recommended formally in 1968 (*54*) that physicians in their offices should: inquire about the smoking habits of all patients; inform each patient about the risks involved in continued smoking and the benefits to be derived from stopping smoking; and advise strongly against smoking. It was also recommended that, to be maximally effective, physicians should actively assist smokers in efforts to stop smoking, create an office environment conducive to cessation, generally prohibit smoking in the office, and provide signs and literature on the subject to emphasize the medical concern. The same report recommended restricting smoking to certain areas of hospitals and prohibiting the sale of cigarettes. More encompassing recommendations were made by Fishman in connection with a survey of Metropolitan hospitals in Washington, D.C. (*21*).

Two lists of recommendations for the control of smoking by health care providers were presented in the 1978 report of the National Commission on Smoking and Public Policy to the Board of Directors of the American Cancer Society. One was prepared by the Veterans Administration (VA) and the second was the Commission's recommendations (*47*). The following are the VA guidelines:

(1) Forbid the distribution of free cigarettes to patients.

(2) Restrict cigarette sales in hospitals, clinics, and other direct care facilities to canteens or similar areas where other products are sold.

(3) Discourage smoking by professional personnel and staff in the presence of patients.
(4) Restrict smoking to specifically designated waiting areas, patients' day rooms, staff lounges, and private offices.
(5) Eliminate smoking among patients with high-risk diseases through aggressive and ongoing patient education.
(6) Encourage all personnel involved in public appearances not to smoke while in the public eye.
(7) Cooperate with community groups in the development and implementation of community-wide programs concerned with the hazards of smoking.

The Commission itself recommended that:
(1) Similar guidelines should be adopted by all government and private hospitals and clinics.
(2) The promotion of healthful lifestyles should be the core of preventive programs offered by physicians, health departments, health plans, and voluntary health associations.
(3) Physicians should counsel patients on the risks of smoking and how to quit smoking or make referrals to various types of smoking cessation programs offered in the community.
(4) Obstetricians, in particular, should take advantage of the "teachable moments" that arise when counseling pregnant patients; expectant mothers are eager to produce healthy infants, and smoking jeopardizes the chance of normal uncomplicated delivery and a normal healthy infant.
(5) State Medicaid programs, prepaid health plans, and insurance companies should either sponsor or pay the cost of smoking withdrawal methods of beneficiaries.

Conclusions

Most studies of health care providers have focused on health professionals (physicians, nurses, dentists, and pharmacists). Therefore, conclusions cannot be drawn regarding the role of others in health care occupations in influencing the smoking behavior of the public. Even for health professionals, there are no studies that quantify and evaluate their impact on smoking practices of the public. However, studies do indicate that the example set by health care providers plays some role in influencing the public, a role recognized by both health care providers and the public.

Health professionals as a group have preceded the general public in improving their smoking habits—they have stopped smoking, reduced health risks by smoking less hazardous forms of tobacco, or reduced the amount smoked. In addition, many who continue to smoke act as exemplars by not smoking when functioning as health care providers.

Health professionals, as a group, by and large recognize their responsibilities as health educators.

Perhaps the most important need at this time is to educate students in the health professions on the health hazards of smoking and their own responsibility to act as exemplars and health educators. As members of the medical hierarchy, their actions will continue to have an influence on others in the health field, as well as on the general public.

The Role of Health Care Providers: References

(1) AMERICAN PUBLIC HEALTH ASSOCIATION. Sixth Report on the Project to Develop a Program on the Smoking Exemplar Role of Public Health Professionals. January 1, 1973. Washington, D.C., American Public Health Association, 1973, 179 pp.

(2) ANDERSON, J. Medical students and smoking. British Medical Journal 4(5727): 120, October 10, 1970. (Letter)

(3) ATWATER, J.B., HEIL, K. A study of cigarette smoking among the American Public Health Association. Summary of Health Administration Section results. In: American Public Health Association. Sixth Report on the Project to Develop a Program on the Smoking Exemplar Role of Public Health Professionals. January 1, 1973. Attachment E. Washington, D.C., American Public Health Association, 1973, 3 pp.

(4) AXEL-LUTE, P. Legislation Regulating Smoking Areas: A Selective, Annotated Bibliography—June 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, December 1976, 23 pp.

(5) BALL, K. Medical students and smoking. British Medical Journal 4(731): 367, November 7, 1970. (Letter)

(6) BARIC, L., MACARTHUR, C., FISHER, C. Norms, attitudes and smoking behaviour amongst Manchester students. Health Education Journal 35(1): 142-150, 1976.

(7) BARIC, L., MACARTHUR, C., SHERWOOD, M. A study of health education aspects of smoking in pregnancy. International Journal of Health Education 19(2, Supplement): 1-17, April-June 1976.

(8) BOURKE, G.J., WILSON-DAVIS, K., THORNES, R.D. Smoking habits of the medical profession in the Republic of Ireland. American Journal of Public Health 62(4): 575-580, April 1972.

(9) BURGESS, A.M., JR., TIERNEY, J.T. Bias due to nonresponse in a mail survey of Rhode Island physicians' smoking habits—1968. New England Journal of Medicine 282(16): 908, April 16, 1970.

(10) BURGESS, A.M., JR., TIERNEY, J.T. Rhode Island physicians' smoking habits revisited 1963-1968. Rhode Island Medical Journal 52(8): 437-440, August 1969.

(11) CAMPBELL, D. Smoking policies in hospitals. Dimensions in Health Service 53(12):20-23, December 1976.

(12) CHRISTEN, A.G. The dentist's role in helping patients to stop smoking. Journal of the American Dental Association 81(5): 1146-1152, November 1970.

(13) COE, R.M., BREHM, H.P. Smoking habits of physicians and preventive care practices. HSMHA Health Reports 86(3): 217-221, March 1971.

(14) COMMITTEE ON YOUTH. A new approach to teen-age smoking. Pediatrics 57(4): 465-466, April 1976.

(15) CROFTON, E.C. The sale of cigarettes in Scottish hospitals. An ASH enquiry. Health Bulletin (Edinburgh) 35(1): 36-39, January 1977.

(16) CROFTON, E.C., HAWTHORNE, V.M., HEDLEY, A.J. Smoking in Scottish hospitals. An ASH survey. Health Bulletin (Edinburgh) 35(1): 29-36, January 1977.

(17) DAVIS, K.M. Connecticut works with health professionals. American Lung Association Bulletin 61(4): 14, May 1975.

(18) DOWDELL, W. Nonsmokers' revolt accelerates. Cancer News 27(2):2-4, Fall/Winter, 1973/74.

(19) EISINGER, R.A. Cigarette smoking and the pediatrician. Findings based on a national survey. Clinical Pediatrics 11(11): 645-647, November 1972.

(20) EYRES, S.J. Public health nursing section report of the 1972 APHA smoking survey. American Journal of Public Health 63(10): 846-852, October 1973.

(21) FISHMAN, L. More rights for airplane passengers than for hospital patients: A report on smoking policies in metropolitan Washington, D.C. hospitals. Washington, D.C., Public Citizen's Health Research Group, April 4, 1976, 21 pp.

(22) FULGHUM, J.E., GROOVER, M.E., JR., WILLIAMS, A.C., BRAATZ, W. Smoking habits of Florida physicians revisited. Journal Florida Medical Association 59(10): 23-28, October 1972.

(23) GAGE, R.W. Letter to the editor. New England Journal of Medicine 269(7): 378, August 15, 1963.

(24) GARFINKEL, L. Changes in cigarette smoking habits among physicians. 1959-1965. CA—A Cancer Journal for Clinicians 17: 193-195, 1967.

(25) GARFINKEL, L. Cigarette smoking among physicians and other health professionals, 1959-1972. CA—A Cancer Journal for Clinicians 26(6): 373-375, November/December 1976.

(26) GREENWALD, P., NELSON, D., GREENE, D. Smoking habits of physicians and their wives. New York State Journal of Medicine 71(17): 2096-2098, September 1, 1971.

(27) HERITY, B.A., BOURKE, G.J., WILSON-DAVIS, K. A study of the smoking habits of medical and non-medical university staff. Irish Medical Journal 69(7): 163-166, April 10, 1976.

(28) HOLMES, J. K. Smokeless hospitals. New England Journal of Medicine 269(7): 377-378, August 15, 1963. (Letter)

(29) KNOPF, A. The medical school and smoking. British Journal of Medical Education 9(1): 17-21, March 1975.

(30) KNOPF, A., WAKEFIELD, J. Effect of medical education on smoking behaviour. British Journal of Preventive and Social Medicine 28(4): 246-251, November 1974.

(31) LEVITT, E.E., DEWITT, K.N. A survey of smoking behavior and attitudes of Indiana physicians. Journal of the Indiana State Medical Association 63(4): 336-339, April 1970.

(32) LIPP, M.R., BENSON, S.G. Physician use of marijuana, alcohol, and tobacco. American Journal of Psychiatry 129(5): 612-616, November 1972.

(33) MATTHEWS, V.L., BOLARIA, R., FEATHER, J. Smoking behavior and attitudes among members of the Canadian Public Health Association. Saskatoon, Canada, University of Saskatchewan, College of Medicine, Department of Social and Preventive Medicine, April 1975, 70 pp.

(34) MAUSNER, J.S. Cigarette smoking among patients with respiratory disease. American Review of Respiratory Disease 102(5): 704-713, November 1970.

(35) MODERN MEDICINE. 1966 Survey results: Fewer doctors now smoke; patients often ignore advice. Modern Medicine 34(6): 14,18, March 14, 1966.

(36) MODERN MEDICINE. Sixty thousand answer MM smoking survey. Modern Medicine 32(5): 18,22,26,30, March 2, 1964.

(37) MODERN MEDICINE. 34,627 Physicians take part in smoking survey. Modern Medicine 38(26): 47,49, December 28, 1970.

(38) MODERN NURSING HOME. Administrators dislike smoking but permit it, survey shows. Modern Nursing Home 28(4): 15-16,20, April 1972.

(39) MONSON, R.R. Cigarette smoking by Massachusetts physicians—1968. New England Journal of Medicine 282(16): 906-908, April 16, 1970.

(40) MURPHY, T.H., TIERNEY, J.T. Current status of cigarette smoking among Rhode Island physicians. Rhode Island Medical Journal 46: 655-657, December 1963.

(41) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, DHEW Publication No. (HSM)73-8727, June 1973, 129 pp.

(42) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1976, 23 pp.

(43) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. State Legislation on Smoking and Health—1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, December 1975, 84 pp.

(44) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. State Legislation on Smoking and Health—1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, December 1976, 73 pp.

(45) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. State Legislation on Smoking and Health—1977. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, HEW Publication No. (CDC) 78-8331, January 1978, 79 pp.

(46) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Survey of Health Professionals: Smoking and Health, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. Bureau of Health Education, National Clearinghouse for Smoking and Health, June 1976, 42 pp.

(47) NATIONAL COMMISSION ON SMOKING AND PUBLIC POLICY. A National Dilemma: Cigarette Smoking or the Health of Americans. New York, American Cancer Society, Inc., January 31, 1978, pp. 61-62.

(48) NOLL, C.E. Health professionals and the problems of smoking and health. Report 2. Dentists' behavior, beliefs, and attitudes toward smoking and health. Report on NORC Survey 4001. Chicago, University of Chicago, National Opinion Research Center, November 1969, 11 pp.

(49) NOLL, C.E. Health professionals and the problems of smoking and health. Report 3. Physicians' behavior, beliefs, and attitudes toward smoking and health. Report on NORC Survey 4001. Chicago, University of Chicago, National Opinion Research Center, November 1969, 105 pp.

(50) NOLL, C.E. Health professionals and the problems of smoking and health. Report 4. Pharmacists' behavior, beliefs, and attitudes toward smoking and health. Report on NORC Survey 4001. Chicago, University of Chicago, National Opinion Research Center, November 1969, 105 pp.

(51) NOLL, C.E. Health professionals and the problems of smoking and health. Report 5. Nurses' behavior, beliefs, and attitudes toward smoking and health. Report on NORC Survey 4001. Chicago, University of Chicago, National Opinion Research Center, November 1969, 99 pp.

(52) PHILLIPS, A.J. The smoking habits of professional groups in Canada. In: UICC Technical Report Series, Volume 6. Public Education About Cancer. Recent Research and Current Programmes, 1969. Geneva, Union Internationale Contre le Cancer, 1970, pp. 34-37.

(53) PINCHERLE, G., WRIGHT, H.B. Smoking habits of business executives. Doctor variation in reducing cigarette consumption. Practitioner 205(1226): 209-212, August 1970.

(54) PROCEEDINGS OF THE NATIONAL FORUM ON OFFICE MANAGEMENT OF SMOKING PROBLEMS. Diseases of the Chest 54(3): 169-220, September 1968.

(55) PURVIS, J.M., SMITH, D.L. Smoking among medical students. Southern Medical Journal 69(4): 413-416, April 1976.

(56) RAVENHOLT, R.T. Work Group 8—Role of physician and other exemplars. In: First World Conference on Smoking and Health, September 11-13, 1967. New York, National Interagency Council on Smoking and Health, 1967, pp. 226-228.

(57) READ, C.R. The teenager looks at cigarette smoking. In: UICC Technical Report Series, Volume 6. Public Education About Cancer, Recent Research and Current Programmes, 1969. Geneva, Union International Contre le Cancer, 1970, pp. 97-104.

(58) ROSE, G., UDECHUKU, J.C. Cigarette smoking by hospital patients. British Journal of Preventive and Social Medicine 25(3): 160-161, August 1971.

(59) SANGSTER, J.F. A no-smoking ward. Lancet 2(519): 765-766, October 7, 1967.

(60) SCHNITZER, K. No smoking in the hospital. Surgeon's Management 2(4): 18-24, April 1967.

(61) SCHROEDER, S.A., SHOWSTACK, J.A. Merchandising cigarettes in pharmacies: A San Francisco survey. American Journal of Public Health 68(5): 494-495, May 1978.

(62) SNEGIREFF, L.S., LOMBARD, O.M. Survey of smoking habits of Massachusetts physicians. New England Journal of Medicine 250(24): 1042-1045, June 17, 1954.

(63) SNEGIREFF, L.S., LOMBARD, O.M. Smoking habits of Massachusetts physicians. Five-year follow-up study (1954-1959). New England Journal of Medicine 261(12): 603-604, September 17, 1959.

(64) STAMLER, J., SCHOENBERGER, J.A., LINDBERG, H.A., SHEKELLE, R., STOKER, J.M., EPSTEIN, M.B., DEBOER, L., STAMLER, R., RESTIVO, R., GRAY, D., CAIN, W. Detection of susceptibility to coronary disease. Bulletin of the New York Academy of Medicine 45(12): 1306-1325, December 1969.

(65) TATE, C.I., FULGHUM, J.E. Seventy percent of Florida physicians are nonsmokers. Journal of the Florida Medical Association 52(1): 47-48, January 1965.

(66) TOBACCO INTERNATIONAL. 8-point anti-smoking drive launched in UK. Tobacco International 129(9): 19-20, April 29, 1977.

(67) U.S. DEPARTMENT OF LABOR. Bureau of Labor Statistics, Occupational Outlook Handbook, 1978-79 Edition. Bureau of Labor Statistics, 1978, p. 447.

(68) VAILLANT, G.E., BRIGHTON, J.R., MCARTHUR, C. Physicians' use of mood altering drugs: A 20-year follow-up report. New England Journal of Medicine 282(7): 365-370, February 12, 1970.

(69) VLASSIS, T. Should pharmacists sell cigarettes? Iowa Pharmacist 24(9): 10,15, September 1969.

(70) WEITMAN, M., MEIGHAN, S.S. Smoking patterns and specialty training of Oregon physicians. Cancer 20(6): 974-982, June 1967.

(71) WESTLING-WIKSTRAND, H., MONK, M.A., THOMAS, C.B. Some characteristics related to the career status of women physicians. Johns Hopkins Medical Journal 127(5): 273-286, November 1970.

(72) WILHELMSEN, L., FAITH-ELL, P. New study on the smoking habits of Swedish physicians. UICC Technical Report Series. Volume 11. Public Education About Cancer, 1974. Geneva, Union Internationale Contre le Cancer, 1974, pp. 66-67.

(73) WILLIAMS, H.O. Routine advice against smoking. A chest clinic pilot study. Practitioner 202(211): 672-676, May 1969.

(74) WITTE, L.M. "I'd rather switch than quit." Mount Auburn Hospital, Cambridge, MA. Anti-smoking project final report. Hospital Topics 54: 28-32, May/June 1976.

(75) WORLD HEALTH ORGANIZATION. Survey on Smoking and Health in the European Region, 1974-75: Data as of 1 September 1975. Copenhagen, World Health Organization, Regional Office for Europe, Document H3/76/4, 1975, 72 pp.

23. THE ROLE OF EDUCATORS.

CONTENTS

LIST OF TABLES

The Status of Education About Smoking in U.S. Schools

Most States support education as a potentially important means of preventing smoking and influencing cessation of smoking, although results to date are not always highly satisfactory. A recent survey of State school health programs by the American School Health Association (ASHA) (*14a*) found that of all the various subject areas within health education, instruction on drugs, tobacco, and alcohol is most frequently required by State legislation. The ASHA report cites 35 States having mandated instruction with respect to tobacco. However, in a number of States with mandated health education, the specific subject areas to be taught may be selected by the individual school systems.

Some States have legislation offering their school districts the option of providing comprehensive health education programs, while other States have mandated many individual areas of health education, with the overall result resembling comprehensive programs. Especially during the past decade, there has been a trend toward mandatory health education instruction at the State level. Only three States appear not to have made provisions for any area of health education. In some cases, individual school districts may have legislation that takes precedence over State laws. In such instances provisions for instruction relating to smoking are generally included in the curriculum. Table 1 provides a synopsis of the present status of State education programs relating to drugs, tobacco, and alcohol in the United States. The table clearly indicates the current position that in most States instruction in the area of tobacco is mandated.

TABLE 1.—State school health education programs

State	*Drugs, Tobacco, Alcohol*
Alabama	No formal program at state level.
Alaska	Health education is not required; however, one unit of physical education is required for graduation of which one half unit may be health education.
Arizona	Optional/Permissive
Arkansas	Mandated
California	Mandated
Colorado	Mandated
Connecticut	Mandated
Delaware	Mandated
Florida	Mandated
Georgia	Mandated
Hawaii	Mandated

Idaho	Mandated
Illinois	Mandated
Indiana	Mandated
Iowa	Mandated
Kansas	Health education is not required; however, one unit of physical education is required for graduation of which one half unit may be health education.
Kentucky	
Louisiana	Mandated/Secondary School Level
Maine	Subject offerings are option of local school district.
Maryland	Mandated
Massachusetts	
Michigan	Mandated
Minnesota	Mandated
Mississippi	In grades 1–6, health instruction is required 30 minutes per day. At the junior and senior high school levels, health instruction is optional.
Missouri	Mandated
Montana	Mandated/Secondary School Level
Nebraska	Content selection is local school option.
Nevada	One half unit of health education is required for graduation.
New Hampshire	Mandated
New Jersey	Mandated/Secondary School Level
New Mexico	Mandated
New York	Mandated
North Carolina	Mandated
North Dakota	Mandated
Ohio	Mandated
Oklahoma	Although no separate program exists, health education content is taught in conjunction with other subject areas.
Oregon	
Pennsylvania	Mandated
Rhode Island	One hundred minutes of instruction in health and physical education per week is required for all students, K–12.
South Carolina	Mandated
South Dakota	No formal program at state level.
Tennessee	Mandated
Texas	Mandated
Utah	Mandated
Vermont	Mandated

Virginia	Mandated
Washington	Mandated
West Virginia	Instruction in physical and mental health is required at the junior high and high school levels.
Wisconsin	Mandated
Wyoming	Health education is taught according to local education mandates.
District of Columbia	Mandated

Unless otherwise noted, programs refer to both elementary and secondary levels.

SOURCE: American School Health Association. (*14a*).

The Development and Implementation of School Policies on Smoking

Laws and Regulations Affecting Smoking Practices

In 35 States, school policies on smoking education are based upon State laws that expressly prohibit minors from smoking on school property. Jacobs (*44*), in a review of the effects of State tobacco laws on high school student smoking throughout the United States, reports that most States have established the age of 18 as the demarcation point below which the individual is considered a minor insofar as tobacco laws are concerned. In those State statutes which indicate an age for attaining majority, the youngest age is 15. Four States make no reference to a specific age when using the term "minor" in their tobacco statutes.

To a large extent, differences in State laws appear to reflect the varying mixture of culture and tradition. Review of State tobacco laws for minors shows wide inconsistency throughout the nation. For example, 28 States penalize those who supply tobacco to minors. In 13 States, parental consent can render minors immune to tobacco laws, and two States waive penalties for minors if they divulge their sources. Four States that have repealed all tobacco laws concerning minors leave control in the hands of local governments. Thus a myriad of laws relate to the regulation of smoking practices of school age youth.

In addition to the diversity of State tobacco laws, penalties for both supplier and minor user vary widely. For a first offense in one State, the penalties may range from $1 for the user and $10 for the supplier to $1,000 and/or 1-year imprisonment for both supplier and user in another. Only two States have involved schools in their codes, establishing the penalty of suspension or expulsion for those minors who violate tobacco laws (*44*).

Thus, although most States have laws relating to the use of tobacco, the impact of these laws on behavior is generally believed to be negligible. The general availability of the product through machines that dispense it to any consumer, coupled with a cultural norm militating against enforcement, renders most laws inoperable and ineffective. Since most reported tobacco violations involving minors are referred to the juvenile courts, few court decisions deal with the use of tobacco by minors. In some communities, local fire ordinances set policy on smoking, leaving the school board without a role in decision-making on student smoking.

In the absence of such State laws and local ordinances regarding the school's legal position on smoking, Ivan Gluckman (*11*), attorney for the National Association of Secondary School Principals (NASSP), states that school boards have the legal authority to regulate smoking on school property. Much of the case law in this area emanates from the concept that school administrators have a broad degree of discretion and can prohibit smoking on the basis of concern for the health and safety of students.

In most school districts specific rules have been developed to prohibit smoking on school property. These rules are usually an outgrowth of local safety ordinances and policies by school administrators in cooperation with school boards. In recent years, a number of schools have initiated designated areas as smoking lounges. In his survey of high school principals, Jacobs (*44*) found that this approach (along with suspension and expulsion) was perceived to be an ineffective procedure for controlling high school smoking problems. Though upheld by some courts, the legality of this issue is extremely complex and can be expected to be tested in light of statutes regarding "contributing to the delinquency" by school administrators.

Specific regulations affecting teacher smoking practices in or on school property are generally considered within the domain of the local school administrator. Thus, there is no uniformity among or within States. The most common policy is to prohibit teacher smoking in other than specified locations such as teacher lunchrooms and lounges.

Policy Statements

A number of national organizations, including health and educational groups, have issued position statements on school smoking intended for the guidance of local policy-making officials. For example, NASSP suggests that intensive educational programs be initiated and that efforts be undertaken which will lead to the termination of student smoking (*60*). A position statement adopted in 1971 by the American Association for Health, Physical Education, and Recreation (AAHPER) (*5*) is forceful and unequivocating, noting that the research on smoking has made it abundantly clear that cigarette smoking is a health hazard. Therefore, the Association recommends that schools

adopt "no smoking policies" for all groups utilizing school facilities and that student and faculty smoking facilities be abolished. Like most health officials, Daniel Horn (*11*), former Director of the National Clearinghouse for Smoking and Health (NCSH),[1] is opposed to smoking in schools.

State Department of Education Policies

A number of State departments of education have developed their own policies. Among the leaders in this area are Oregon and Michigan. Oregon's policy recognizes that smoking is hazardous, that most public schools were not designed to accommodate a large number of smokers of any age, that the health, safety, and educational responsibilities of schools are factors to be considered in developing a tobacco policy, and that the rights of nonusers must also be weighed together with the rights of lawful users (*66*).

As expressed in the Oregon policy, "Those 18 years of age or older are allowed to use tobacco in accordance with the times and places designated by the school board. However, there is the further stipulation that students are liable for their habits to the extent that they may preclude their participation in other school activities" (*66*).

In Michigan, students who are 18 years old may legally purchase tobacco. However, schools are urged to discourage young people from taking up the habit. To this end, educational programs are to be developed which point out the dangers of smoking. In addition, Michigan laws prohibit smoking in the school building, on the school premises, or at school functions (*55*).

Institutional Climate and Its Influence on Smoking

While antismoking campaigns are credited with helping to reduce the number of adult smokers in the United States, surveys of youth smoking indicate a consistent pattern of increase over the past decade. This is especially true of teenage girls from ages 13 to 17. The rate of smoking by boys of this age group seems to have slowed and begun to level off (*61*). However, smoking in schools still represents a major problem to school officials. According to one State school administrator, the largest single discipline problem faced by public schools is student smoking (*11*). Despite the fact that most schools have rules against smoking in buildings, more and more students seem to ignore such prohibitions.

Historically, the institutional climate of the schools has been one of prohibition of student smoking on school property. In most school districts, this is the present policy. Thus the position of the schools is quite clear, but there is no evidence that this acts as a deterrent. To the

[1] Effective July 1978, all information functions of the National Clearinghouse for Smoking and Health were incorporated into the Office on Smoking and Health, Department of Health, Education, and Welfare, Rockville, Maryland.

contrary, some have maintained that such policies contribute to a greater incidence of youth smoking. In our society, smoking is a common, accepted behavior in most settings such as the home, work, or recreation. The school is one of the few institutions that prohibits this behavior. Complicating the issue is the fact that the prohibition of smoking on school grounds generally applies to only one population, the students. Others, faculty and staff, are allowed to smoke publicly in designated areas. Thus, the school as an institution is placed in a position contrary to other institutions in our society and in conflict with notions of equality. In addition, while the institutional policies of most schools regarding smoking are somewhat uniform, the individual behaviors of the teachers and staff of different schools are not. These differing behaviors may result in varying degrees of enforcement, which in turn may produce widely differing institutional climates even though controlling regulations seem similar.

Many school districts have attempted to address the role of their institutional climate and its influence on smoking. A review of the literature on school smoking points out the difficulties faced by the school administrator in attempting to solve the problem. Some have attempted to enforce strict policies against smoking via suspensions and expulsions. In an effort to develop realistic and workable policies, school officials are often placed in the position of having to compromise the larger purposes of education. While acknowledging that it is the school's responsibility to inform students about the hazards of smoking, school administrators are often faced with the realization that the prevention of student smoking is beyond their practical power to control (*60*). Because of the apparent ineffectiveness of antismoking policies and the difficulties of enforcement, or because of expediency, officials "accept reality" and permit smoking, usually out-of-doors or in some well-defined area, during the students' free time. This resigned acceptance on the part of the school administration is illustrated by the statement: "You either have to put up with smoking inside your building or outside your building. We'd rather have it outside" (*11*).

Horn summarizes the basic issue confronting the school regarding the smoking issue: "Does a school want to sanction smoking by permitting it, and thus say, 'We approve of your doing things that will harm your health'? Or does it want to say, 'We will not permit it. We will not help you do something that is not in your interest'?"(*11*). Although most schools which have adopted a limited smoking policy have done so out of expedience more than conviction, the result is a paradoxical one. Such schools include smoking education in their curriculum yet provide students with smoking areas. Although the trend has been for schools to become more permissive in their policies, the more recent emphasis on the rights of nonsmokers, the potential physical effects of passive smoking, and the increasing limitations placed on smoking in public places may result in a reversal of present

patterns. Few directly involved in smoking education efforts advocate overt or tacit approval of youth smoking by the schools.

In addition to formal policies, attention has been directed toward the impact of teachers as contributing factors in the institutional climate and their role in influencing student smoking. A consensus is that since much of what students learn is gained through observation, it is essential that school personnel serve as effective models for their students (*25*, *30*).

NASSP acknowledges the problem in their statement: "There is a general agreement that it is one thing to assume moral positions and another to implement those positions" (*60*). Adopting the policy of providing outdoor areas for student smoking has been justified on the grounds that students are going to smoke, and this solution at least protects the rights of the nonsmokers. One school reported that enforcement of the no-smoking rule in school lavatories required too much time and effort on the part of school faculty. However, it was also reported that the new school policy of permitting outdoor smoking called for a stricter enforcement of the rules against smoking in school buildings which in turn required increased faculty supervision (*31*).

School officials of the Niles Township High School, Skokie, Illinois, have a different solution to the problem of student smoking. The offender can choose either a 3-day suspension from school or a seminar composed of four 2-hour sessions on the effects of smoking. The seminar is conducted by two teachers at the school who use instructional materials provided by the American Heart Association, the American Cancer Society, and the American Lung Association. A follow-up survey was conducted of students who had participated in the seminars. The results showed that 12 percent of the students had stopped smoking and another 85 percent stated that they intended to cut down on their smoking (*35*).

Del Campo High School in Sacramento, California, employed an approach similar to that of the Niles Township High School. Students who were caught smoking were sent to a 5-day clinic conducted by the county medical society. This program was well-received by both students and adults and was judged a success (*11*).

Despite the fact that many U.S. high schools have come to accept some form of smoking in school, others are prohibiting smoking anywhere on school grounds. For example, Unified School District 457 in Garden City, Kansas, instituted a policy which banned all smoking on school grounds. This policy applies to students, teachers, and school board members. Students who violate this ban receive an automatic 5-day suspension from school. While enforcing this policy has caused some difficulty in the community, it appears to be working (*64*).

A novel and democratic approach to policy development has been employed by the Edina, Minnesota, school district. Instead of the school board alone establishing smoking policy, the district has sought the

active involvement of students, parents, teachers, school administrators, smokers, and nonsmokers. Individual community members were thus given the opportunity to help the school determine its policy on school smoking. Citizens were invited to select one of three different options or to make their own suggestions. The options included (1) continuation of the current school board policy of prohibiting student smoking; (2) not only continuation of the existing policy, but also the hiring of additional personnel to police or enforce the school smoking ban; or (3) designation of smoking areas for those students 18 years and older (*64*).

Teachers have the potential to influence the values and behaviors established by youth during the socialization process at school. Habits of lifelong duration are often acquired during the school years and are, in part, dependent upon the school environment. The attitudes and examples set by school personnel are factors which should be considered relevant to student smoking. Teachers gain or lose credibility depending, in part, on the consistency of their instruction and their behavior. Support for the potential influence of the teacher as an exemplar model has been observed by Creswell, et al. (*22*), Chen and Rakip (*17*), Mettlin (*54*), and Downey and O'Rourke (*26*). A study by Newman (*65*) attempted to determine how elementary and secondary teachers view their own behavior, their awareness of the smoking problem, and whether they would make changes if they believed it would favorably influence their students. Results showed that teachers were mindful of their responsibilities and were willing to restrict smoking as an example to students; they were also more likely to report a smoking student if they were smokers themselves; and by a 5:1 ratio, they believed that teachers should not smoke where smoking by students is prohibited. Newman concluded that teachers display a readiness to assume their exemplar role in smoking education.

In summary, the institutional climate is considered an important factor influencing youth smoking. While peers and parents have been shown to be more potent as influencing agents, the important role of the school environment cannot be minimized. According to the Office on Smoking and Health, the general climate of acceptability of smoking is probably one of the strongest influences in making smoking attractive to children. There appears to be a consensus that, faced with the significant counterforces of advertising and the smoking practices of parents, other adults, peers, and other people youth admire, reduction of youth smoking cannot be achieved by the schools alone (*18, 39, 47, 81*).

Responsibilities for Education About Smoking

Much of the teaching in today's schools about the effects of tobacco on the body had its origins with the Scientific Temperance Movement in the late 1800's. The Women's Christian Temperance Union (WCTU) led

a highly successful crusade which resulted in the passing of legislation requiring the teaching about the effects of alcohol, tobacco, and narcotics. During the 1880's and 1890's, 38 States and Territories passed laws requiring the teaching of physiology and hygiene. Every State passed laws requiring instruction on the effects of alcohol and narcotics. Many of these same laws also required instruction about tobacco and the effects of smoking.

In general, schools combined the instruction about specific topics of alcohol, tobacco, and narcotics with the broader subject of physiology and hygiene. Despite the success of the WCTU effort in securing the widespread adoption of its legislative proposals, however, the movement was never considered to be effective in terms of achieving a successful program of instruction. It has been characterized as the moralizing and preaching of zeal and negation, with the subject matter frequently containing inaccuracies, myths, and facts that were inappropriate to the age group being taught (*52*).

Contemporary School Programs

In many of today's schools, yesteryear's instruction in physiology and hygiene has led to acceptance in concept and, to a lesser degree, implementation of a comprehensive program of health instruction. In theory, this type of curriculum is designed to reach all students at their various levels of educational development with appropriately graded activities and materials. Teaching about the effects of cigarette smoking is planned as a part of many health instruction programs.

As a result of the curriculum reform movement of the early 1960's and the issuance of the 1964 Surgeon General's Report on Smoking and Health, schools have shown renewed interest in the area of health education and smoking education. School officials' awareness of their responsibilities for smoking education can often be traced to activities of voluntary health agencies such as the cancer, heart, and lung associations and to the extensive work with schools sponsored by the NCSH (now the Office on Smoking and Health).

Recognition of School Responsibility

Stressing the importance of the school's responsibility for education in regard to smoking, NASSP (*60*) has noted the implications to be drawn from establishing school smoking lounges: Such an action "may well implicitly promote smoking in the public schools." In lieu of approving school smoking, NASSP suggests that an intensive educational program be designed and instituted to prevent or terminate smoking among school-age students.

AAHPER urges all schools to take appropriate action to establish policies that are consistent with current information on the hazards of cigarette smoking. Specifically, AAHPER recommends that schools assume "responsibility for curriculum experiences in smoking educa-

tion which are timely and stimulating and provide accurate content, as an integral part of the ongoing, unified health instruction program, kindergarten through the twelfth grade" (*4*).

School codes and regulations have been adopted by State and local school agencies acknowledging the school's obligation to provide smoking education. In Massachusetts, the school code specifies that students be taught the adverse effects of smoking. In establishing its policy governing smoking on school grounds, the local school district of Montgomery County, Maryland, recognized its educational responsibilities by calling for "a forceful, meaningful program of education highlighting the hazardous effects of smoking." The program as adopted provides instruction for students commencing in the upper elementary grades and continuing through the senior high school (*64*).

In 1974, Jacobs (*44*), using a random sample of high school principals drawn from throughout the United States, conducted a mail-questionnaire study, "Effects of State Tobacco Laws on High School Student Smoking." Questions were directed to the principals on a number of key points relating to the school smoking issue. In response to the question, "What is the situation with regard to student smoking at your school?," 49 percent of the principals responding said that the problem was increasing, 29.4 percent reported no change, and 21.6 percent stated that the problem was declining.

If students are permitted to smoke, it is clear that principals would prefer that they either smoke in an outdoor area (48.8 percent) or that they smoke off-campus (34.8 percent). Only a small minority of principals would have students smoke in a designated area of the school building (11.6 percent). Two questions asked in this survey bear directly on the school's role in smoking education. In reply to the question, "Do schools have a responsibility for discouraging smoking?" 65.3 percent of the principals said yes, 20.5 percent said no, and 14.3 percent were uncertain about this role.

When principals were asked to select the most effective procedure for controlling smoking in schools, an educational program was the choice by a clear majority (49.5 percent), with school athletic events identified (14.5 percent) as another procedure to help control school smoking. Less than 1 percent of the principals selected supervision as a measure for controlling the problem.

School and Community Agencies: Cooperation, Delineation of Responsibilities, Use of Available Resources

School and community agencies are involved in efforts aimed at the prevention and cessation of smoking. School programs by their very nature are focused upon the youth population generally through planned instructional intervention incorporated into the health curriculum. The major emphasis of the school program is on prevention. A lesser but emerging effort is also being developed on cessation of youth

smoking. On the other hand, community agencies concerned with smoking and health issues often direct their educational programs at the entire age range, with youth an important component in their total efforts.

Community agency involvement is most frequently evident in mass media programs, antismoking education curricula, and smoking-cessation programs aimed primarily at the adult population. Less evident are instances where community agencies develop and conduct youth programs. Such instruction is generally perceived as a function of the schools. This, however, does not imply a strict dichotomy. Often, schools utilize materials developed by community agencies or consult with agency personnel in an attempt to improve instruction. Yet, a review of related literature shows that most youth antismoking programs do not involve a direct school-community agency type of partnership. It is possible that on a local level varying degrees of cooperation occur, but such efforts are not commonly cited. One recent program that has attempted to involve both school and community health agencies directly is the School Health Curriculum Project (Berkeley Project) developed by NCSH (*24*) which is examined in greater detail in another section. Besides providing much of the materials used, voluntary health- and education-related organizations have played an active role through their local community agencies with respect to the Health Curriculum. This type of direct involvement by school, community, and health agencies is now being incorporated in numerous school districts throughout the country. The approach seems to be an operational model reflecting the consensus of those in the area of smoking education that the problems of youth smoking must be confronted through a cooperative community effort involving school and community officials and voluntary health agencies. Such programs involving active and direct working relationships should be encouraged and promoted. The alternative would be a fragmented and less effective approach to the prevention and cessation of youth smoking.

Curriculum

Requirements in Elementary and Secondary Schools

By State law, instruction in the areas of alcohol, tobacco, and drugs is mandated in at least 35 States with the tendency to incorporate such programs in States currently without such a requirement (*14a*). For example, a 1977 New York State law requires that all schools include instruction to discourage misuse of alcohol, tobacco, and other drugs. Mandated instruction is usually required at both the elementary and secondary levels. Even in States without mandated programs, the inclusion of some degree of instruction about tobacco is commonplace at some point along the continuum from kindergarten through 12th grade.

Whereas requirements about smoking education are generally mandated, the amount of instruction actually occurring at one or more periods of the K-12 cycle varies greatly. Most States leave the decisions of implementation, such as time devoted to a given area, up to the teachers. Thus, individual teachers decide how much time and resources are to be devoted to education about tobacco and health.

It should also be realized that tobacco education is but one of the many areas included in school health programs and that such programs are limited during the K-12 cycle. The actual time devoted to this specific area would appear to be minimal. The extent to which mandated programs that include tobacco education are actually conducted is currently unknown.

Development of Curriculum Procedures

The term "curriculum" as employed by specialists in the field usually means either (1) an educational plan for the learner, or (2) a field of study. In relating a curriculum to smoking education, it is helpful to consider some general principles that have derived from work done in the field of curriculum study and the application of such knowledge to the specific "plan for action" or "plan which guides instruction" (*92*) in the field of smoking education.

Curriculum Foundations

Most curriculum specialists agree that the determinants or foundations of a curriculum would include some, if not all, of the following areas:

1. *Philosophy and the Nature of Knowledge:* Basic assumptions about the nature of knowledge and the philosophy which guides beliefs about knowledge have particular relevance to the formulation of the curriculum (*92*).
2. *Society and Culture:* The school is the institution invented by society to transmit the cultural heritage and to assure its survival. Societal values, assumptions, and concepts of good and bad are translated into the curriculum objectives and learning activities.
3. *The Individual:* The nature of humankind, its biological and psychological characteristics, needs, and capacity to learn have placed certain limits on the curriculum, such as the content included, the organization of the curriculum, and the types of learning activities selected.
4. *Theory of Learning:* While some elements of learning theory enjoy wide acceptance, much difference of opinion exists. Obviously, a particular theory of learning embraced by the curriculum developer will exert marked influence upon the design. For example, Dewey's well-known theory of "learning by doing" has been applied directly to certain types of learning activity. The theory of learning and the importance environment places upon learning have serious implications for the contemporary curriculum developer.

Planning the Curriculum

Tyler, in Schaffarzick and Hampson (*78*), stresses the importance of conducting a careful preliminary analysis of the curriculum in order to determine clearly the needs to be met. All too often, curriculum projects are developed without first making a systematic analysis of the problem. Such an analysis may call for extensive work with the local community, parents, peer groups, and school officials. If the curriculum to be developed is to be accepted and used by the teachers, special efforts must be made to seek their active involvement and to give careful consideration to their needs.

Curriculum Construction

In his extensive work in curriculum development, Tyler, in Schaffarzick and Hampson (*78*), has developed a series of steps to be followed:

1. *Selecting and Defining the Objectives:* Curriculum developers must resist the temptation to write their own objectives and must, instead, involve many different groups in the selection process, seeking group deliberation and judgments. Involvement of teachers is essential to their ultimate commitment to the curriculum. Subject matter specialists, curriculum specialists, psychologists, sociologists, and specialists in human development all offer judgments in this area. The level of generality for objectives must be considered; objectives that are too general are nonfunctional, and overly specific objectives are burdensome.

2. *Developing a Philosophy or Point of View:* The theory of learning which is adopted influences the philosophy or point of view of the curriculum developer.

3. *Selecting and Creating Learning Experiences:* The purpose of the learning experience is to meet the curriculum objective, i.e., to perform and to practice the behavior called for in the objective. Appropriate learning activities will invite the attention and interest of the learner and provide satisfaction. Such activities, which can be carried out alone or with peer groups, should be balanced.

4. *Organizing Learning Experiences:* The learning activities should provide maximum impact on the learner. They should be sequenced to build relationships, so that the student's learning builds from one activity to the next.

5. *Curriculum Evaluation:* Evaluation of the curriculum involves determining: (a) the effectiveness of the curriculum approach in its development stage; (b) whether school teachers can, in fact, use the curriculum at the point of implementation; (c) how effective the curriculum is in its operational stage; and (d) the extent to which students have achieved the objectives selected for the curriculum.

Some Pitfalls of Curriculum Implementation

Experience gained through implementation of the many curriculum projects developed during the 1960's indicated some shortcomings. In some cases, teachers were not sufficiently involved in the curriculum planning or writing process. Quite frequently, funding was lacking to train the teacher in the use of the new curriculum.

Two other difficulties have also been identified: (1) the failure to provide for the dissemination of the newly developed curriculum, and (2) confusion over the term "experimental" with reference to new curricula. Hampson, in Schaffarzick and Hampson (*78*), contends that a true experimental design is not suitable for the school setting. The procedure commonly employed in experimental studies of varying the curriculum and of using control groups raises serious political if not moral questions for the curriculum developer. Instead, Hampson suggests that the curriculum developer consider alternative ways of collecting data by using a method of systematic observation over time, such as that employed by the astronomer, and by using in-depth clinical studies.

Opportunities for Smoking Education

The comprehensive health education curriculum has traditionally included the topic of tobacco and its effects on human health. This curriculum, as it has been viewed and widely advocated by professional groups, is designed as a program of health learning experiences beginning at the kindergarten level and continuing through senior high school. The curriculum is considered comprehensive in that it is designed to cover the full range of the subject matter of human health.

A nationwide project, the School Health Education Study (SHES), emerged from the curriculum reform movement of the 1960's. This study, with its conceptual approach to curriculum design, gave renewed emphasis to the comprehensive curriculum plan. One of the 10 major concepts providing the structure of the SHES curriculum involves the study of tobacco, the effects of smoking, and the motivations for smoking. In several other areas of this curriculum, the hazards of smoking are integrated into the conceptual network of the curriculum structure (*80*).

Following closely on the curriculum reform movement, several States enacted legislation calling for comprehensive health education curriculum programs. New York was the first, in 1967, to enact a law requiring a statewide program of health education to be implemented at all levels of instruction. A syllabus developed by the State Department of Education incorporated a five-strand format that included the following elements: physical health, sociological health, mental health, environmental and community health, and education for survival. Tobacco, alcohol, and drugs are included as topics in the sociological health strands. Smoking and health are taught at the

upper elementary grades and at junior and senior high school levels (*48*).

In 1972, the California State Department of Education published *Framework for Health Instruction*, a comprehensive instructional plan for kindergarten through the 12th grade. The curriculum includes 10 major content areas that are sequentially organized according to conceptual structure. The topic of tobacco receives emphasis at the junior high school level (*29*).

A scope and sequence chart developed by Willgoose (*90*) shown in Table 2 is representative of the comprehensive curriculum plans discussed in this section. The assumption is that a school antismoking program has its greatest positive impact on students when it is presented on a systematic schedule, according to a planned progression of expanded and reinforced activities for the student, as depicted in this table.

In contrast to the comprehensive approach to curriculum development, a number of voluntary, commercial, and governmental agencies have developed a great many materials designed to assist and encourage schools to teach about a variety of special or categorical disease problems. For example, curriculum units have been written for schools on such topics as alcohol, drugs, smoking, venereal disease, nutrition, cancer, and heart and lung disease.

Still another approach to curriculum development, initially encouraged by NCSH through the School Health Curriculum Project (SHCP) (*23,24*), is now being continued by the Bureau of Health Education, Center for Disease Control, in Atlanta, Georgia. This curriculum is designed for the elementary and middle school grades, and while it is not comprehensive, it is a broad-based program of health instruction. Curriculum units are organized around the study of body systems which are presented in sequence with a unit for each grade level. Instruction about smoking and health is integrated throughout this curriculum.

Among the more recent curriculum developments in health education and smoking are programs designed to instruct students about the cardiovascular system and the several risk factors related to cardiovascular disease. Some of these materials have been designed for self-instruction or programed learning in order to alleviate the problem of training teachers and finding class time for instruction in the school day. An example of this approach is provided by the Cardiovascular Curriculum Education Project (CCEP) (*89*), sponsored by the National Heart and Blood Vessel Research and Demonstration Center (NRDC) at the Baylor College of Medicine in Waco, Texas.

TABLE 2.—A scope and sequence chart for a comprehensive health education curriculum

Suggested topics	Grade emphasis			
	K–3	4–6	Junior high	Senior high
Personal cleanliness and appearance	X	X	Omit	Omit
Physical activity, sleep, rest, and relaxation	X	X	X	Omit
Nutrition and growth	X	X	X	Omit
Dental health	X	X	X	Omit
Body structure and operation (including the senses and skin)	X	X	X	Omit
Prevention and control of disease	X	X	X	Omit
Safety and first aid	X	X	X	Omit
Mental health	X	X	X	X
Sex and family living education	X	X	X	X
Environmental and community health	X	X	X	X
Alcohol, drugs, and tobacco	Omit	X	X	X
Consumer health	Omit	X	X	X
World health	Omit	Omit	Omit	X
Health careers	Omit	Omit	X	X

SOURCE: Willgoose, C.E. (*90*).

Application of Curriculum Procedures to Smoking Education—Evaluative Comments

To what extent have the aforementioned principles of curriculum development been applied to smoking education curriculum projects? The comprehensive curriculum projects appear to have applied many of these principles successfully. The content materials reflect an awareness of individual and societal health needs and in most cases reflect a careful and detailed organization of an extensive subject-matter base. However, with the possible exception of SHES, little attention appears to have been given to a theory of learning that would characterize the approach being taken by a particular project. Weaknesses are evident in the areas of evaluation and in-service training of teachers in the use of the materials. Evaluation efforts have been confined largely to the acknowledgement of overall

achievement. Exceptions would be SHES and the New York State curriculum, which were developed with complete sets of curriculum materials and guides for use at all grade levels.

A serious problem is the lack of resources to develop and implement comprehensive curriculum programs. Several States have mandated a comprehensive curriculum without providing the funds needed to carry the project through to a satisfactory conclusion. The extensive in-service education program for the teachers of New York State, supported by the New York State Department of Education, is noteworthy. The health education curriculum developed and implemented in Florida is another example of the effective application of curriculum-development principles.

With regard to the curriculum materials by nonschool agencies on special topics or categorical disease problems, a difficulty arises in the application of the usual procedures to the principles of curriculum development. Much of this material is of excellent quality and technically accurate with regard to the particular problem under study. The difficulty is in applying it to the school situation. The teacher may not be adequately prepared to use the material effectively, or it may be inappropriate for the level at which it is being used. Little opportunity is available for tryout and revision of the material. The most serious difficulty encountered in using special categorical-problem material is determining an effective context in which to relate the special materials to the ongoing curriculum in order to assure an effective learning experience for the student.

These problems can be solved, however, as evidenced by the SHCP (Berkeley Model) curriculum. Designed for the elementary and middle school grades, it has been school-based from the outset and has been extensively tested and used by schools throughout the United States. The careful training of teachers to enable them to follow the curriculum plan precisely, the variety of learning activities and resource materials, and the extensive involvement of students in the learning process are obvious strengths of this program (*23*).

The fact that the project is so process-oriented may prove to be the most serious problem in disseminating the model. As the project has developed, all teacher-training for use of the program has been confined to the project staff. As a consequence, the curriculum has never been incorporated into the formal programs of preservice teacher preparation in higher education. In addition, original published materials describing the program are lacking; most of the materials used successfully in the curriculum are drawn from existing publications by careful selection and adaptation.

CCEP, representing a categorical disease interest, is considerably broader in scope than many such programs. As reported by White, et al. (*89*), this program is presently being taught as part of the secondary school health education program in Texas. The curriculum, covering

the cardiovascular system, cardiovascular disease, and associated risk factors, involves approximately 4 weeks of class time at each of the four senior high school grade levels. It has been designed as a programed self-instruction learning guide to supplement teacher instruction in the classroom.

At this point, relatively little has been reported about the effectiveness of this curriculum. However, as noted by White and associates, teachers have rated the materials above-average to excellent. Despite the effort to provide schools with "ready-for-use" self-instruction materials, a survey of teachers indicates that they are clearly in need of in-service training on how to use the CCEP units (*89*).

Development of Demonstration Projects and Identification of Successful Programs

Particularly in the past decade, a number of promising approaches have been developed to prevent youth from smoking. In this section several innovative approaches are identified. Other projects and programs are presented in the following section, which focuses on the evaluation of educational programs designed to prevent smoking. The information presented reflects a sample of the current literature devoted to these areas.

Assuming that the cigarette smoking habit is a health hazard of sufficient gravity that youth should be encouraged to resist the pressure to smoke, Irwin (*42*) developed a five-lesson unit on smoking education for seventh-graders. Three different approaches were used: (1) the individual approach, (2) the peer-led approach, and (3) the teacher-led approach. Teacher preparation was also tested; that is, a regular classroom teacher was contrasted with one trained in smoking education. A total of 575 seventh-grade students participated. Results indicated the individual study approach provided the most favorable changes.

The School Health Curriculum Project (SHCP) is another promising educational approach. SHCP is based on the concept that the best way to reduce smoking-related disease to a minimum is to develop broad-based, primary prevention education that leads one to decide with understanding and conviction not to begin smoking (*24*). The curriculum objectives, teaching methods, learning materials and resources, and pupil activities are organized around the following aspects of the human body: what a wonder it is, how it works, the nature and function of its various parts, what it needs and can do without, what can happen to it, how individual and community choices and the environment affect it, how its problems and diseases can be prevented, and what can be done about them when they do arise. The curriculum is further organized around body systems at different grade levels. Smoking in all of its ramifications is carefully integrated into the

curriculum project. School administrators, nurses, health educators, and other basic curriculum specialists who work with teachers are trained as a team. After intensive training, the teams return to their work setting to develop the model curriculum in two classrooms at their own grade levels. Recognizing the importance of family health practices, the need for parent reinforcement of that which the school curriculum seeks to teach, and the potential of carrying on adult education through children, the model curriculum has many activities specifically designed to involve parents. This project is constantly being evaluated and is currently being incorporated into school curricula throughout the country and abroad (*1*, *74*, *75*).

Evaluation of Educational Programs Designed to Prevent Smoking

As previously mentioned, most States have mandated instruction with respect to tobacco. Even in States lacking mandated instruction, programs designed to prevent youth smoking are commonplace. The literature abounds with information relating to specific educational efforts and curricula concerned with the development of objectives, methods and materials, intended outcomes, and teacher training. Generally, the resulting curricula have focused on the development of knowledge about the effects of smoking, creating a greater self awareness of the body structures and functions, altering or reinforcing smoking attitudes, the initiation and continuation of a nonsmoking behavior, or the cessation of an existing smoking habit. However, while the literature is replete with examples of educational programs, evaluative results on their effectiveness are much less obvious. More often than not such programs are merely assumed to be effective. When evaluation is conducted, it is generally limited to assessing effectiveness in the cognitive and affective domains. Less frequent are evaluative studies of educational programs relating to behavioral outcomes and, in particular, measures of long-term effectiveness. Evaluations of programs using retrospective and prospective designs are infrequent. The absence of control groups or studies involving assessment of the interaction between teacher and method is evident (*68*). Even when evaluative efforts demonstrate the inherent success of a program, replication rarely occurs.

Another difficulty that limits generalizations from assessments of educational programs to prevent smoking is the lack of uniformity in classifying behavioral groups. That is, different rates of smoking behavior between studies may be due in part to the utilization of dissimilar criteria. The principal difficulty in making meaningful comparisons of study results is the lack of a standard definition of the smoker. To illustrate this problem, the definitions employed in youth smoking research include the following: Sallack's study (*77*) of junior

and senior high school students in Erie County, New York, identified a smoker as a person who has smoked at least five packages of cigarettes. Haynes, et al. (*34*) defined a smoker as one who has smoked at least one cigarette a day. Salber, et al. (*76*), in their study of high school students in Newton, Massachusetts, defined a smoker as one who had smoked at least 10 cigarettes or was personally described as a smoker at the time of the survey.

Obviously, attention should be directed to developing a standard glossary that precisely defines a particular behavior. Also, researchers should specify their operational definitions when discussing their findings. Because of difficulties in these areas, NCSH (now the Office on Smoking and Health) has encouraged the use of a common definition of a smoker in investigations conducted in the United States (*86*). For example, a current regular smoker is defined as one who reports smoking one or more cigarettes per week or one or more cigarettes per day. A current occasional smoker is one who reports smoking regularly but who smokes less than one cigarette per week. An experimenter is one who has smoked at least 1 cigarette, even if only for a few puffs, but who has smoked less than 100 cigarettes in his or her life.

The result of the above-mentioned limitations is that education programs generally reflect a fragmented, shotgun approach to the prevention of smoking by youth. In 1967, Davis summed up in these words the state of affairs at that time: "It can't be overstressed that general or shotgun approaches have got as much effect as indiscriminately relying on aspirin as the treatment for every person entering a doctor's office. Yet, in many regards this is similar to what we do in our smoking and other health teaching" (*32*). Nearly a decade later, he repeated this same theme at the Third World Conference on Smoking and Health (*24*).

Despite present limitations, a review of the literature indicates a broad range of experimentation with educational programs. Approaches include traditional methods, such as lectures or group discussions, as well as techniques like emotional role playing.

A useful method of categorizing programs designed for youth has been developed by Thompson (*84*). He classified programs into four general, but not mutually exclusive, categories: schoolwide antismoking campaigns, youth-to-youth programs, comparisons of teaching methods, and studies of the relative effectiveness of various message themes. Following are brief discussions summarizing the results of projects grouped by category.

Schoolwide Campaigns

Schoolwide antismoking campaigns have generally been found to be ineffective in changing smoking behavior (*28, 36, 45, 56, 58, 72*). A variety of techniques have been used, including lectures, discussions,

rap sessions, demonstrations, and assemblies. Frequently, mass media approaches, including pamphlets, films, posters, and information in school newspapers, have been attempted. While there is some support for such programs with respect to attitudes and behavior concerning smoking (*27, 28*), most of them have failed to assess or demonstrate any significant effect upon smoking behavior.

Youth-to-Youth Programs

A commonly used approach in youth antismoking programs is one in which older students, usually at the junior or senior high school level, conduct activities designed for students at a lower grade (*8, 9, 14, 15, 37, 41, 46, 51, 71*). Generally, evaluative results of the effectiveness of these programs are not included in the literature describing them.

One youth-to-youth program that included an evaluative component and has reported results is the Saskatoon study (*46, 70, 71*). This student-directed program on smoking education was initiated in the fall of 1968 in 39 schools of the Saskatoon Rural Health Region. Two major objectives were to obtain information on the smoking behavior of 7th- to 12th-grade students and to assess the effectiveness of peer group involvement in smoking education programs that were developed by the students. Emphasis was placed on the healthful aspects of nonsmoking rather than the harmful effects of smoking. Eighth-grade students attended a regional seminar on smoking and health and were encouraged to plan projects on smoking education in their schools. After the 2-year study period, no significant difference was noted between the smoking habits of the students who were exposed to the student-directed educational program and those who were not.

Teaching Methods

Studies in this area generally focus upon the relative effectiveness of one method compared with another (*19–22, 40, 42, 53, 88*). Most of them include a pre/post test design, but few include a control group. Effectiveness is most commonly assessed in the cognitive or affective domains. Less frequently assessed is the effectiveness of varying methods upon smoking behavior. When this component is evaluated, the amount of positive behavioral change is found to be relatively minor.

Prior reference was made to Irwin (*43*), who compared the effectiveness of teacher-led, peer-led, and independent study approaches upon students' attitudes, beliefs, and knowledge of smoking. In the individual approach, the educational effect depended on the student's own study and interpretation of the curricular materials, and any teacher contact had to be student-initiated. Students assigned to the peer-led approach studied the same materials, but presumably were also affected by the class discussion with their peers. The teacher-led approach had the combined effect of the materials, individual

study, peer-group discussion and the teacher's skill in an attempt to achieve the maximum educational effect. Results indicated that students taught by the individual study approach showed more favorable changes than did students instructed by either the teacher-led or peer-led methods.

In another study concerning the effectiveness of three methods of teaching about smoking, Crawford (*19, 20*) found that neither the committed approach (teacher said that she felt smoking was undesirable) nor the neutral approach (effects of smoking were related to other topics in the five short incidents during the semester) were associated with behavioral change. The committed approach was found most effective with regard to increased knowledge while the neutral method was determined to be least effective.

Watson (*88*) reported mixed findings in a study on the effectiveness of four teaching methods upon student knowledge, attitudes, and behavior. The four techniques were a didactic approach, group discussion, psychological persuasion, and a combination of all three approaches. Behavior was most affected by the didactic approach, attitudes most by the psychological persuasion technique, and knowledge by the combination method. In all instances, the group discussion method was found to be the next most effective and was considered overall to be the most promising technique.

Several studies have compared the effectiveness of three approaches: presenting both sides of an issue, encouraging students to assume adult roles, or presenting all educational material in an authoritarian manner. Conflicting results from these three approaches have been noted. Horn (*40*), in a study of Portland youth, found the two-sided approach most effective. Neither of the other techniques resulted in a greater degree of behavioral change than in the control group. In a replication study involving Illinois youth, part of a larger University of Illinois Antismoking Education Study (UIAES), Creswell, et al. (*21, 22*) reported the adult-role method most effective and the two-sided approach least effective.

In another aspect of UIAES, Merki, et al. (*53*) found no significant differences in changing smoking behavior between a mass-media and a student-centered approach at the 11th grade level. Both methods were found equally effective in changing behavior at the 8th grade level. Also at that level, the student-centered approach resulted in a significantly more desirable change in smoking attitudes.

Message Themes

As in other types of programs previously mentioned, the evaluation of various message themes has generally shown that such programs have little effect on smoking (*45, 49, 73*). One of the most commonly used themes is the health hazards of smoking. Although some programs using this theme have resulted in significant changes in knowledge and

attitude generally (*67, 69, 73*), no effectiveness has been demonstrated with respect to smoking behavior. In fact, one program reported an increase in smoking (*7*).

Also, studies comparing the effectiveness of immediate short-term versus remote or long-term effects have failed to produce consistent results. Horn (*40*) found the remote theme more effective in reducing smoking among boys. For girls, both methods appeared equally effective in changing behavior. In the University of Illinois study, Creswell, et al. (*21, 22*) found the contemporary theme more effective, while Merki, et al. (*53*) reported both themes equally effective.

In summary, a variety of educational approaches involving both mass media and instructional methods have been implemented and evaluated. Results most frequently indicate a lack of measurable effectiveness. When effectiveness is demonstrated, replication often fails to support a given approach. Inconsistency of findings is commonplace. Thus, in terms of effectiveness, educators have relatively few tested models to channel their efforts. This state of affairs dramatizes the necessity of program evaluation research in this area. For those concerned and involved in preventing or reducing the smoking habits of youth and adults, Dr. Luther Terry, former Surgeon General of the United States, offered sage advice. In concluding the World Conference on Smoking and Health, Dr. Terry commented: "This is our job, to educate people. I don't think it will take us a hundred years, but it will take much more time, much more effort, and much more imagination than we have exercised thus far" (*91*).

Dissemination and Promotion of Successful Practices and Products

A broad range of publications exists for the dissemination of information relating to successful program practices and products concerning education to prevent youth smoking. These publications generally take the form of professional journals or abstracts of current literature. One of the most useful of all sources is the abstracts of current literature published by the Office on Smoking and Health. Their *Smoking and Health Bulletin* is published approximately every 6 weeks and is printed annually with a cumulative author and subject index as the *Bibliography on Smoking and Health* (*62, 63*). All items cited are part of the permanent holdings of the Office on Smoking and Health and are maintained in its Technical Information Center (TIC). The technical collection presently consists of over 26,000 documents. One of the major areas covered in these abstracts is behavioral and educational research related to smoking. TIC also provides bibliographic and reference services to researchers and others and publishes and distributes a number of titles in the field of smoking. Through its Automated Search and Retrieval System, containing over 10,000

citations, TIC has computer capability to generate comprehensive bibliographic print-outs on many topics of current interest, including education programs, in smoking and health. Generally, the materials disseminated by the Office on Smoking and Health and other health-related governmental agencies provide an adequate departure point for those with a particular interest in the area of education about smoking.

A wide variety of information and materials are also disseminated by those voluntary health agencies having an interest in smoking education, many of which have developed, tested, and supported research focused upon the prevention of smoking by youth. A number of these agencies have developed and packaged curriculum materials in this area, generally available at little or no cost to educators.

However, problems exist with respect to dissemination of information about successful practices and programs. In part, this situation arises because of the magnitude of the total amount of information available on smoking and health. There is simply so much written about the overall issue that information regarding successful educational endeavors is often buried in the literature or presents an overwhelming challenge to the individual looking for one aspect of the larger issue. Another problem is the lack of generalization of available information. Currently, most studies are isolated in that they are conducted at the local level. Lacking the advantage of generalization, at least at a regional or State level, these efforts often go unreported, get lost in a multitude of other such projects, or are dismissed as being too narrow to permit generalization to the broader population. Unfortunately, among the few programs reported to be successful, replication is uncommon. Thus, it is not surprising that dissemination of information from replication of successful programs is infrequent.

One of the most useful actions to improve this situation would be a periodic focusing upon both successful and unsuccessful educational programs. In this manner, the information would more likely filter down to the classroom teacher and develop a greater interest in the research community to conduct, replicate, and evaluate programs dealing with the education of youth.

Teacher Education

Certification of Teachers and Consultants

As with most areas of education in our nation, there is a pluralistic approach to instruction on youth and to the responsibilities for education about smoking. As previously mentioned, most States have some formal requirement for mandated instruction regarding tobacco. The status of instruction and certification in the area of smoking has been assessed in a nationwide survey conducted by the American School Health Association (*14a*). Most often, smoking education

instruction was found to be the responsibility of a teacher certified in health education or health/physical education. Specifically, 30 States certify teachers of health education; 10 of these States offer dual certification in health and physical education. Two States and the District of Columbia offer only dual certification in health and physical education. One State offers certification in physical education only. Another State offers certification in health and safety education. The remaining 17 States have either no specific requirements or have only general teacher-certification requirements for school health educators.

While the trend is for increased certification for instructors in the health area, the fact that nearly one-third of the States have either no requirement or only general teacher-certification requirements for school health educators raises a serious question as to the quality of instruction about smoking. Instruction in health is often delegated to teachers with insufficient training in health education in general and smoking education in particular. There is also significant variation between States as to what comprises certification in the area of health education. At present, no uniform standards exist. This condition, coupled with the lack of certification in many States and the importance of education about smoking, creates a significant challenge in this area. It appears that the potential of education related to youth smoking is most enhanced when the instructor meets the requirements of a certified school health educator. Where health education certification is required, the instructor almost invariably has had course work in the areas of drug education, including tobacco. Generally, curricula in health education include preparation in personal health, growth and development, health behavior, educational psychology, mental health, group dynamics, anatomy, and physiology, as well as formal training in materials and methods of teaching health education. A summary of the current status of school health educator certification is presented in Table 3.

TABLE 3.—School health educator certification

State	*Health education*	*Health, physical education*	*Comments*
Alabama			Must have minor in health, physical education, and/or recreation
Alaska			Teacher certification only
Arizona			Teacher certification only

Arkansas	X		17 semester hours of health education
California	X		
Colorado			Teacher certification; additional requirements may be set by local school district
Connecticut	X		
Delaware	X		
Florida	X		
Georgia	X	X	
Hawaii	X	X	
Idaho	X	X	
Illinois	X		
Indiana	X		
Iowa	Teacher certification only. Certification in health education pending		
Kansas	X		
Kentucky	X		
Louisiana	See Comment		Listed as health and safety education certification
Maine			Teacher certification only
Maryland	X		
Massachusetts	X		
Michigan	X		
Minnesota	X	X	
Mississippi			
Missouri			No requirements
Montana	X	X	
Nebraska	X	X	
Nevada			No requirements
New Hampshire			No requriements
New Jersey			NASDTEC standards
New Mexico	X		
New York	X		
North Carolina			
North Dakota			No requirements
Ohio	X		
Oklahoma		X	
Oregon	X		
Pennsylvania	X		

Rhode Island			Physical education certification
South Carolina	X	X	
South Dakota			No requirements
Tennessee		X	
Texas	X	X	
Utah			Major or minor in secondary education in health
Vermont			No requirements
Virginia	X	X	
Washington	X	X	
West Virginia			Competency-based teacher education certification
Wisconsin	X		Separate certification for health and physical education
Wyoming	X		No requirements
District of Columbia		X	

SOURCE: American School Health Association. (*14a*).

Preparation of Elementary Teachers and Health Education Specialists on Smoking Education

The school as an institution is particularly sensitive to the forces of a democratic society, which often are reflected in the school's programs and in the teacher's preparation. The dynamic condition of modern life and the related societal pressures spawn new issues and problems which place special demands upon the teacher and the school. The role of the school and the purposes of education in today's society remain a source of continuing debate.

Massanari, et al. (*50*) observed that there is "a continuing and sometimes increased expectation that schools as social institutions should cure a variety of social ills." In addition, they pointed out that "there is a growing realization of the inadequacy of the knowledge base which supports the education of teachers, as well as an increased awareness that education research should focus on current problems faced by classroom teachers." If, in fact, the knowledge base of teachers presently employed in the nation's schools is inadequate, retraining and in-service education assume paramount importance. If current problems facing teachers require more carefully researched answers, educational research must delve into those areas.

Elementary School Classroom Teacher Preparation in Smoking Education

The generalization could be made that in the United States the undergraduate program of teacher preparation of elementary teachers includes little or no course work in health education, or more specifically, in smoking education. The course time required for preparation in the areas of language, the arts, mathematics, social studies, and science is so extensive that very little time remains for other subject areas. For example, Illinois requires that students preparing for the field of elementary education elect 3 to 5 hours of physical education or health education course work in the total 4 years of their preparation. Occasionally, students may elect more course work in this area, but that would be the exception.

As a result, when health education courses or smoking education are added to the instructional program at the elementary school level, either by State mandate or local decision, in-service training must be employed. Recognizing the need for in-service education of teachers, NCSH contracted with AAHPER in 1970 for the development of a leadership training program for health educators. It was envisioned that these health educators could be prepared to conduct a series of in-service training programs on smoking and health education for classroom teachers, who would then be prepared to teach this material in the classroom.

The project developed a training program to be presented in a workshop format of 1 to 3 weeks' duration. Topics usually covered in these workshops included: (1) the physiological and behavioral aspects of smoking, (2) a review of local, regional, and national health agency resources available to teachers, and (3) a study of the methodology of teaching for behavioral change (*3*).

Other workshops were held that dealt with issues related to smoking and health, such as curriculum development and the development of new models for integrating smoking and health with other subject areas. These special training workshops were unique in that they were not related to a specific program of smoking and health. Instead, they were created to meet an obvious need of the classroom teacher, or as Massanari, et al. (*50*) postulated, to focus on the inadequacy of the knowledge base of teachers, as well as to develop an increased awareness of problems currently faced by the classroom teacher.

Another problem confronting the classroom teacher is the need for training to implement a new curriculum or an innovative curriculum design. SHCP is a good example of such teacher training. This program offers the teacher 2 weeks or 60 hours of intensive training on each of the body system units. Teachers are given specific training in only one unit of the program at a time. After the training, they return to their schools to teach the program to their students, using the materials and the teaching activities studied in their training session.

After the teacher has successfully taught the program presented at the training session, he or she must then conduct a training session for other teachers in that district in order to assure the dissemination of the model. This type of training has been used successfully with classroom teachers who have had little or no formal preparation in health education.

Professional Preparation in Health Education

While the report of the Society for Public Health Education, Inc. (*82*) does not speak directly to the preparation of teachers, its recently adopted guidelines for preparation of health educators are a significant influence throughout the field of health education. Moreover, the Society's statement on health education that accompanies the report effectively sets forth the purposes and the methodology of the professional health educator:

> Health Education is concerned with the health-related behavior of people. Therefore, it must take into account the forces that affect those behaviors and the role of human behavior in the prevention of disease. As a profession, it uses education processes to stimulate desirable change or to reinforce health practices of individuals, families, groups, organizations, communities, and larger social systems. Its intent is the development of health knowledge, its exploration of options of behavior and change and their consequences (*82*).

In recent years, several national professional organizations have issued reports on the guidelines or recommended standards of preparation for health education. In 1972, AAHPER issued a report; in 1976, the report by the ASHA Committee on Professional Preparation and College Health Education was released; and, in 1977, the Society for Public Health Education, Inc. published its guidelines (*3, 12, 82*).

These reports have taken the form of performance standards, competencies, functions, knowlege concepts, and course content experiences. Schaller (*79*), in an article published in 1978, reviewed the reports and identified common areas of professional preparation in health education. The common areas included the following: (1) foundational sciences of physical and biological science, (2) behavioral sciences, (3) a common core of health content courses, and (4) the skills of professional practice.

Preparation experiences of relevance to planning and to the conduct of smoking education programs are evident in each of the programs being recommended for preparation in health education.

Traditionally, these curricula of study have been designed to prepare the student for work either in school or in community health education. However, as the field has evolved, it has become evident that the foundational preparation of the undergraduate is becoming more

closely aligned with both school and community objectives. The student is benefited greatly from study and experience in both the school and the community settings. The skills and knowledge required in each area are in fact complementary and serve to increase the effectiveness of the health educator. Of special benefit is the increased time devoted to professional practice experiences resulting from participation in school observations, practice teaching, and in the community field work experience.

The Effects of Teacher Training and Teaching Methodology

Some experimental research has been conducted to test the effectiveness of teacher preparation. Irwin, et al. (*43*) conducted an experimental study using a factorial design to test the effectiveness of teacher preparation by comparing the regular classroom teacher and a health education specialist with special training in smoking and health. Three different instructional approaches were employed: a teacher-led group, a peer group, and an individual study approach. Each of the approaches (or teaching methods) employed the same curriculum material and sequence of lessons. This was done in order to hold constant the influence of the materials in each of the experimental groups while varying the educational approaches. In general, the experimental program was favorably received by both teachers and students. Perhaps the finding of greatest importance in this study was that students taught by the regular classroom teachers achieved significantly higher attitude belief scores (more favorable nonsmoking scores) than did the students taught by the specially trained teachers. While the specialists successfully imparted information, they apparently were less effective than the classroom teachers in developing positive nonsmoking attitudes, perhaps because, as outsiders, they may have upset the emotional climate of the classroom.

An experiment conducted by Swanson (*83*) examined the relative effectiveness of two educational approaches in drug-abuse education (including the area of smoking). A values-oriented approach was compared to a more traditional approach to teacher training. The experimental treatment involved a 3 1/2 day intensive live-in training session for 78 elementary school teachers in Illinois. The immediate effects were measured in terms of the teachers' knowledge gains and attitude changes resulting from the effects of the workshop training sessions. After the teachers returned to their schools and taught their classes, a further assessment of the training was determined by testing for effects on the students. The students were evaluated on the educational experience they had received and on how they evaluated the teacher, their knowledge gains, and their attitude changes.

The effects of the workshop-training experience on the teachers produced significant knowledge gains in both the values-oriented and

traditional-approach groups. Both groups made significant shifts toward healthy attitude scores.

The effects of the teacher training on the students were significant knowledge gains produced by both values- and traditionally-trained teachers, with the traditionally-trained teacher's students making significantly greater knowledge gains. The investigator suggested that the evidence supported an educational program that includes a combination of traditional and values activities.

The Teacher's Role In Smoking and Health

A number of studies have been conducted on the smoking behavior of adults since the issuance of the 1964 Surgeon General's report. However, relatively little research has been done on the teacher's smoking habits. This is significant since it is often acknowledged that teachers have the greatest potential influence upon the developing attitudes and smoking behaviors of the young. One of the first of these studies was that of Morris, et al. (*59*) on the smoking habits and attitudes of Oregon high school coaches. The principal objectives of the study were to determine the past and present smoking habits and the attitudes of the coaches towards cigarette smoking as a health hazard. Results showed that 44.4 percent of the coaches had at some time been regular smokers. At the time of the survey only 29.2 percent were still smoking. A large majority of those who had stopped smoking had done so because of the scientific evidence linking cigarette smoking to disease. It is apparent that these coaches had accepted their responsibility for smoking education. Moreover, they believed that their own attitudes towards smoking have a significant influence on their students and athletes.

Newman (*65*) conducted a study of smoking among New York City teachers. The assumption underlying her study was that teachers will necessarily play a key role in any solution to the problem of youth smoking because of their influence as a role model. Thus, the purpose of this investigation was to determine how teachers perceived their roles in smoking education. In response to questions about their own smoking behavior, most teachers expressed the belief that they could not be effective in smoking education if they themselves were also smokers. Among this sample of teachers, 31 percent were current smokers. While a large majority approved of teachers smoking in a teachers' lounge, they did not approve of teachers smoking on school grounds in front of students. Also, they did not approve of the school providing smoking facilities for junior high school students. Approximately three-fourths of these teachers believed that they could influence student smoking and that teachers who were nonsmokers and ex-smokers would be most effective with students.

Chen and Rakip (*16, 17*), writing about their own research on the smoking behavior of teachers, suggest that school antismoking

education efforts have not been successful because these programs have not been attractive to youth. They point up the importance of the teachers' role, contending that schools need the services of a teacher who is prepared in health education to help schools develop policies and to implement more effective educational approaches. They also stress the importance of the teacher as a role model. In their study of a sample of New England teachers, Chen and Rakip found a relatively low rate of smoking among teachers, with 26.5 percent of them current smokers and another 27.2 percent ex-smokers. As pointed out earlier, students generally overestimate the number of teachers who smoke. With respect to smoking education, the nonsmoker and ex-smoker teachers expressed a sense of responsibility for setting "a good example" for students. Again ex-smokers and nonsmokers appeared to be much more convinced of the relationship between smoking and disease than current smokers. The researchers concluded that the general climate in schools today is conducive to smoking education.

The Teacher as a Role Model

As noted, there is a general recognition of the importance of the teacher's role in smoking education. While there has been a lack of research on the effects of the teacher, the uniqueness of the teacher's position as a role model is repeatedly stressed. As expressed in the position statement of AAHPER, to be effective in smoking education, the teacher's position must be clear and unequivocal:

> In addition to having the facts correct in smoking education, it is also equally important to know how you truthfully stand on this vital health issue—what your own personal feelings and attitudes are about smoking. It is essential that your behavior honestly reflect your convictions (5).

Recommendations

The Status of Education About Smoking in U.S. Schools

1. A nationwide study should be conducted to assess the effect of current teaching efforts on the prevention and cessation of smoking behavior.

2. A study of the different patterns of instruction should be undertaken in order to determine the effects of this instruction on the attitudes and smoking behavior of youth. For example, is there a relationship between the knowledge, attitudes, and smoking practices of students and particular instructional programs, such as special units on smoking education or instruction organized through a comprehensive health education curriculum?

3. Retrospective surveys of student smoking should be initiated in mandated and nonmandated instructional programs in order to assess

the comparative effects of such instruction on student knowledge, attitudes, and smoking behavior.

4. A study should be undertaken to assess the degree to which States with mandated programs are meeting their responsibility.

The Development and Implementation of School Policies on Smoking

5. School districts should take the initiative to develop interagency advisory committees on smoking and health to assist schools in the development of school smoking policies. A supervisory committee might include such groups as the local health department, voluntary health agencies, PTA's, and law enforcement agencies.

6. A study should be conducted on the effects of different types of school policies on student smoking behavior. For example, are some school policies more effective in reducing overall smoking behavior both in and outside school settings?

7. The effects of a permissive school policy that permits older students to smoke should be investigated as they bear on the concomitant smoking attitudes and behaviors of younger students.

8. The rate of respiratory illnesses among smoking and nonsmoking school-age students should be investigated.

9. Comparative studies should be conducted of the different approaches employed by school boards in developing school policies on smoking (such as policies by school board edict and policies democratically developed) in order to test the possible relationship between policies and the institutional climate of the school (that is, "sense of freedom" and "control"). Also, such studies should provide further information about relationships between policies, institutional environment, student attitudes, and smoking behavior.

10. Retrospective studies should be conducted of contrasting school policies on smoking, such as nonsmoking and student-approved smoking, to examine the possible relationship between school policy, student attitudes, and smoking behaviors.

11. School and community-based educational programs aimed at the prevention and cessation of smoking should be promoted.

12. Research comparing the effectiveness of school- and community-based approaches with traditional school instructional programs should be supported.

Curriculum

13. School officials should initiate steps to integrate special smoking education programs into those established areas of the school curriculum which have natural or logical relationships to the subject matter of smoking and health.

14. Agencies sponsoring the development of educational materials on smoking and health should provide sufficient resources for the orientation and training of teachers in the use of these new materials.

15. Agencies providing funds for research and evaluation of new curricula should encourage innovative research methodology that will enable the investigator to assess the effects of these new curricula and, at the same time, to overcome some of the weaknesses in attempting to apply traditional experimental methods in the school setting.

16. Efforts should be undertaken to develop materials that have been specifically designed for use with the School Health Curriculum Project (SHCP). Such school materials should be readily available to schools and to teacher education institutions to facilitate the testing, evaluation, and implementation of the SHCP program.

Development of Demonstration Projects and Identification of Successful Practices

17. In light of the encouraging results of several projects, strong consideration should be given to continued support of promising demonstration projects.

18. Replication of successful practices should be promoted.

Evaluation of Educational Programs Designed to Prevent Smoking

19. Evaluation should be incorporated into all programs designed to prevent smoking, utilizing both retrospective and prospective designs.

20. The evaluation component of educational programs designed to prevent smoking should include assessment of cognitive, affective, and behavioral outcomes.

21. Evaluation should include both short- and long-term measures of program effectiveness.

22. The use of uniform definitions to classify behavioral groups (regular smokers, occasional smokers, ex-smokers, nonsmokers, and never smokers) should be encouraged for purposes of establishing a basis for comparison.

23. The lack of demonstrable effects of most educational programs shows the need for continued support of program development and education.

24. Provision for replication should be incorporated into the evaluation process.

Dissemination and Promotion of Successful Practices and Products

25. Greater attention should be directed toward the dissemination of research findings and successful educational programs specifically designed to prevent or modify smoking practices. This information should be readily available for incorporation into school curricula.

26. Programs and practices identified as successful in one setting should be replicated in others in order to evaluate the consistency of findings.

27. Projects identified as successful should be replicated before being implemented on a State or regional level.

Teacher Education

28. Greater emphasis should be placed on the preparation of specialists in health education, including the area of smoking and health.

29. All prospective elementary teachers should have some preparation in health education, including the relationship between smoking and health, as a part of their pre-service preparation.

30. The extent of teacher preparation in smoking education provided by teacher education institutions should be assessed.

31. Efforts should be made to establish uniform minimal State certification standards for the preparation of health-education specialists and for the health education preparation of classroom teachers on the subject of smoking and health.

32. Special emphasis should be given to the development of alternative mechanisms for providing in-service and continuing education for classroom teachers in health education, including smoking and health. These programs should be formally linked to institutions of higher education to enable teachers to receive academic credit for special preparation.

33. Research should be encouraged to test the relationship of teachers' smoking behavior to students' attitudes and smoking behavior.

34. Longitudinal studies should be conducted to test the effects of different instructional patterns and different patterns of teacher preparation on students' attitudes and smoking practices.

The Role of Educators: References

(1) ALBINO, J., DAVIS, R. A health education program that works. Phi Delta Kappan 57(4): 256-259, December 1975.

(2) AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION AND RECREATION. National Leadership Development Conference on Smoking and Health Education, Washington, D.C., National Education Association, 1968, 108 pp.

(3) AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION AND RECREATION. Professional Preparation in Safety Education and School Health Education. Washington, D.C., American Association for Health, Physical Education and Recreation, 1974, pp. 12-38.

(4) AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION AND RECREATION. Smoking education: The school's responsibility. Journal of School Health 41(8): 444-445, October 1971.

(5) AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION AND RECREATION. What Educators Can Do About Cigarette Smoking: An American Association for Health, Physical Education and Recreation Guide for Leaders in Smoking and Health Education. Washington, D.C., American Association for Health, Physical Education and Recreation, 1971, 24 pp.

(7) ANDRUS, L.H., HYDE, D.F., FISCHER, E. Smoking by high school students: Failure of a campaign to persuade adolescents not to smoke. California Medicine 101(4): 246-247, October 1964.

(8) ARRIGONI, E.A. Teenage antismoking campaign in the elementary schools. School Health Review 3(2): 15, March/April 1972.

(9) ARRIGONI, E.A. Teenagers to younger kids: Don't smoke. American Biology Teacher 35(4): 219-222, April 1973.

(10) BERMAN, L.M. Smoking and health: The school's responsibility. In: American Association for Health, Physical Education and Recreation. National Leadership Development Conference on Smoking and Health Education. Washington, D.C., National Education Association, 1968, pp. 34-43.

(11) BRODY, J.A. To permit or prohibit smoking in high schools: It's a burning issue. American School Board Journal 164(5): 19-21, May 1977.

(12) BRUESS, C.E. (Editor). Professional preparation of the health educator. Report of the ASHA Committee on Professional Preparation and College Health Education Conference at Towson State University, January 29-30, 1976. Journal of School Health 46(7): 418-421, September 1976.

(13) BRUESS, C.E., GAY, J.E. Professional preparation of the health educator. A report of a forum sponsored by the ASHA committee on college health education and professional preparation. Journal of School Health 46(7): 222-225, April 1976.

(14) CAMPBELL, L.P. Modifying attitudes of upper elementary students toward smoking. Journal of School Health 44(2): 97-98, February 1974.

(14a) CASTILE, A.S., JERRICK, S.J. (Editors). School Health in America—A Survey of State School Health Programs. Kent, Ohio, American School Health Association, 1976, pp. 3-11.

(15) CHALKE, H.D. An approach to antismoking activities in school. International Journal of Health Education 7(4): 183-187, 198, October-December 1964.

(16) CHEN, T.L., RAKIP, W.R. Are teachers prepared to implement smoking education in the schools? Journal of School Health 44(8): 438-441, October 1974.

(17) CHEN, T.L., RAKIP, W.R. The effect of the teachers' smoking behavior on their involvement in smoking education in the schools. Journal of School Health 45(8): 455-461, October 1975.

(18) CORWIN, E. Smoking—A world problem. HSMHA Health Reports 86(6): 501-506, June 1971.

(19) CRAWFORD, M. The effects of selected teaching methods on cigarette smoking in college women. Journal of the American College Health Association 16(4): 348-379, 1968.

(20) CRAWFORD, M. The relative effects of selected teaching methods in influencing smoking patterns among college women. In: Zagona, S.V. (Editor). Studies and Issues in Smoking Behavior. Tucson, University of Arizona Press, 1967, pp. 57-59.

(21) CRESWELL, JR., W.H. HUFFMAN, W.J., STONE, D.B., MERKI, D.J., NEWMAN, I.M. University of Illinois antismoking education study. Illinois Journal of Education 60(3): 27-37, March 1969.

(22) CRESWELL, W.H., JR., STONE, D.B., HUFFMAN, W.J., NEWMAN, I.M. Antismoking education study at the University of Illinois. HSMHA Health Reports 86(6): 565-576, June 1971.

(23) DAVIS, R.L. Making health education relevant and exciting in elementary and junior high school. Health Services Reports 88(2): 99-105, February 1973.

(24) DAVIS, R.L. Positive smoking education programs for the school-age child. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Health Consequences, Education, Cessation Activities, and Social Action, Volume II. Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 237-244.

(25) DELARUE, N.C. How to stop smoking. Canadian Family Physician 16(4): 49-53, April 1970.

(26) DOWNEY, A., O'ROURKE, T.W. The utilization of attitudes and beliefs as indicators of future smoking behavior. Journal of Drug Education 6(4): 283-295, Winter 1976.

(27) ESTRIN, E.R., QUERRY, D.L. A 'no smoking' project for ninth and tenth grades. Journal of School Health 35(8): 381-382, October 1965.

(28) EVANS, R.R., BORGATTA, E.F. An experiment in smoking dissuasion among university freshmen: A follow-up. Journal of Health and Social Behavior 11(1): 30-36, March 1970.

(29) FODOR, J.T., GMUR, B.C., SULTON, W.C. Framework for Health Instruction in California Public Schools. Sacramento, California State Department of Education, 1972, 56 pp.

(30) GLOVER, E.D. Modeling—A powerful change agent. Journal of School Health 48(3): 175-176, March 1978.

(31) GOLDSTEIN, W., LOVELY, E.C. A compromise on the smoking dilemma. NASSP Bulletin 58(379): 22-26, February 1974.

(32) GORDON, I. Smoking education— Where, when, and how. In: Goodman, H.A. (Editor). World Conference Smoking and Health—A Summary of the Proceedings. New York, 1967, pp. 144-161.

(33) HARDY, A.C. The role of the classroom teacher. In: AAHPER National Leadership Development and Conference on Smoking and Health Education. Washington, D.C.: National Education Association, 1968, pp. 32-33.

(34) HAYNES, W.F., JR., KRSTULOVIC, V.J., BELL, A.-L. Smoking habit and incidence of respiratory tract infections in a group of adolescent males. American Review of Respiratory Diseases 93(5): 730-735, May 1966.

(35) HERZOG, M. Seminar or suspension. Education or punishment for teenage smokers. Clearing House 45(3): 146-149, November 1970.

(36) HOLLAND, W.W., ELLIOTT, A. Cigarette smoking, respiratory symptoms and antismoking propaganda. An experiment. Lancet 1(7532): 41-43, January 6, 1968.

(37) HORINE, L.E. Elementary school antismoking project involving high school students. Journal of School Health 29(1): 43-45, January 1969.

(38) HORN, D. Behavioral aspects of smoking. In: AAHPER National Leadership Development Conference on Smoking and Health Education. Washington D.C. National Education Association 1968, pp. 44-56.

(39) HORN, D. The cigarette smoking picture— Bright spots and shadows. Bulletin of the National Tuberculosis and Respiratory Disease Association 36(10): 7-9 November 1970.

(40) HORN, D. Modifying smoking habits in high school students. Children 7(2): 63-65, March/April 1960.

(41) HORNE, T. Smoking and health: The activities of a high school student committee. Journal of School Health 33(10): 451-456, December 1963.

(42) IRWIN, R.P. The effect of the teacher and three different classroom approaches on seventh grade students' knowledge, attitudes, and beliefs about smoking In: Creswell, J.M., Creswell, W.H., Jr. Stone, D.B. (Editors). Youth Smoking Behavior Characteristics and Their Educational Implications. A Report of the University of Illinois Antismoking Education Study. Champaign, University of Illinois, June 30, 1970, pp. 38-47.

(43) IRWIN, R.P., CRESWELL, JR., W.H., STAUFFER, D.J. The effect of the teacher and three different classroom approaches on seventh grade students' knowledge, attitudes and beliefs about smoking. Journal of School Health 40(7): 355-359, September 1970.

(44) JACOBS, C. Effects of State Tobacco Laws on High School Student Smoking Throughout the United States: Suggestions from High School Principals Concerning Student Smoking Problems, Doctoral Dissertation, University of Utah, Department of Educational Administration, August 1974, 152 pp. University Microfilms 74-29, 553.

(45) JEFFERYS, M., WESTAWAY, W.R. Catch them before they start: A report on an attempt to influence children's smoking habits. Health Education Journal 19(1): 3-17, March 1961.

(46) JONES, J.A., PIPER, G.W., MATTHEWS, V.L. A student-directed program in smoking education. Canadian Journal of Public Health 61(3): 253-256, May/June 1970.

(47) KAHN, E.B., EDWARDS, C.N. Smoking and youth: Contributions to the study of smoking behavior in high school students. Journal of School Health 49(10): 561-562, December 1970.

(48) LITCHFIELD, T.B. A school system with a comprehensive program in health education. Journal of School Health 43(4): 235-239, April 1973.

(49) MARTENS, J.U., WEIDENMANN, B. Die theoretische konzeption eines antirauchen programme (The theoretical concepts of an antismoking program). International Journal of Health Education 15(2): 83-93, 1972.

(50) MASSANARI, K., DRUMMOND, W.H., HOUSTON, W.R. Emerging Professional Roles for Teacher Educators. Washington, D.C., American Association of Colleges for Teacher Education and the Eric Clearinghouse on Teacher Education, February 1978, pp. 1-35.

(51) MCRAE, C.F., NELSON, D.M. Youth to youth communication on smoking and health. Journal of School Health 41(8): 445-447, October 1971.

(52) MEANS, R.K. Historical Perspectives on School Health. Thorofare, New Jersey, Charles B. Slack, Inc., 1975, pp. 19-41.

(53) MERKI, D.J., CRESWELL, W.H., JR., STONE, D.B., HUFFMAN, W., NEWMAN I. The effects of two educational methods and message themes on rural youth smoking behavior. Journal of School Health 38(7): 448-454, September 1968.

(54) METTLIN, C. Peer and other influences on smoking behavior. Journal of School Health 46(9): 529-536, November 1976.

(55) MICHIGAN STATE DEPARTMENT OF EDUCATION. The Age of Majority—18: Guidelines for Local Districts. Lansing, Michigan State Department of Education, July 1971, 20 pp.

(56) MONK, M., TAYBACK, M., GORDON, J. Evaluation of an antismoking program among high school students. American Journal of Public Health 55(7): 994-1004, July 1965.

(57) MORISON, J.B. Cigarette smoking: Surveys and a health education program in Winnepeg, Manitoba. Canadian Journal of Public Health 55(1): 16-22, January 1964.

(58) MORISON, J.B., MEDOVY, H., MACDONNELL, G.T. Health education and cigarette smoking: A report on a three year program in the Winnepeg school division, 1960-1963. Canadian Medical Association Journal 91(2): 49-56, July 1964.

(59) MORRIS, J.F., TICHY, M.W. Smoking habits and attitudes of Oregon secondary school coaches. American Journal of Public Health 60(7): 1271-1277, July 1970.

(60) NATIONAL ASSOCIATION OF SECONDARY SCHOOL PRINCIPALS. Concerning smoking in the public schools. A Legal Memorandum: 1-6, March 1972.

(61) NATIONAL CANCER INSTITUTE. AMERICAN CANCER SOCIETY. Cigarette Smoking Among Teen-Agers and Young Women. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1203, 1977, 31 pp.

(62) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Bibliography on Smoking and Health: 1972. U.S. Department of Health, Education and Welfare, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health. DHEW Publication No. (HSM) 73-8719, Public Health Service Bibliography Series No. 45, May 1973, 314 pp.

(63) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Bibliography on Smoking and Health: 1976. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, Bureau of Health Education, National Clearinghouse for Smoking and Health, DHEW Publication No. (CDC) 78-8309, Public Health Service Bibliography Series No. 45, January 1978, 343 pp.

(64) NATIONAL SCHOOL BOARD ASSOCIATION. School Board Policies on Smoking in Schools. Educational Policies Development Kit. Evanston, National School Board Association, 1973, 20 pp.

(65) NEWMAN, A.N. How teachers see themselves in the exemplar role in smoking education as evidenced by their attitudes and practices. Journal of School Health 41(5): 275-279, May 1971.

(66) OREGON STATE BOARD OF EDUCATION. Minimum Standards for Student Conduct and Discipline, Including Suggested Guidelines and Model Codes, Oregon Administrative Rules 21-050–21-085. Salem, Oregon State Board of Education, May 12, 1972, 16 pp.

(67) O'ROURKE, T.W. Assessment of the effectiveness of the New York State drug curriculum guide with respect to drug knowledge. Journal of Drug Education 3(1): 57-66, Spring 1973.

(68) O'ROURKE, T.W. Research on smoking behavior: Some limitations and suggestions for improvement. Public Health Reviews 2(1): 105-112, February 1973.

(69) O'ROURKE, T.W., BARR, S.L. Assessment of the effectiveness of the New York State drug curriculum with respect to drug attitudes. Journal of Drug Education 4(3): 347-356, Fall 1974.

(70) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study: Results of the first year. Canadian Journal of Public Health 62(5): 432-441, September/October 1971.

(71) PIPER, G.W., JONES, J.A., MATTHEWS, V.L. The Saskatoon smoking study: Results of the second year. Canadian Journal of Public Health 65(2): 127-129, March/April 1974.

(72) POULTON, P. Cigarette smoking among grammar school girls. Health Education Journal 32(4): 114-119, 1973.

(73) RABINOWITZ, H.S., ZIMMERLI, W.H. Effects of a health education program on junior high school students' knowledge, attitudes, and behavior concerning tobacco use. Journal of School Health 44(6): 324-330, June 1974.

(74) REDICAN, K.J. Analyzing the Effects of a Special Health Program on Lower Socioeconomic Sixth Grade Students. Doctoral Dissertation, University of Illinois, 1976, 139 pp.

(75) REGIONAL EDUCATION SERVICE AGENCY OF APPALACHIAN MARYLAND. A Progress Assessment of the School Health Education Project of Appalachian Maryland. Cumberland, Maryland, Regional Education Service Agency of Appalachian Maryland, December 1977, 25 pp.

(76) SALBER, E.J., GOLDMAN, E., BUKA, M., WELSH, B. Smoking habits of high school students in Newton, Massachusetts. New England Journal of Medicine 265(20): 969-974, November 1961.

(77) SALLACK, V.J. Study of smoking practices of selected groups of junior and senior high school students in public schools in Erie County, New York (Exclusive of the City of Buffalo). Journal of School Health 31(9): 307-314, November 1961.

(78) SCHAFFARZICK, J., HAMPSON, D.H. (Editors). Strategies for Curriculum Development. Berkeley, McCutchin Publishing Corporation, 1975, pp. 1-33.

(79) SCHALLER, W.E. Professional preparation and curriculum planning. Journal of School Health 48(4): 236-240, April 1978.

(80) SCHOOL HEALTH EDUCATION STUDY. Health Education: A Conceptual Approach to Curriculum Design. St. Paul, 3M Education Press, 1967, pp. 84-93.

(81) SCHWARTZ, J.L. Adolescent smoking behavior: Curiosity, conformity and rebellion. In: Bruess, C.E., Fisher, J.T. (Editors). Selected Readings in Health, London, Collier-Macmillan Limited, 1970, pp. 109-120.

(82) SOCIETY FOR PUBLIC HEALTH EDUCATION, INC. AD HOC TASK FORCE ON PROFESSIONAL PREPARATION AND PRACTICE OF HEALTH EDUCATION. Guidelines for the preparation and practice of professional health education. Health Education Monographs 5(1): 75-89, Spring 1977.

(83) SWANSON, J.C. Drug abuse: An in-service education program. Journal of School Health 43(6): 391-393, June 1973.

(84) THOMPSON, E.L. Smoking education programs 1960-1976. American Journal of Public Health 68(3): 250-257, March 1978.

(85) TROUPE, C.H. The role of the elementary school principal. In: AAHPER National Leadership Conference on Smoking and Health Education. Washington, D.C., National Education Association, 1968, pp. 28-31.

(86) U.S. PUBLIC HEALTH SERVICE. Teenage Smoking: National Patterns of Cigarette Smoking, Age 12 Through 18, in 1968 and 1970. U.S. Department of Health, Education and Welfare, Public Health Service, Health Services and Mental Health Administration, Regional Medical Program Services, National Clearinghouse for Smoking and Health, PHS Publication No. (HSM) 72-7508, 1972, 144 pp.

(87) WATNE, A.L., MONTGOMERY, R.L., PETTIT, W. A cigarette information program. Journal of the American Medical Association 188(10): 872-874, June 1964.

(*88*) WATSON, L.M. Cigarette smoking in school children: A study of the effectiveness of different health education methods in modifying behavior, knowledge and attitudes. Health Bulletin 24(1): 5-12, January 1966.

(*89*) WHITE, R.C., WEINBERG, A.D., SPIKER, C., ROUSH, R.E. Cardiovascular disease education in Texas health education classes—A needs assessment. Journal of School Health 48(6): 341-349, June 1978.

(*90*) WILLGOOSE, C.E. Saving the curriculum in health education. Journal of School Health 43(3): 189-191, March 1973.

(*91*) WORLD CONFERENCE ON SMOKING AND HEALTH. What should society do to control cigarette smoking? Panel discussion of work group recommendations. In: Goodman, H.A. (editor). World Conference on Smoking and Health—A Summary of the Proceedings. New York, 1967, 257 pp.

(*92*) ZAIS, R. Curriculum Principles and Foundations. New York, Thomas Y. Crowell, Co., 1976, pp. 3-21.

APPENDIX: CIGARETTE SMOKING IN THE UNITED STATES, 1950–1978.

Office on Smoking and Health

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Introduction

During the past three decades, there have been numerous changes in the population of cigarette smokers, in the style of cigarette smoking, and in the composition of the cigarette product.

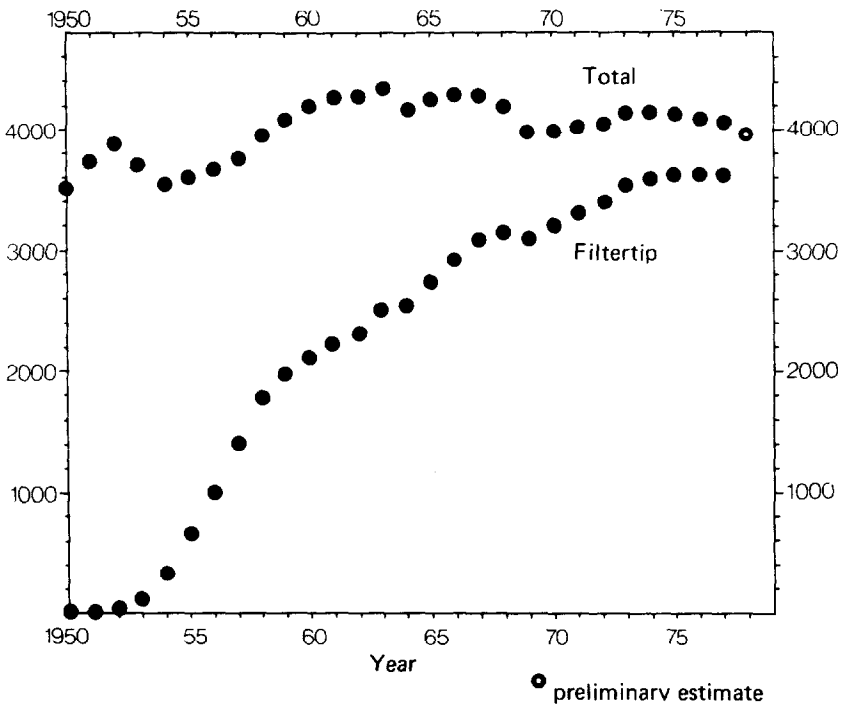


FIGURE 1. Annual consumption of cigarettes and filtertip cigarettes per person aged 18 years and over, 1950—1978
SOURCE: Miller, R.H. (*32,33*), U.S. Department of Agriculture (*47—51*).

Per Capita Consumption

Figure 1 depicts the annual consumption of cigarettes per person aged 18 years and over for the period 1950 to 1978 (*47–51*). In addition to total per capita cigarette consumption, the per capita consumption of filtertip cigarettes is shown, as derived from annual data on the filtertip share of total cigarette production (*32, 33, 47–51*). The choice of a population base of potential smokers aged 18 years and over is necessarily somewhat arbitrary; however, results qualitatively similar to those depicted in Figure 1 are obtained when a population base aged 12 years and over is used.

During the period 1925 to 1950 (not shown in Figure 1), annual per capita consumption increased steadily from 1,285 to 3,522 cigarettes

per person aged 18 years and over. As shown in Figure 1, annual per capita consumption declined temporarily in 1953 and 1954, but then continued to increase to a peak value of 4,336 in 1963. Per capita consumption again declined temporarily in 1964 and from 1968 to 1970. Since 1973, per capita consumption has declined at an average rate of about 0.9 percent annually. The preliminary estimate for 1978 is 3,965 cigarettes per person aged 18 years and over, which represents the lowest recorded value of per capita consumption since 1958.

Figure 2 describes in more detail the observed changes in cigarette consumption from 1963 to 1977. Four alternative per capita consumption series are shown. Series "1" in Figure 2 duplicates the total per capita consumption series of Figure 1. This series, reported by the Department of Agriculture (*47–51*), is based upon federal taxable removals, plus domestic tax-exempt deliveries, plus shipments to U.S. overseas forces, plus imports. Because the federal excise tax is applied to cigarettes transferred from manufacturers' factories to regional warehouses where they await distribution to wholesalers, these data may differ from actual cigarette consumption. Since 1970, the Department of Agriculture has adjusted this series for estimated changes in warehouse inventory.

Series "2" in Figure 2 represents total per capita consumption reported by the Federal Trade Commission (*68,69*), based upon reports of cigarette sales filed by individual manufacturers pursuant to the Public Health Cigarette Smoking Act. Series "3" represents domestic per capita consumption, calculated from Department of Agriculture data, in which shipments to U.S. overseas forces are excluded from total consumption, and in which overseas forces are excluded from the population base (*52*). Finally, Series "4" is calculated from total domestic consumption, gross of inventory adjustment, as published in various Maxwell Reports (27–30).

Despite different methods of measurement, all four time series reveal a temporary decline in 1964, a more marked, temporary decline from 1968 to 1970 (which may have actually begun as early as 1966), and a continuing decline after 1973. The observed declines in per capita consumption are not attributable to changes in inventories, cigarette imports, or shipments to overseas forces.

The temporary declines in total per capita consumption in 1953–54 (Figure 1), 1964, and 1968–70 (Figures 1 and 2) are of particular interest because they coincide with periods of increased publicity concerning the health hazards of cigarette smoking. Reports seriously suggesting a link between cigarette smoking and lung cancer first appeared in the popular press in 1953 and 1954 (*10, 25, 31, 36*). The first report of the Advisory Committee to the Surgeon General appeared in January 1964 (*53*). The Federal Cigarette Labelling and Advertising Act (P.L. 89–92), requiring a health warning in all adverti ing and on every package, became effective July 1966 (*1, 34*). In June 1967, the

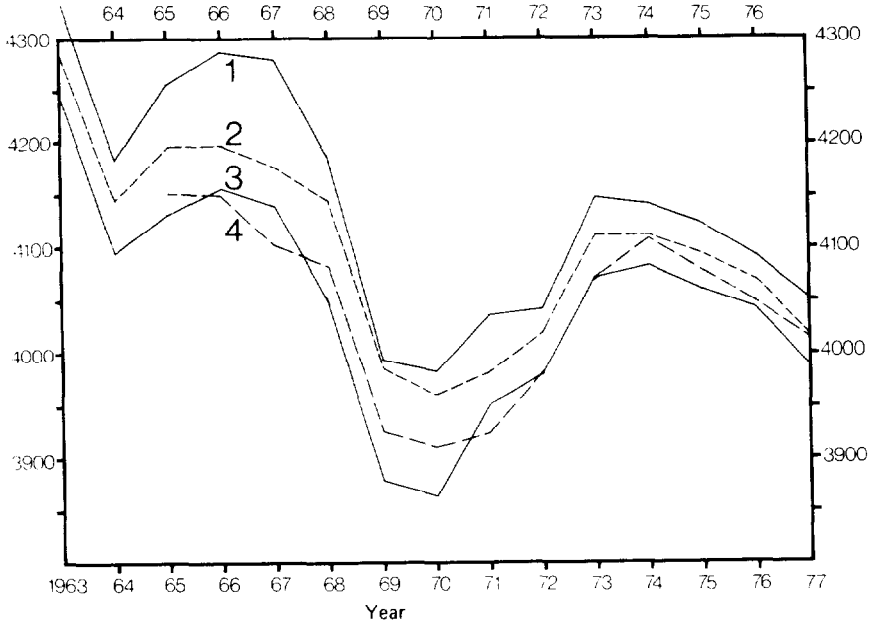


FIGURE 2. Annual consumption of cigarettes per person aged 18 years and over, 1963—1977

1. Based on Department of Agriculture total U.S. consumption series.
2. Based on Federal Trade Commission consumption series.
3. Based on Department of Agriculture domestic consumption series.
4. Based on Maxwell Reports' domestic consumption series.

SOURCE: Federal Trade Commission (*68,69*), Maxwell, J.C.C. (*27—30*), U.S. Department of Agriculture (*47—51*), U.S. Department of Commerce, Bureau of the Census (*52*).

Federal Communications Commission, applying the Fairness Doctrine to cigarette advertising, ruled that broadcast stations carrying cigarette commercials must devote a significant amount of time to informing listeners of the health hazards of smoking (*1, 7, 34*). In November 1967, the Federal Trade Commission issued its first periodic report on "tar" and nicotine contents of the cigarette smoke of various brands (*67*). In March 1969, the Federal Communications Commission ruled that television stations must present a significant number of anti-smoking messages during prime viewing hours when cigarette commercials were presented (*1, 34*). The value of these anti-smoking messages was estimated at $75 million. In April 1970, the Public Health Cigarette Smoking Act (P.L. 91–222) strengthened the health warning required in cigarette advertisements and packages and banned broadcast cigarette commercials starting January 2, 1971. These and other government actions were bolstered by those of numerous public and private organizations which took stands against cigarette smoking and began their own anti-smoking initiatives (*1*).

Although these events are often cited as being coincident with the observed declines in per capita consumption, there is disagreement concerning their actual quantitative impact on cigarette use (*12, 16, 17, 24, 27, 32–35, 74*). Of particular significance is the possible effect of broadcast anti-smoking messages during 1968 to 1970. As a result of application of the Fairness Doctrine, the statutory ban on broadcast cigarette advertisements virtually eliminated anti-smoking messages from prime viewing hours after 1971 (*66*). Some studies have in fact attributed the subsequent increase in consumption in 1972 and 1973 (see Figures 1 and 2) to the discontinuation of these anti-smoking commercials (*16, 17*). The statistical technique employed to isolate such anti-smoking publicity effects has been the inclusion of a binary explanatory variable in the time series analysis of per capita cigarette consumption (*5, 6, 24, 32–35, 74*). This variable is assigned a value of 1 during those years in which the anti-smoking publicity occurred (usually 1953–54, 1964, and 1968–69) and a value of 0 in all other years. However, such a technique only tests the hypothesis that some additional factors affected cigarette consumption in those years. Even if one can reasonably attribute these effects to a single intervention, such as the anti-smoking television messages, it may not be appropriate to confine the quantitative influence of such commercials solely to the month or year of its occurrence (*39*).

Most important, analyses of aggregate per capita consumption provide little direct insight into the impact of these public policy actions on individual smoking decisions.

The Prevalence of Cigarette Smoking

Table 1 summarizes the results of several different surveys of tobacco use in the adult U.S. population during the period 1949 to 1978. As indicated in the notes to Table 1, these surveys differ in sampling techniques, possible inclusion of proxy respondents, use of telephone versus direct interview techniques, eligible respondent age, and in those questions asked to identify regular, current cigarette smokers. In addition to these studies, prevalence data are available from isolated, one-time surveys (*13, 46*), and from large-scale epidemiological studies (*19–22*), but these may not be representative of the entire U.S. population. Detailed surveys of adult use of cigarettes have also been performed for marketing purposes.

The survey results in Table 1 must be interpreted in light of possible non-response biases or possible underreporting of smoking (*75*). In particular, comparison of the post-1969 survey data of the American Institute of Public Opinion (Gallup Poll) with the other series suggests that not all individuals who smoke cigarettes during any single week would consider themselves "regular" smokers. Nevertheless, despite numerous differences in methodology, the results in Table 1 present a

TABLE 1.—Estimates of the percentage of current, regular cigarette smokers, adults, United States, 1949—1978

Year	Supplement to Current Population Survey[1] (17 yrs. and over)			Health Interview Survey[1,2] (17 yrs. and over)			National Clearinghouse for Smoking & Health[3,4] (21 yrs. and over)			Gallup Poll[5] (18 yrs. and over)		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
1949										44		
1954										45		
1955	37.6[6,7]	52.6	24.5									
1957										42	52	34
1958										45		
1964							40.3	52.9	31.5			
1965				41.7[8]	51.1	33.3						
1966	40.6[4]	50.0	32.3				42.2	51.9	33.7			
1967	40.1[4]	49.1	32.1									
1968	38.6[4]	47.0	31.2									
1969										40	44	36
1970				36.9[8]	43.5	31.1	36.2	42.3	30.5			
1971										42	47	37
1972										43	48	38
1973										40		
1974				37.0[4,9]	42.7	31.9				40	45	36
1975							33.8	39.3	28.9			
1976				36.7[4,10]	41.9	32.0						
1977										38	41	36
1978				33.2[4,11]	37.5	29.6				36	39	34

[1] Results displayed as percentage of respondents with known smoking status.

[2] Both self and proxy respondents in 1965 and 1970. Only self-respondents in 1974, 1976, and 1978.

[3] Personal interviews in 1964 and 1966. Telephone surveys supplemented by personal interviews in 1970 and 1975.

[4] Current smokers defined as those responding affirmatively to: "Do you now smoke?"

[5] In 1967, current smokers defined as those responding "cigarettes" to the question: "Do you smoke cigarettes, a pipe, cigars, or don't you smoke?" Individual percentages for males and females in 1967, however, also included cigar and pipe smokers. For 1969 and later years, current smokers defined as those responding affirmatively to: "Have you, yourself, smoked any cigarettes in the past week?" In other years, definition of current smoker not provided in report.

[6] Current smokers defined as those smoking at least one cigarette everyday.

[7] Ages 18 years and over.

[8] *Current smokers defined as those respondents who reported a current rate of smoking.*

[9] Data provided by Health Interview Survey, National Center for Health Statistics.

[10] Ages 20 years and over.

[11] Preliminary estimate based on sample of over 4,400 respondents during July - September 1978. Data provided by Health Interview Survey, National Center for Health Statistics.

SOURCE: American Institute of Public Opinion (*2–4*), Bonham, G.S. (*8*), Haenszel, W. (*15*), National Center for Health Statistics (*55–59*), National Clearinghouse for Smoking and Health (*60,62,64*)

TABLE 2.—Estimated percentages of current and former smokers, adults, according to age and sex, United States, 1955—1975

	1955		1964		1966		1970		1975	
Males	Current smoker	Former smoker	Current smoker	Former smoker	Current smoker	Former smoker	Current smoker	Former smoker	Current smoker	Former smoker
21-24	51.4*	3.6*	67.0	9.5	61.9	7.2	49.8	20.0	41.3	16.0
25-34	63.4	9.0	59.9	18.0	59.9	19.7	46.7	27.9	43.9	22.5
35-44	62.1	11.1	59.9	22.9	59.0	21.9	48.6	31.4	47.1	25.8
45-54	56.9	12.6	53.1	25.3	53.8	26.0	43.1	34.4	41.1	36.0
55-64	43.6	15.7	50.9	24.5	47.7	31.0	37.4	41.4	33.7	38.8
65+	22.3	13.6	29.9	27.0	27.8	29.5	22.8	43.8	24.2	36.2
All ages	52.6	10.9	52.9	22.2	51.9	23.6	42.3	32.6	39.3	29.2
Females										
21-24	29.7*	3.5*	41.9	7.6	49.2	7.9	32.3	13.2	34.0	19.9
25-34	35.8	5.8	40.6	9.3	45.1	12.0	40.3	18.9	35.4	16.5
35-44	32.4	4.9	39.2	9.4	40.6	10.5	38.8	15.8	36.4	17.7
45-54	22.8	3.9	36.4	6.8	42.0	9.6	36.1	15.5	32.8	15.5
55-64	10.8	2.6	20.5	7.0	20.6	10.5	24.2	16.0	25.9	15.0
65+	3.5	1.6	7.8	3.3	7.6	5.2	10.2	8.2	10.2	10.7
All ages	24.5	3.9	31.5	7.4	33.7	9.4	30.5	14.8	28.9	14.5

*Ages 18-24 for 1955 only.

SOURCE: Haenszel, W. (*15*), Green, D. (*14*), National Clearinghouse for Smoking and Health (*60,62,64*).

consistent picture. The prevalence of male adult cigarette smoking has declined significantly. The prevalence of female adult cigarette smoking appears to have increased from 1955 to 1965. Since then, it has declined by no more than 3 or 4 percentage points.

The decline in the prevalence of smoking was most significant during 1965 to 1970, and particularly striking for males during 1968 to 1970. (Except for 1978, the absolute standard errors of the Current Population Survey estimates and the Health Interview Survey estimates were less than 0.3 percent.) Much less significant changes in prevalence were observed from 1971 to 1974. Since 1974, however, the prevalence of adult smoking has continued to decrease. Preliminary estimates from the 1978 Health Interview Survey suggest a very recent significant decline in both male and female smoking. (The absolute standard errors of the 1978 preliminary Health Interview Survey estimates were 1.1 percent for males, 0.9 percent for females, and 0.7 for both sexes.) This conclusion is supported by the Gallup Poll results for 1974, 1977, and 1978. These preliminary findings indicate that in 1978 the prevalence of cigarette smoking among adults reached its lowest recorded point in over 30 years.

As a result of population growth, this net decline in the prevalence of adult cigarette smoking is not necessarily matched by a decline in the absolute number of cigarette smokers. Although the percentage of adults who regularly smoke cigarettes fell from an estimated 41.7 percent in 1965 to an estimated 33.2 percent in 1978 (Health Interview Survey data in Table 1), the total number of U.S. resident cigarette smokers aged 17 and over increased from an estimated 53.3 million in 1965 to an estimated 54.1 million in 1978. This relatively small change represented the net effect of an estimated 8.5 percent decrease in the absolute number of adult male smokers and an estimated 11.1 percent increase in the absolute number of adult female smokers.

The pattern of changes in the prevalence of adult cigarette smoking, as shown in Table 1, corresponds qualitatively to the observed changes in per capita consumption over time, as depicted in Figures 1 and 2. In general, changes in the number of cigarette smokers represent the net effect of new initiation of smoking, cessation of smoking, recidivism, and exit from the population by emigration or death. A detailed, longitudinal analysis of changes in individual smoking habits would be required to distinguish accurately among these sources of change in smoking prevalence. Such a longitudinal analysis of changes in individual smoking for the past 10 to 15 years has not been published. However, follow-up data from continuing prospective epidemiological studies (e.g., *19–22*) may be a potential source of this type of information. In the absence of a long-term, longitudinal study, an analysis of changes in the prevalence of cigarette smoking must rely upon serial cross-sections of different individuals.

Table 2 presents estimates of the percentages of current and former adult cigarette smokers, by age and sex, for the period 1955 to 1975. In this table, the results of the 1955 Current Population Survey have been combined with those from the 1964, 1966, 1970, and 1975 National Clearinghouse for Smoking and Health surveys. These data permit an approximate assessment of changes in smoking habits for a given age/sex category over time. For example, the percentage of adult female current smokers, aged 55 to 64, has increased progressively from 1955 to 1975. The data also permit an approximate analysis of changes in smoking habits among 10-year birth cohorts. For example, in 1955, 62.1 percent of males born from 1920 to 1929, then aged 35 to 44, were current smokers. By 1965, the prevalence of current smoking among the same birth cohort, then ages 45 to 54, was about 53.5 percent (the population-weighted average of 1964 and 1966). By 1975, the prevalence of current smoking among this birth cohort, then aged 55 to 64, was 33.7 percent.

Among adult males, the percentage of current smokers for each birth cohort has declined, while the percentage of former smokers has increased. Changes in the percentage of those who have never smoked depend on the particular cohort. For example, the percentage of those born from 1920 to 1929 who never smoked decreased from 26.8 percent in 1955 to 20.9 percent in 1965, presumably as more individuals began but later quit smoking. From 1965 to 1975, however, the percentage of those born from 1920 to 1929 who never smoked increased to 27.5 percent. This finding is consistent with—but does not prove—the hypothesis of a longer life expectancy among those who have never smoked. Moreover, as the prevalence of cigarette smoking among older birth cohorts continues to decline, the prevalence of smoking among new, younger male birth cohorts has also been declining. (The prevalence data for the youngest age group in 1955 represent individuals aged 18 to 24, as opposed to ages 21 to 24 for other survey years, and cannot be strictly compared.)

Among female birth cohorts, there is also a general but less marked decline in smoking prevalence, which is accompanied by an increase in the percentage of former cigarette smokers. The prevalence of smoking among females in the older age groups has increased, as women born from 1910 to 1939 replaced those born from 1890 to 1909. As in the case of men, the percentage of women born from 1920 to 1929 who never smoked decreased from 62.7 percent in 1955 to 52.9 percent in 1965 and then increased to 59.1 percent in 1975. Again, this finding is consistent with—but does not prove—the hypothesis of a longer life expectancy among women who have never smoked cigarettes. In contrast to the case of men, the decline in prevalence of smoking among new, younger female birth cohorts is less consistent.

A decline in the percentage of current smokers and an increase in the percentage of former smokers, as shown in Table 2, suggests that

TABLE 3.—Estimates of the percentage of recent former cigarette smokers, adults, 1964, 1966, 1970, and 1975, United States

Year	Percentage of adults who quit smoking within 1 year of survey			Percentage of adults who quit smoking within 2 1/2 years of survey		
	Total	Male	Female	Total	Male	Female
1964 (Fall)	2.6	4.3	1.5	4.9	7.6	3.1
1966 (Spring)	2.2	2.8	1.7	4.6	6.1	3.3
1970 (Spring)	4.2	5.6	2.9	8.1	10.6	5.8
1975 (Summer)	2.1	2.4	1.8	3.1	4.5	2.8

SOURCE: National Clearinghouse for Smoking and Health (*60,62,64*).

the cessation of cigarette smoking was a significant factor in explaining the overall decline in smoking prevalence. This finding has been supported by a similar analysis of changes in smoking prevalence from the Health Interview Survey data (*8*).

Table 3 presents estimates of the percentage of recent, former cigarette smokers, obtained during the survey years 1964, 1966, 1970, and 1975. These data reflect the responses of adults who had discontinued smoking within 1 year or within $2^1/_2$ years of the survey date. These results must be interpreted in light of possible errors in respondents' recall of recent smoking behavior. Nevertheless, the results are strongly consistent with the conclusion that the cessation of cigarette smoking was a major factor in the decline in smoking prevalence, especially during the period 1966 to 1970. These results also suggest that the cessation of cigarette smoking was a major factor in the observed decline in per capita consumption during 1968 to 1970 (Figure 2), and possibly in 1964.

The great majority of adult cigarette smokers begin regular smoking before the age of 21 (*41,60,62,64*). Therefore, an examination of teenage smoking prevalence would contribute to the understanding of recent changes in the initiation of cigarette smoking. Table 4 presents estimates of the percentage of current, regular cigarette smokers among teenagers aged 12 to 18, as determined from surveys conducted by the National Clearinghouse for Smoking and Health (*61,63,65*). In addition to these surveys, there have been numerous other studies of teenage smoking habits in specific geographic regions or among specific teenage population groups, such as high school students (*11,23,40,41,46,71*). Comparision of these studies, however, is made particularly difficult by variations in study definitions of current, regular teenage smokers (*11,12,77*). In the surveys cited in Table 4, current, regular teenage smokers include those who regularly smoke cigarettes at least once per week.

TABLE 4.—Estimates of the percentage of current, regular cigarette smokers, teenagers, aged 12 to 18, United States, 1968—1974

Year	Ages 12–14		Ages 15–16		Ages 17–18		Ages 12–18	
	Male	Female	Male	Female	Male	Female	Male	Female
1968	2.9	0.6	17.0	9.6	30.2	18.6	14.7	8.4
1970	5.7	3.0	19.5	14.4	37.3	22.8	18.5	11.9
1972	4.6	2.8	17.8	16.3	30.2	25.3	15.7	13.3
1974	4.2	4.9	18.1	20.2	31.0	25.9	15.8	15.3

NOTE: Current regular smoker includes respondent who smokes cigarettes at least weekly.
SOURCE: National Clearinghouse for Smoking and Health (*61,63,65*).

Table 4 indicates that there was little overall change in the prevalence of current regular smoking among teenage males during 1968 to 1974. By contrast, the percentage of teenage female smokers has significantly increased. For both sexes, the small but significant increase in smoking prevalence among those 12 to 14 years old suggests that the average age of initiation of cigarette smoking is declining.

Other nationwide studies of teenage smoking have been recently conducted, including studies sponsored by the American Cancer Society in 1969 and 1975 (*26,54,79*), and a study conducted as part of the Gallup Youth Survey (*4*). A comparison of the two American Cancer Society studies confirms the general findings of an increase in smoking prevalence among teenage females and of little change in the smoking prevalence among teenage males. However, these studies employed definitions of a current, regular smoker which differ from those used by the National Clearinghouse for Smoking and Health.

Table 5 presents the observed changes in smoking prevalence among white and black adults, derived from the Health Interview Survey (*59*). The prevalence of smoking declined among male adults of both races. The prevalence data for females are more difficult to interpret.

Table 6 presents the observed changes in smoking prevalence among adults according to level of educational attainment, as reported by the National Clearinghouse for Smoking and Health (*60,62,64*). The prevalence of adult male smoking declined among all educational groups. The prevalence of adult female smoking declined among all groups except those with grade school education or less. The decline was more marked among those women who graduated from college. It is noteworthy that the prevalence of smoking among adults who graduated from college declined significantly during the years 1964 to 1966, whereas the observed declines in prevalence among other educational groups were generally confined to later years.

TABLE 5.—Estimates of the percentage of current, regular cigarette smokers among white and black adults, aged 20 years and over, United States, 1965—1976

Year	White		Black	
	Male	Female	Male	Female
1965	51.5	34.2	60.8	34.4
1970	43.7	31.9	54.0	33.1
1974	41.9	31.8	55.3	36.8
1976	41.2	31.8	50.5	35.1

NOTE: Results displayed as percentage of respondents with known smoking status.
SOURCE: National Center for Health Statistics (*59*).

TABLE 6.—Estimates of the percentage of current, regular cigarette smokers among adults, aged 21 years and over, according to highest level of educational attainment, United States, 1964–1975

	1964	1966	1970	1975
Males				
1. Grade school or less	49.5%	49.9%	39.2%	37.4%
2. Some high school	62.0	60.4	51.0	47.8
3. High school graduate	56.8	55.1	47.7	45.6
4. Some college	50.4	53.4	37.3	36.1
5. College graduate	42.5	36.8	30.6	28.1
Females				
1. Grade school or less	18.2	18.2	19.7	18.2
2. Some high school	36.5	39.8	34.4	33.2
3. High school graduate	35.4	43.2	32.2	31.9
4. Some college	36.1	35.9	36.3	32.2
5. College graduate	35.0	28.2	26.0	21.1

SOURCE: National Clearinghouse for Smoking and Health (*60,62,64*).

Table 7 shows the prevalence of current, regular cigarette smoking among adults aged 20 years and over according to family income, selected occupational groups, and marital status for 1976 (*8*). Among adult males with higher family incomes there is a lower prevalence of smoking. By contrast, the prevalence of adult female smoking increases with family income. This finding is reproduced in the surveys conducted by the National Clearinghouse for Smoking and Health (*60,62,64*). The prevalence of smoking among professionals is relatively low for both sexes. It is also relatively low for those not in the labor force, which includes students and housewives. By contrast, managers

TABLE 7.—Estimates of the percentage of current, regular cigarette smokers, adults aged 20 years and over, according to family income, selected occupation groups, and marital status, United States, 1976

Category	Male	Female
1. Family income		
Under $5,000	42.5	28.3
$5,000 to 9,999	45.5	33.5
$10,000 to 14,999	45.5	32.5
$15,000 to 24,999	40.4	33.0
$25,000 or more	34.7	35.1
2. Occupation groups		
White collar	36.6	34.3
Professional, technical and kindred workers	30.0	29.1
Managers and administrative, non-farm	41.0	41.6
Sales workers	39.9	38.1
Clerical and kindred workers	40.4	34.8
Blue collar[1]	50.4	39.0
Farm	36.9	31.3
Currently unemployed	56.8	40.0
Not in labor force	32.9	28.2
3. Marital Status		
Never married	40.1	28.3
Currently married	41.1	32.4
Widowed	32.6	20.4
Separated	63.3	45.1
Divorced	59.9	54.8

[1]Craftsmen and kindred workers, operatives including transport, non-farm laborers.
SOURCE: Bonham, G.S. (*8*).

and administrative personnel have higher prevalence rates. In this occupational group, in fact, the percentage of current regular female smokers exceeds that for adult males. Prevalence rates are also especially high for blue-collar workers and those currently unemployed. Those individuals who are either separated or divorced have higher prevalence rates. The prevalence of smoking among currently married women is somewhat higher than that of single women.

Although the survey results of the National Clearinghouse for Smoking and Health permit a similar trend analysis for these socio-economic groups, relatively large standard errors for many categories permit few strong conclusions. In general, the decline in the prevalence of smoking among adult males occurred in all socio-economic groups. A similar, but less consistent conclusion applies to adult females.

Beyond publication of these nationwide survey results in tabular form, little detailed analysis of the data has been performed. Hence,

more specific conclusions concerning trends among certain high-risk groups cannot be drawn.

Cigarette Dosage and Product Changes

Comparison of the net changes in per capita consumption (Figure 2) with net changes in the prevalence of smoking (Tables 1 and 4) suggests that the percentage of smokers has declined to a greater extent than the per capita consumption of cigarettes. This finding must be interpreted in light of possible underreporting in surveys. It is possible that many of those respondents recorded as former smokers in a particular survey had quit smoking only temporarily. Nevertheless, this finding suggests an overall increase in the number of cigarettes consumed per current smoker.

Table 8 presents estimates of the percentage of adult, current, regular cigarette smokers who reported they consumed more than one pack per day. Table 9 presents estimates of the percentage of teenage current, regular cigarette smokers who reported they consumed more than one-half pack per day. Because the existing adult survey data differ in eligible age group, reported ranges of cigarette consumption, and the percentage of those respondents with unknown consumption, the results of three different adult surveys are displayed separately. The results of Tables 8 and 9 are consistent with the hypothesis that the number of cigarettes consumed by the average cigarette smoker has increased over time. This conclusion applies to both sexes, especially to females.

Possible explanations for an increase in cigarette consumption frequency include the following: (1) Lighter cigarette smokers may have a higher rate of discontinuation than heavier smokers. Hence, discontinuation by lighter smokers would result in a higher proportion of heavier smokers remaining. (2) Those who continue to smoke might increase their consumption. (3) New entrants into the current smoking population may be consuming more cigarettes than established current smokers.

The available studies neither clearly exclude nor clearly prove any one of these hypotheses. It is possible that different explanations apply to different age and sex groups. Hammond and Garfinkel, reporting on the 2-year follow-up of the American Cancer Society study (*20*), noted an increase in the proportion of female current smokers who smoked more than one pack per day but no clear-cut change among male current smokers. In their 6-year follow-up report (*22*), they noted that, for male smokers, the proportion of light smokers who quit smoking was far greater than the proportion of heavy cigarette smokers who gave up the habit. This conclusion does not appear to be an artifact produced by the practice of decreasing the number of cigarettes one smokes prior to quitting (*21*). On the other hand, the evidence

TABLE 8.—Estimates of the percentage of current, regular cigarette smokers who consume more than one pack per day, adults, United States, 1955—1976

Year	Supplement to Current Population Survey (17 yrs. and over) 21 cigarettes or more daily			Health Interview Survey (17 yrs. and over) 25 cigarettes or more daily			National Clearinghouse for Smoking and Health (21 yrs. and over) 25 cigarettes or more daily		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
1955	20.2[1]	25.5	9.8						
1964							25.7	32.4	17.7
1965				19.9	24.5	13.7			
1966	21.6	26.3	15.7				27.2	34.7	16.9
1967	21.9	26.2	16.3						
1968	22.4	26.5	16.8						
1970				23.3	27.6	18.1	25.2	31.1	17.1
1974				24.7[2]	30.3	18.4			
1975							30.1	36.0	22.8
1976				25.3[3]	30.8	19.4			

[1]18 years and over.
[2]Data provided by Health Interview Survey, Natonal Center for Health Statistics.
[3]20 years and over.
SOURCE: National Center for Health Statistics (*55-59*), National Clearinghouse for Smoking and Health (*60,62,64*).

TABLE 9.—Estimates of the percentage of current, regular cigarette smokers who consume 10 or more cigarettes daily, teenagers, aged 12 to 18, United States, 1968—1974

Year	Males	Females	Total
1968	45.7	39.0	43.2
1970	43.4	43.7	43.5
1972	54.0	47.3	50.9
1974	66.8	56.4	61.7

NOTE: Current regular smoker includes respondent who smokes cigarettes at least weekly.
SOURCE: National Clearinghouse for Smoking and Health (*61,63,65*).

supporting the hypothesis that a higher proportion of female light smokers quit smoking was not clear-cut.

The observation of an increase in the percentage of heavier smokers is particularly relevant because it parallels certain significant changes in the composition of the cigarette product. In the years following the initial publicity concerning the health hazards of cigarettes, in 1953

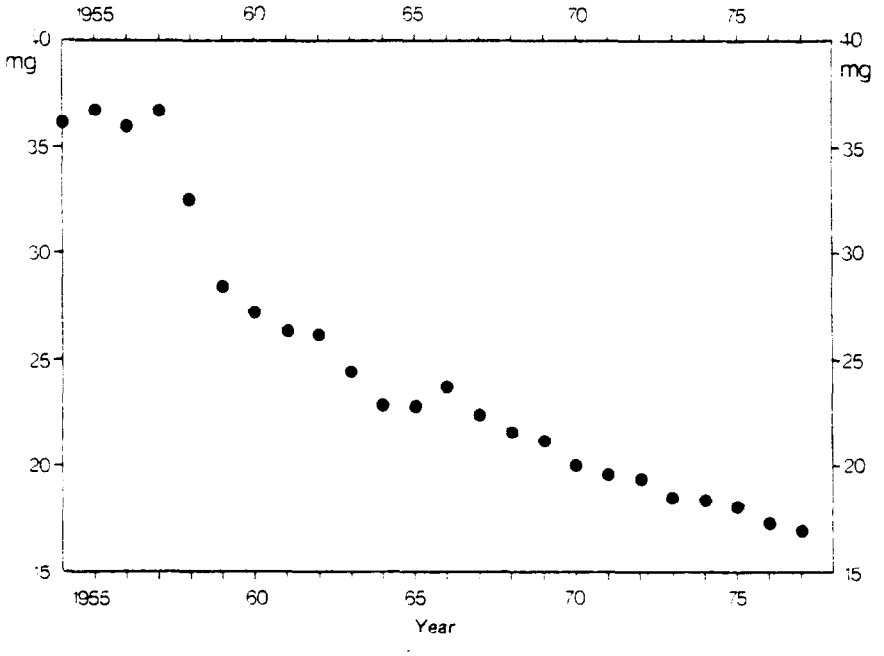


FIGURE 3. Sales weighted average "tar" per cigarette, 1954—1977

SOURCE: Consumers Union (*9*), Hammond, E.C. (*20*), Maxwell, J.C.C. (*27—30*), Owen, T.B. (*38*), Philip Morris, Inc. (*39a*), U.S. Federal Trade Commission (*67*) Wakeham, H. (*73*), Weber, K.H. (*76*), Wynder, E.L. (*78*).

and 1954, the consumption of filtertip cigarettes increased rapidly (Figure 1). By the time of the first Surgeon General's Report (1964), 65 percent of current smokers reported that they smoked filtertip brands (*60*). By 1975, 85 percent of current smokers consumed filtertip brands (*64*). From 1964 to 1977, the market share of filtertip cigarettes increased from 60 percent to 90 percent.

At the same time, the "tar" and nicotine contents of cigarettes have declined. This trend is illustrated in Figure 3, which depicts the sales-weighted average "tar" delivery per cigarette from 1954 to 1977 (*9, 20, 27–30, 38, 39a, 67, 70, 73, 76, 78*). For the years after 1967, periodic measurements of cigarette "tar" by the Federal Trade Commission (*67*) permit reliable calculations of sales-weighted average "tar" delivery. Prior to 1967, calculations of average "tar" are necessarily based upon reports of less standardized measurements. The results in Figure 3 for this period are based upon those reported by Wakeham (*73*), Weber (*76*), and Philip Morris, Inc. (*39a*). (See also Figures 15 and 16 of Chapter 14.)

From 1954 to 1965, sales-weighted average "tar" decreased from approximately 37 mg to approximately 23 mg. Although this change

paralleled the rapid increase in filtertip market share, it also reflected a decrease in the "tar" content of both filtertip and nonfilter cigarettes. Since 1966, the sales-weighted average "tar" has continued to decrease. However, the overall percentage change in average "tar" delivery for the period 1966 to 1977 has been much less than the percentage change in average "tar" from 1957 to 1965 (Figure 3). The observed decreases in sales-weighted average "tar" have been paralleled by declines in the sales-weighted nicotine per cigarette. Over the period 1959 to 1978, the sales-weighted average nicotine per cigarette decreased from about 2.0 mg to about 1.1 mg. (See Figure 16 of Chapter 14).

Although the average "tar" delivery of cigarettes has declined throughout the last two decades, the period from 1970 in particular reflects the growing popularity of new, lower "tar" brands. Figure 4 depicts the market share of those cigarettes with "tar" delivery 15 mg or less for 1967–78. The market share of these brands increased from about 3 percent in 1970 to an expected 30 percent in 1978. It should be noted, however, that a substantial part of the observed decline in average "tar" during this period is attributable to the reformulation of existing brands (*68,69*). To some extent, this continuing decline in average "tar" has been retarded by the increasing market share of longer, relatively higher "tar" brands. The market share of cigarettes 95 mm or longer has increased from 9 percent in 1967 to 28 percent in 1977 (*69*).

The relation between the observed increases in cigarette consumption among current smokers and the observed decline in "tar" and nicotine is not well understood. This empirical issue is of particular interest in view of the accepted conclusion that nicotine is a significant addictive component of cigarettes (Chapter 15 of this report). Studies of changes in cigarette consumption among those who voluntarily switched to lower "tar" and nicotine cigarettes (e.g., *42*) have yielded equivocal results, with some smokers reporting increased consumption, many smokers reporting no change, and still others reporting a decrease. However, the underlying reasons for individual decisions to switch to a lower "tar" and nicotine cigarette may be varied and have not been thoroughly explored. It is also unclear whether the decrease in average "tar" and nicotine delivery has led to an increased consumption frequency of new initiators of cigarette smoking. This possibility is at least raised by observation of a recent increase in heavier smoking among teenagers (Table 9).

Short-term experiments which monitor individuals' changes in consumption in response to changes in cigarette "tar" and nicotine delivery have also yielded varied results (*42,45*). In one study (*45*), the dilution of cigarette smoke by means of special filters was associated with a compensatory increase in constituent intake but without a significant change in the number of cigarettes smoked. Individuals

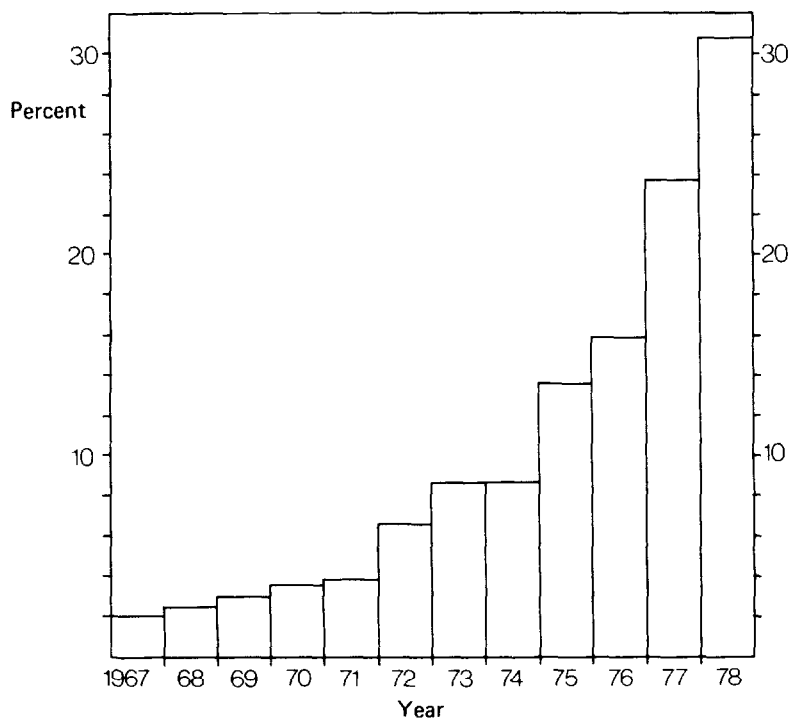


FIGURE 4. Market share of cigarettes with "tar" 15 mg or less, 1967—1978 (1978 projected)

SOURCE: Maxwell, J.C.C. (*27–30*), Standard and Poor's Corporation (*44*), U.S. Federal Trade Commission (*67–69*).

were apparently able to compensate for the lowered "tar" and nicotine concentrations by inhaling more deeply and by smoking a greater fraction of the cigarette.

Table 10 presents some selected survey results concerning changes in the style or pattern of cigarette smoking over time. Because the data are derived from respondents' self-assessments of inhalation patterns and butt lengths, they may not be reliable. Hammond (*18*), for example, discarded a similar analysis of respondent-reported butt lengths because questionnaire results did not correspond to individuals' observed smoking habits.

The results in Table 10 do suggest some downward trends in the percentage of deep inhalers, but they are hardly conclusive. A change in the formulation of the National Clearinghouse on Smoking and Health questionnaire between 1966 and 1970 complicates the analysis of Category 3 in Table 10. Nevertheless, if respondent answers are to be taken at face value, there appears to be an increase in the

TABLE 10.—Respondent-reported styles of cigarette smoking, current, regular cigarette smokers, selected categories, adults, United States, 1964—1975

Category	1964		1966		1970		1975	
	Male	Female	Male	Female	Male	Female	Male	Female
1. Inhaling deeply into the chest	36.5%	22.5%	31.8%	15.5%	34.3%	17.5%	30.3%	16.4%
2. Inhaling almost every puff	63.1	54.8	63.0	52.1	60.5	47.2	58.5	50.7
3. Smoking cigarette as far as possible	15.9	7.5	13.5	10.0	9.6	10.4	10.9	12.9

1. In 1964 and 1966, the questionnaire response was phrased "as deeply into the chest as possible." In 1970 and 1975, the questionnaire response was phrased "deeply into the chest".

2. In each survey year, the questionnaire response was "inhale almost every puff of each cigarette."

3. In 1964 and 1966, the respondent was asked to draw a line on a diagram of a cigarette, indicating the average length of the discarded cigarette butt length. In 1970 and 1975 the verbal questionnaire response was smoking cigarette "as far as possible." The data for 1964 and 1966 correspond to those respondents indicating a discarded cigarette butt length no greater than 20mm.

SOURCE: National Clearinghouse for Smoking and Health (*60,62,64*)

percentage of adult female smokers who smoke their cigarettes "as far as possible."

Research Issues

1. It remains unclear how anti-smoking publicity affects individual behavior. Available data indicate that declines in aggregate consumption during recent periods of anti-smoking publicity reflect individuals' quitting cigarette smoking. The aggregate effect of anti-smoking publicity on the rate of initiation of smoking has not been determined; similarly, its effect on individual brand choices is unclear.

2. Trends in cigarette smoking among specific high-risk groups require further investigation. A wealth of survey data is available for this purpose but has not been analyzed.

3. The relation between changes in cigarette "tar" and nicotine and changes in smoking behavior remains poorly understood. The product changes may influence the rate of initiation of cigarette smoking, the rate of cessation, and the consumption frequency of current smokers.

4. Frequent monitoring of cigarette smoking habits is critical for the design and evaluation of future public policy actions. Longitudinal studies are essential for this purpose.

Summary

1. The per capita consumption of cigarettes decreased temporarily from 1953 to 1954, in 1964, and from 1968 to 1970. It has declined

steadily since 1973. Per capita consumption in the year 1978 was approximately 9 percent less than its peak value in 1963.

2. The observed temporary declines in per capita consumption coincided with periods of increased publicity concerning the health hazards of smoking.

3. From 1955 to 1978, the percentage of adult males who regularly smoke cigarettes declined from approximately 53 percent to approximately 38 percent. From 1955 to 1965, the percentage of adult females who regularly smoke cigarettes increased from approximately 25 percent to 32 percent. From 1965 to 1978, the prevalence of regular cigarette smoking among females declined by no more than 3 or 4 percent. In 1978, the estimated percentage of all adults who regularly smoke cigarettes reached its lowest recorded point in over 30 years.

4. During the past decade, the percentage of teenage males regularly smoking cigarettes has not declined significantly. The percentage of teenage females regularly smoking cigarettes has increased markedly and may now exceed the prevalence of regular cigarette smoking among teenage males.

5. The observed decline in the prevalence of adult male cigarette smoking occurred in all socioeconomic groups and in all age ranges. Cessation of cigarette smoking among women also occurred in all socioeconomic groups and in all age ranges, but was counterbalanced by a high rate of initiation of smoking.

6. The available data suggest that the observed temporary declines in per capita consumption from 1953 to 1954, during 1964, and from 1968 to 1970 represent primarily individuals' quitting cigarette smoking, either permanently or temporarily.

7. The available data suggest that the average cigarette consumption frequency among regular current smokers has increased over time, particularly among female smokers. Possible explanations for this effect include: (a) a supposedly higher rate of quitting among lighter cigarette smokers, (b) an increase in cigarette smoking frequency among those who continue to smoke, and (c) an increased frequency of smoking among new entrants into the population of cigarette smokers.

8. Available information on changes in the depth of inhalation, the fraction of burning cigarette actually smoked, or the length of discarded cigarette butt are inconclusive.

9. From 1950 to 1960, the market share of filtertip cigarettes increased rapidly from 0.6 percent to 50.9 percent. In 1978, the market share of filtertip cigarettes is expected to exceed 90 percent. By 1975, 85 percent of current regular smokers consumed filtertip cigarettes.

10. From 1954 to 1977, the sales-weighted average "tar" per cigarette declined from approximately 36 mg to 17 mg. The decline in average "tar" delivery was observed for both filtertip and nonfilter cigarettes. A decline in the sales-weighted average nicotine per

cigarette was also observed. These changes reflect the introduction of filtertip cigarettes, the reformulation of existing cigarette brands, a decline in the sales of relatively higher "tar" and nicotine brands, and, more recently, the rapidly increasing share of relatively lower "tar" and nicotine cigarettes. From 1970 to 1978, the market share of cigarettes with "tar" less than or equal to 15 mg has increased from about 3 percent to over 30 percent. The effects of these product changes on the composition of the cigarette smoking population and on the behavior of cigarette smokers are not well understood.

Appendix: Cigarette Smoking in the United States, 1950–1978: References

(1) ACTION ON SMOKING AND HEALTH. Smoking and Health, History of the Battle, 1964-1971. ASH Newsletter 1(1): January/February 1971.

(2) AMERICAN INSTITUTE OF PUBLIC OPINION (GALLUP). The Gallup Poll Public Opinion, 1935-1971 Series, p. 477-1501; 1972-1977 Series, p. 274-1203.

(3) AMERICAN INSTITUTE OF PUBLIC OPINION (GALLUP). The Gallup Opinion Index, September 1970, July 1971, July 1972, June 1978.

(4) AMERICAN INSTITUTE OF PUBLIC OPINION (GALLUP). Gallup Youth Survey, Princeton, N.J., September 7, 1977.

(5) ATKINSON, A.B., SKEGG, J.L. Anti-Smoking Publicity and the Demand for Tobacco in the U.K. Manchester School of Economic and Social Studies 41(3): 265-282, September 1973.

(6) ATKINSON, A.B., SKEGG, J.L. Control of Smoking and Price of Cigarettes—A Comment. British Journal of Preventive and Social Medicine 28: 45-48, 1974.

(7) BANZAF v. F.C.C. 405 F. 2d 1082(C.A.D.C. 1968) cert. denied 396 U.S. 842(1969).

(8) BONHAM, G.S., LEAVERTON, P.E. Use Habits of Four Common Drugs: Cigarettes, Coffee, Aspirin and Sleeping Pills, United States, 1976. National Center for Health Statistics, Vital and Health Statistics, Series 10, 1979. (In press)

(9) CONSUMERS UNION. Cigarettes. Consumer Reports, 18: 58-74, February 1953; 20: 56-73, February 1955; 22: 100-110, March 1957; 22: 460-461, October 1957; 22: 542-543, November 1957.

(10) CONSUMERS UNION. Cigarette Smoking and Lung Cancer. Consumer Reports 19: 54-92, February 1954.

(11) CRESWELL, J.M., CRESWELL, W.H., JR. Youth Smoking Behavior Characteristics and Their Educational Implications. A Report of the University of Illinois Anti-Smoking Education Study. Champaign, University of Illinois June 30, 1970 164 pp.

(12) FISHBEIN, M. Consumer Beliefs and Behavior with Respect to Cigarette Smoking: A Critical Analysis of the Public Literature. Report Prepared for the Staff of the Federal Trade Commission. In: U.S. Federal Trade Commission, Report to Congress Pursuant to the Public Health Cigarette Smoking Act for the year 1976, Appendix A, May 1977.

(13) FRIEDMAN, G.D., SELTZER, C.C., SIEGELAUB, A.B., FELDMAN, R., COLLEN, M.F. Smoking Among White, Black and Yellow Men and Women: Kaiser-Permanente Multiphasic Health Examination Data, 1964-1968. American Journal of Epidemiology 96(1): 23-25, 1972.

(14) GREEN D.E., NEMZER, D.E. Changes in Cigarette Smoking by Women—An Analysis, 1966 to 1970. Health Services Reports 88(7): 631-636, August-September 1973.

(15) HAENSZEL, W., SHIMKIN, M.B., MILLER, H.P. Tobacco Smoking Patterns in the United States. Public Health Monograph No. 45, Public Health Service Publication No. 463. U.S. Department of Health, Education, and Welfare, Public Health Service, November 1956.

(16) HAMILTON, J.L. The Demand for Cigarettes: Advertising, the Health Scare, and the Cigarette Advertising Ban. Review of Economics and Statistics 54(4): 401-411, November 1972.

(17) HAMILTON, J.L. The Effect of Cigarette Advertising Bans on Cigarette Consumption. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). Proceedings of the Third World Conference on Smoking and Health. Volume II. Health Consequences, Education, Cessation Activities, and Social Action. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 77-1413, 1977, pp. 829-840.

(18) HAMMOND, E.C. Inhalation in Relation to Type and Amount of Smoking. Journal of the American Statistical Association, 54: 35-51, March 1959.
(19) HAMMOND, E.C., GARFINKEL, L. Smoking habits of men and women. Journal of the National Cancer Institute 27: 419-442, 1961.
(20) HAMMOND, E.C., GARFINKEL, L. Changes in cigarette smoking. Journal of the National Cancer Institute 33: 49-64, 1964.
(21) HAMMOND, E.C., GARFINKEL, L. Influence on Health on Smoking Habits. National Cancer Institute Monograph No. 19: 269-285, 1966.
(22) HAMMOND, E.C., GARFINKEL, L. Changes in cigarette smoking 1959-1965. American Journal of Public Health 58(1): 30-45, January 1968.
(23) HORN, D., COURTS, F.A., TAYLOR, M.A., SOLOMON, E.S. Cigarette smoking among high school students. American Journal of Public Health 49(11): 1497-1511, November 1959.
(24) KELLNER, I.L. The American Cigarette Industry—A Reexamination. Doctoral dissertation, New School for Social Research, New York, 1973, pp. 114-37.
(25) LIEB, C.W. Can the poisons in cigarettes be avoided? Reader's Digest 63: 45-47, December 1953.
(26) LIEBERMAN RESEARCH, INC. The Teenager Looks at Cigarette Smoking. Report of a Study Conducted for the American Cancer Society. New York, 1969.
(27) MAXWELL ASSOCIATES. The Maxwell Fact Book. Richmond, Virginia, Maxwell Consumer Services Reports, March 31, 1975, p. 17.
(28) MAXWELL, J.C. Philip Morris has become the leader of the pack. Barron's, October 27, 1975, p. 9.
(29) MAXWELL, J.C. Low-tar entries are the hottest selling cigarettes. Barron's, November 8, 1976, p. 11.
(30) MAXWELL, J.C. Lighting up. Low-tar Cigarettes have become the leaders of the pack. Barron's, November 28, 1977, pp. 9 and 88.
(31) MILLER, L.M., MOHAHAN, J. The facts behind the cigarette controversy. Reader's Digest 65: 1-6, July 1954.
(32) MILLER, R.H. The Demand for Cigarettes in the United States. Department of Agriculture, Economic Research Service, 1970.
(33) MILLER, R.H. Tobacco and Tobacco Products Consumption for 1980. U.S. Department of Agriculture, Economic Research Service, 1972.
(34) MILLER, R.H. Government actions relating to smoking and health, 1964-74. Tobacco Situation 148: 33-37, June 1974.
(35) MILLER, R.H. Factors Affecting Cigarette Consumption. U.S. Department of Agriculture, Economic Research Service, 1974.
(36) NORR, R. Cancer by the carton. Reader's Digest 61: 7-8, December 1952.
(37) O'KEEFE, M.T. The anti-smoking commercials: A study of television's impact on behavior. Pubic Opinion Quarterly 35(2): 242-248, Summer 1971.
(38) OWEN, T.R. Tar and nicotine from U.S. cigarettes: trends over the past twenty years. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). Proceedings of the Third World Conference on Smoking and Health. Volume I. Modifying the Risk for the Smoker. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH) 76-1221, 1976, pp. 73-80.
(39) PETO, J. Price and consumption of cigarettes: A case for intervention? British Journal of Preventive and Social Medicine 28: 241-245, 1974.
(39a) PHILIP MORRIS, INC. Testimony. Hearings Before the Consumer Subcommittee of the Committee on Commerce. Public Health Cigarette Amendments of 1971. S. 1454. United States Senate 92nd Congress, 2nd Session. Serial No. 92-82, February 1972, p. 599

(40) SALBER, E.J., GOLDMAN, E., BUKA, M., WELSH, B. Smoking habits of high school students in Newton, Massachusetts. New England Journal of Medicine 265(20): 969-974, November 16, 1961.
(41) SALBER, E.J., ABELIN, T. Smoking behavior of Newton school children 5-year follow up. Pediatrics 40(3, Part I): 363-372, September 1967.
(42) SCHACHTER, S. Pharmacological and psychological determinants of smoking. Annals of Internal Medicine 88: 104-114, 1978.
(43) SCHUMAN, L. Patterns of smoking behavior. In: Jarvik, M.E., Cullen, J.W., Gritz, E.R., Vogt, T.M., West, L.J. (Editors). Research on Smoking Behavior. NIDA Research Monograph No. 17. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institute on Drug Abuse, December 1977, pp. 36-66.
(44) STANDARD AND POOR'S CORPORATION. Tobacco, Basic Analysis. Standard and Poor's Industry Surveys, May 26, 1977.
(45) SUTTON, S.R., FEYERABEND, C., COLE, M.B., RUSSELL, M.A.H. Adjustment of smokers to dilution of tobacco smoke by ventilated cigarette holders. Clinical Pharmacology and Therapautics 24(4): 395-405, October 1978.
(46) U.S. COMMISSION ON MARIHUANA AND DRUG ABUSE. Drug Use in America: Problems in Perspective. Washington, D.C., 1973, P. 46.
(47) U.S. DEPARTMENT OF AGRICULTURE, AGRICULTURAL MARKETING SERVICE. Annual Report on Tobacco Statistics 1963, Statistical Bulletin No. 343, April 1964.
(48) U.S. DEPARTMENT OF AGRICULTURE, AGRICULTURAL MARKETING SERVICE. Annual Report on Tobacco Statistics 1977, Statistical Bulletin No. 605, May 1978.
(49) U.S. DEPARTMENT OF AGRICULTURE, ECONOMIC RESEARCH SERVICE. Tobacco Situation 112:7, June 1965.
(50) U.S. DEPARTMENT OF AGRICULTURE, ECONOMIC RESEARCH SERVICE. Tobacco Situation 151:6, March 1975.
(51) U.S. DEPARTMENT OF AGRICULTURE, ECONOMIC RESEARCH SERVICE. Tobacco Situation 165:2, September 1978.
(52) U.S. DEPARTMENT OF COMMERCE, BUREAU OF THE CENSUS. Estimates of the Population of the United States by Age, Sex, and Race. Current Population Reports. Series P-25, No. 310, June 1965; No. 519, April 1974; No. 614, November 1975; No. 643, January 1977.
(53) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE. Smoking and Health, Report of the Advisory Committee to the Surgeon General of the Public Health Service, Public Health Service Publication No. 1103, 1964.
(54) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CANCER INSTITUTE. Cigarette Smoking Among Teen-Agers and Young Women. DHEW Publication No. (NIH) 77-1203, 1977.
(55) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CENTER FOR HEALTH STATISTICS. Cigarette Smoking Status—June 1966, August 1967, and August 1968. Monthly Vital Statistics Report 18(9): 1-4, Supplement, December 5, 1969.
(56) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CENTER FOR HEALTH STATISTICS. Changes in Cigarette Smoking Habits Between 1955 and 1965. Vital and Health Statistics, Series 10, Number 59, April 1970.
(57) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CENTER FOR HEALTH STATISTICS. Changes in Cigarette Consumption Between June 1966 and August 1968. Monthly Vital Statistics Report 19(9): 1-4, Supplement, December 18, 1970.

(58) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CENTER FOR HEALTH STATISTICS. Cigarette Smoking: United States, 1970. Monthly Vital Statistics Report 21(3): 1-8, Supplement, June 2, 1972.

(59) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CENTER FOR HEALTH STATISTICS, NATIONAL CENTER FOR HEALTH SERVICES RESEARCH. Health, United States, 1978. 1979.

(60) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Use of Tobacco, Practices, Attitudes, Knowledge, and Beliefs, United States—Fall 1964 and Spring 1966. July 1969.

(61) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE ON SMOKING AND HEALTH. Teenage Smoking, National Patterns of Cigarette Smoking, Ages 12 through 18, in 1968 and 1970. DHEW Publication No. (HSM) 72-7508, 1972.

(62) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco 1970, June 1973.

(63) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Patterns and Prevalence of Teenage Cigarette Smoking: 1968, 1970, 1972, and 1974. July 1974.

(64) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco 1975. 1976.

(65) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CLEARINGHOUSE ON SMOKING AND HEALTH. Teenage Smoking, National Patterns of Cigarette Smoking, Ages 12 through 18, in 1972 and 1974. DHEW Publication No. (NIH) 76-931, 1976.

(66) U.S. FEDERAL COMMUNICATIONS COMMISSION. Report and Order re Further Regulatory Policies Concerning Cigarette Advertising and Anti-Smoking Presentations, December 15, 1970.

(67) U.S. FEDERAL TRADE COMMISSION. Report of Tar and Nicotine Content of the Smoke of 59 Varieties of Cigarettes. November 20, 1967, and subsequent issues, 1968-1978.

(68) U.S. FEDERAL TRADE COMMISSION. Statistical Supplement to Report to Congress Pursuant to the Public Health Cigarette Smoking Act for the Year 1975, May 1978.

(69) U.S. FEDERAL TRADE COMMISSION. Statistical Supplement to Report to Congress Pursuant to the Public Health Cigarette Smoking Act for the Year 1977, 1978.

(71) WAINGROW, S., HORN, D., IKARD, F.F. Dosage patterns of cigarette smoking in american adults. American Journal of Public Health 58(1): 54-70, January 1968.

(72) WAINGROW, S., HORN, D. Relationship of Number of Cigarettes Smoked to "Tar" rating. National Cancer Institute Monographs 28: 29-33, June 1968.

(73) WAKEHAM, H. Sales weighted average tar and nicotine deliveries of U.S. cigarettes from 1957 to present. In: Wynder, E.L., Hecht, S. (Editors). Lung Cancer. International Union Against Cancer, UICC Technical Report Series, Volume 25, Geneva, 1976, pp. 151-152.

(74) WARNER, K.E. The effects of the anti-smoking campaign on cigarette consumption. American Journal of Public Health 67(7): 645-650, July 1977.

(75) WARNER, K.E. Possible increases in the underreporting of cigarette consumption. Journal of the American Statistical Association 73(362): 314-318, June 1978.

(76) WEBER, K.H. Recent changes in tobacco products and their acceptance by the consumer. In: Sixth International Tobacco Scientific Conference, CORESTA Information Bulletin, Paris, 1976, pp.15-30.

(77) WILLIAMS, T.M. Summary and Implications of Review of Literature Related to Adolescent Smoking. U.S. Department of Health, Education and Welfare, Public Health Service, National Clearinghouse for Smoking and Health, September 1971.

(78) WYNDER, E.L., MABUCHI, K., BEATTIE, E.J. The epidemiology of lung cancer, recent trends. Journal of the American Medical Association 213(13): 289-296, September 28, 1970,(Figure 4).

(79) YANKELOVICH, SKELLY, AND WHITE, INC. A Study of Cigarette Smoking Among Teen-Age Girls and Young Women. Summary of the Findings. Conducted for the American Cancer Society, February 1976.

HOW TO USE THIS INDEX

The Surgeon General's Report on Smoking and Health consists of 23 chapters and an Appendix. Each includes a detailed table of contents to lead the reader to the information sought and to give a quick overview of content.

The index reflects the contents of all 23 chapters and the Appendix. It was attempted to use the natural language of the Report whenever possible, but to achieve consistency in the terminology, some concepts had to be reworded.

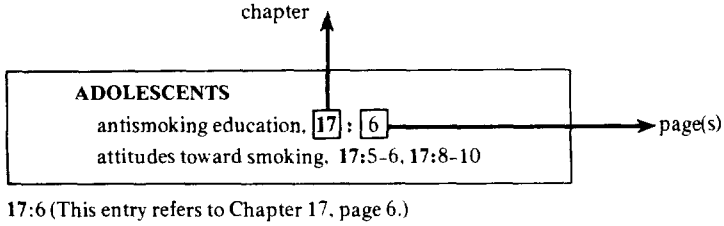
Major concepts are expressed in primary terms (in bold, all upper case letters), which are modified by the secondary terms (indented, lower case, followed by page numbers), in order to convey the specific topic. In order to lead the reader to primary terms related to the one of interest, cross references follow many primary terms, e.g.

ALLERGY
(See also **ALLERGY, TOBACCO; HYPERSENSITIVITY)**

If a certain concept could have appeared as more than one primary term, the reader is referred to the primary term actually used in the following manner:

Areca nut
See **BETEL NUT**

Secondary terms are followed by the pagination. The latter consists of one bold figure, referring to the Report chapter, a colon, followed by the page number(s). The following examples illustrate this:



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