

The Health Consequences of SMOKING

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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Health Services and Mental Health Administration

The
Health Consequences
of Smoking

January 1973

**U.S. DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE
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Preface

This report is the seventh in a series issued by the Public Health Service reviewing and assessing the scientific evidence linking cigarette smoking to disease and premature death. The current report reiterates, strengthens, and extends the findings in earlier reports that cigarette smoking is a major health problem in the United States.

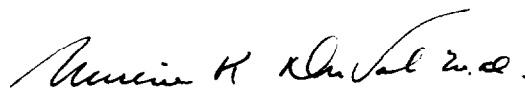
The evidence has broadened dramatically in recent years. A Public Health Service assessment of evidence available in 1959 was largely focused on the relationship of cigarette smoking and lung cancer. The first formal report on this subject in 1964 found that cigarette smoking was not only a major cause of lung cancer and chronic bronchitis, but was associated with illness and death from chronic bronchopulmonary disease, cardiovascular disease, and other diseases.

The 1973 report confirms all these relationships and adds new evidence in other areas as well. The evidence in the chapter on pregnancy strongly indicates a causal relationship between cigarette smoking during pregnancy and lower infant birth weight and a strong, probably causal, association between cigarette smoking and higher late fetal and neonatal mortality. Also reported is the convergence of other evidence which suggests that cigarette smoking during pregnancy interacts with other risk factors to increase the risk of an unfavorable outcome of pregnancy for certain women more than others.

For the first time in this series of reports, a separate chapter is devoted to pipe and cigar smoking and the health hazards involved. Included is an assessment of the health implications of the new small cigars which look like cigarettes.

A final chapter, new to the reports, concerns cigarette smoking and exercise performance. A review of a number of fitness tests comparing smokers to nonsmokers indicates that cigarette smoking impairs exercise performance for many types of athletic events and activities involving maximal work capacity.

The interrelationships of smoking and health are no less complex today than they were reported to be in the 1964 report. But since that time we have greatly broadened our knowledge and understanding of the problem. The current report symbolizes this progress.



MERLIN K. DUVAL, M.D.,
Assistant Secretary for Health.

DECEMBER 13, 1972.

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Preparation of the Report and Acknowledgments

“Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service,” subsequently referred to as the “Surgeon General’s Report,” was published in 1964. The National Clearinghouse for Smoking and Health, established in 1965, has the responsibility for the continuous monitoring, compilation, and review of the world’s medical literature which bears upon the health consequences of smoking. As called for by Public Law 89–92, the following three reviews of the medical literature on the health consequences of smoking, which had come to the attention of the Clearinghouse since the original “Surgeon General’s Report,” were sent to the Congress:

1. “The Health Consequences of Smoking, A Public Health Service Review: 1967” (submitted July 1967).
2. “The Health Consequences of Smoking, 1968 Supplement to the 1967 PHS Review” (submitted July 1968).
3. “The Health Consequences of Smoking, 1969 Supplement to the 1967 PHS Review” (submitted July 1969).

Public Law 91–222 was signed into law on April 1, 1970, and called for an 18-month interval between the 1969 supplement and the next report. During this period, a comprehensive review of all of the medical literature available to the Clearinghouse relating to the health consequences of smoking was undertaken, with an emphasis upon the most recent additions to the literature. The product of this review was: “The Health Consequences of Smoking, A Report of the Surgeon General: 1971,” submitted to the Congress in January of 1971. Subsequently, a review of the medical literature in the field, which had come to the attention of the Clearinghouse since the publication of the 1971 report, was published as, “The Health Consequences of Smoking, A Report of the Surgeon General: 1972,” submitted in January of 1972.

Every report published since the original "Surgeon General's Report" has contained a review of the medical literature relevant to the association between smoking and cardiovascular disease, nonneoplastic bronchopulmonary disease, and cancer. Several of the reports included reviews of the relationship between smoking and peptic ulcer disease (1967, 1971, 1972) and cigarette smoking and pregnancy (1967, 1969, 1971, 1972). Other topics relating to the use of tobacco have received special emphasis in single reports:

1. Tobacco Amblyopia (1971 Report).
2. Allergy (1972 Report).
3. Public Exposure to Air Pollution From Tobacco Smoke (1972 Report).
4. Harmful Constituents of Cigarette Smoke (1972 Report).
5. Noncancerous Oral Disease (1969 Report).

The present document, "The Health Consequences of Smoking: 1973," includes reviews of the relationships between smoking and cardiovascular disease, bronchopulmonary disease, cancer, and peptic ulcer disease which are based upon medical literature which has become available to the Clearinghouse since the publication of the 1972 report. It also includes special reviews of the health consequences of pipe and cigar smoking and of the relationship between cigarette smoking and the outcomes of pregnancy. The material in these two latter chapters reflects a comprehensive review of the pertinent world medical literature which has come to the attention of the Clearinghouse since the publication of the original "Surgeon General's Report," including material which has become available since the 1972 report. The final chapter in this year's report is a review of the relationship between smoking and exercise performance, an area not covered previously in any report.

With the exception of "Chapter 4. Pregnancy," each chapter is organized in a similar fashion. The introduction to each chapter is a summary of the work reviewed in previous reports. The summary of each chapter encompasses only the work which has most recently become available to the Clearinghouse. The pregnancy chapter is organized into separate sections according to several different outcomes of pregnancy. Each section includes a brief review of previously reported work and contains its own separate summary, in place of an overall summary for the entire chapter.

The preparation of this report was accomplished in the following fashion:

1. The continuous monitoring and compilation of the medical literature on the health consequences of smoking was accomplished through several mechanisms.
 - (a) An information science corporation is on contract to extract articles on smoking and health from the medical literature of the world. This organization provides a semimonthly accessions list with abstracts and copies of the various articles. Translations are called for as needed. Articles are classified according to subject and filed by a series of code words and phrases.
 - (b) The National Library of Medicine, through the Medlars system, sends the National Clearinghouse for Smoking and Health a monthly listing of articles in the smoking and health area. These are reviewed, and articles not identified by the information science corporation are ordered.
 - (c) Staff members review current medical literature and identify pertinent articles.
2. The first drafts of the individual chapters were sent to reviewers for criticism and comment with respect to the articles reviewed, articles not included, and conclusions. The drafts were then revised until they met with the general approval of the reviewers. The final drafts were reviewed as a whole by the Director of the National Clearinghouse for Smoking and Health, the Director of the National Cancer Institute, the Director of the National Heart and Lung Institute, the Director of the National Institute of Environmental Health Sciences, the Surgeon General, and by additional experts both within and outside of the Public Health Service.

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CHAPTER 1

Cardiovascular Diseases

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Introduction

In the United States, coronary heart disease (CHD) is the leading cause of death and is the largest contributor to excess deaths among cigarette smokers. The following is a brief summary of the major relationship between smoking and cardiovascular diseases as outlined in previous reports of the health consequences of smoking (62, 63, 64, 65, 66, 67).

Many prospective and retrospective epidemiological studies have identified cigarette smoking, elevated serum cholesterol, and high blood pressure as major risk factors for the development of coronary heart disease. Cigarette smoking acts independently of and synergistically with the other CHD risk factors to greatly increase the risk of developing coronary heart disease. The risk of developing CHD for pipe and cigar smokers is much less than it is for cigarette smokers, but more than it is for nonsmokers. In the United States, cigarette smoking can be considered the major cause of cor pulmonale since it is the most important cause of chronic nonneoplastic bronchopulmonary disease.

Autopsy studies have demonstrated that aortic and coronary atherosclerosis are more common and severe, and myocardial arteriole wall thickness is greater, in cigarette smokers than in nonsmokers.

Those who stop smoking cigarettes experience a decreased risk of death from coronary heart disease compared to that of continuing smokers.

Experimental studies in humans and animals suggest that cigarette smoking may contribute to the development of CHD through the action of several independent or complementary mechanisms: The formation of significant levels of carboxyhemoglobin, the release of catecholamines, inadequate myocardial oxygenation which may result from a number of mechanisms, and an increase in platelet adhesiveness which may contribute to acute thrombus formation. There is evidence that cigarette smoking may accelerate the pathophysiological changes of preexisting coronary heart disease and therefore contributes to sudden death from CHD.

Recently published epidemiological, autopsy, and experimental investigations have added to the understanding of the association between smoking and cardiovascular diseases.

Coronary Heart Disease

Epidemiological Studies

SMOKING AND CERTAIN RISK FACTORS

A prospective epidemiological study of the factors associated with cardiovascular diseases was conducted among the 4,847 white and 2,434 black men and women of Evans County, Ga. (23). The investigation was initiated with a private census and preliminary examinations beginning in 1960. Followup examinations were conducted after 7 years. Cassel (13) reported that high blood pressure, elevated serum cholesterol, and cigarette smoking were major risk factors for the development of coronary heart disease. Increased body weight, an elevated hematocrit, and ECG abnormalities were additional factors that were associated with elevated CHD rates. A significant finding of this study was the very low prevalence and incidence of coronary heart disease (myocardial infarction and angina pectoris) in black men. The age-adjusted prevalence rates among black men were only half those of white men. The study showed that blacks were affected by the various risk factors for CHD in a similar fashion to whites but at a lower level of disease. This appeared to be true for any level of any risk factor or any combination of risk factors. Greater physical activity of blacks as compared to whites appeared to account for part of the observed difference in rates.

In this study, subjects were classified on the basis of their smoking history at enrollment and both current smokers and exsmokers were considered smokers. Both black and white male smokers had a higher

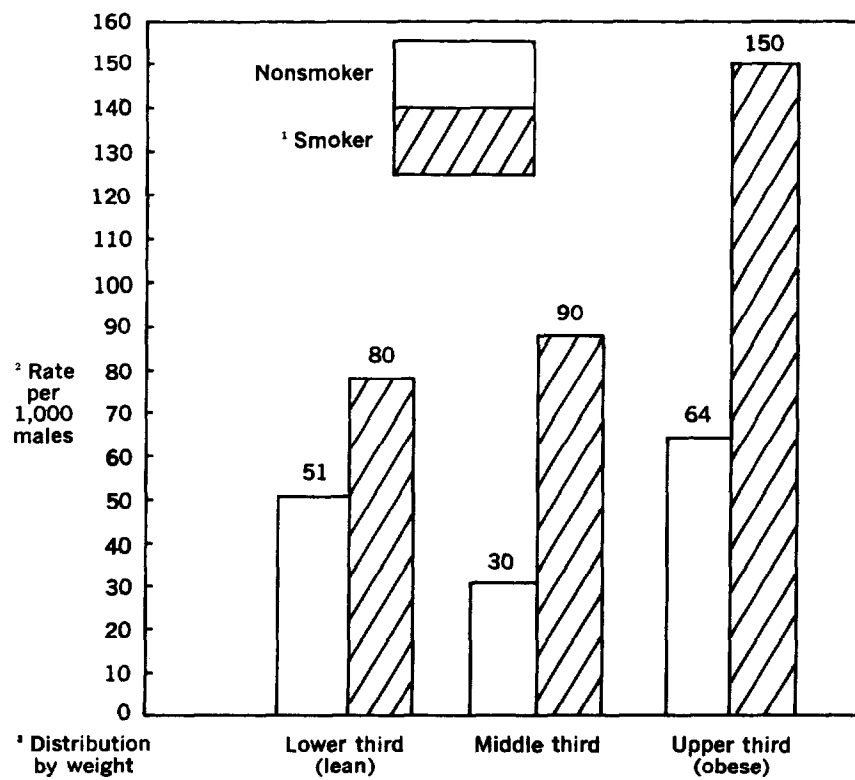
incidence of CHD than did nonsmokers, but white males had a higher incidence than blacks whether they were smokers or not. The age-adjusted incidence rate for white nonsmokers was 52.7 per thousand compared to 9.8 per thousand for black nonsmokers. White smokers had an incidence of 101, whereas the rate in black smokers was only 32.5. The prevalence of CHD increased with the number of cigarettes smoked per day in both groups.

The combined effect of body weight and cigarette smoking on the incidence of CHD was also examined (26). The "Quetelet index"¹ was used to determine relative weight. The risk of developing CHD did not change with increases in relative weight among nonsmokers, but smokers experienced a substantial risk of developing CHD with increases in weight (fig. 1).

The relationship of smoking to occupation and CHD was examined (14). Farmers who performed sustained physical activity had lower rates of CHD than nonfarmers. Figure 2 shows that, while smoking increased the risk of CHD in both farmers and nonfarmers, farmers had lower rates than nonfarmers whether or not they smoked.

¹ Quetelet index = $\frac{\text{weight}}{\text{height}^2} \times 100$.

Figure 1.—Age-adjusted incidence rates of CHD by ³ body weight and ¹ cigarette smoking (white males).

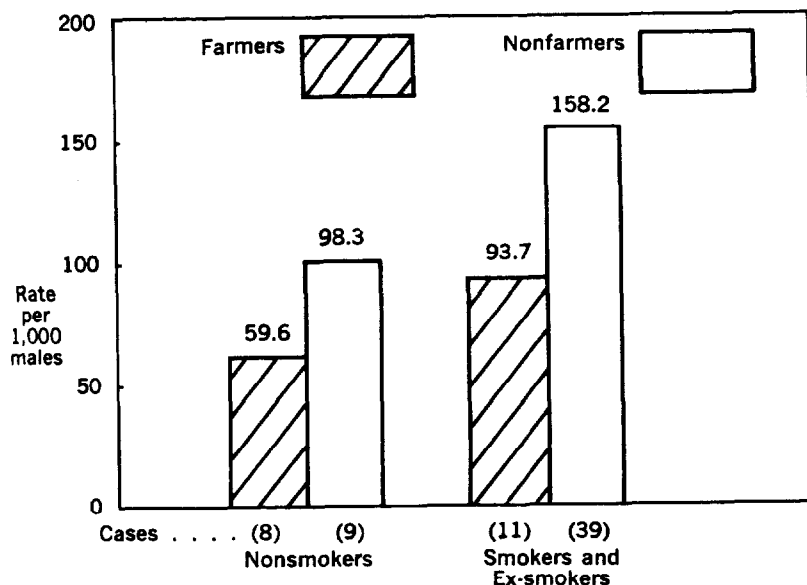


¹ Distribution by weight	Lower third (lean)		Middle third		Upper third (obese)	
	Number	Cases	Number	Cases	Number	Cases
Number	90	183	99	161	127	119
Cases	5	15	3	14	16	9

¹ Smokers excluding ex-smokers.
² 87 months follow-up period.
³ Based on Quetelet index.

SOURCE: Heyden, S., et al. (26).

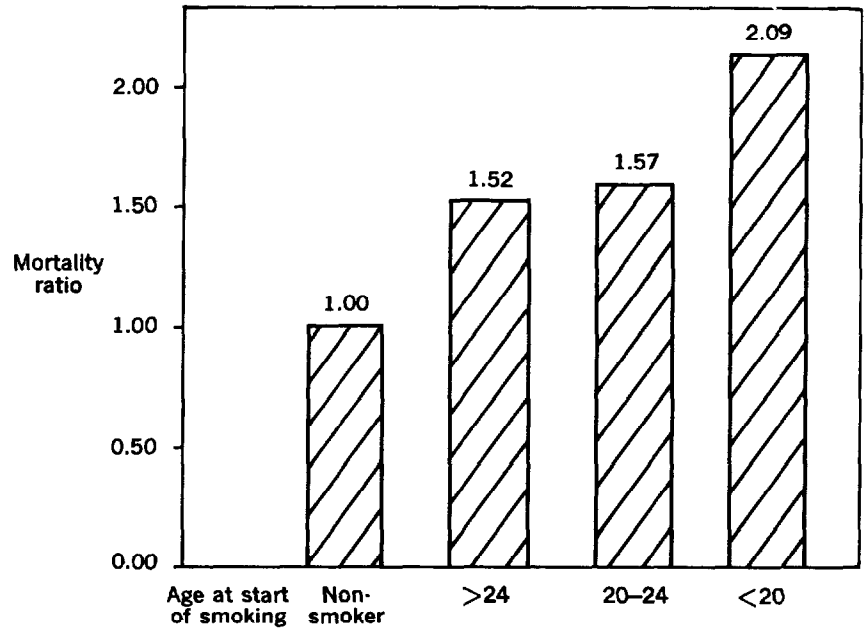
Figure 2.—Age-adjusted incidence rates of CHD comparing farmers who smoke cigarettes with nonsmoking farmers.



SOURCE: Cassel, J. C., et al. (14).

Hirayama (27) reported 5-year followup data on smoking in relation to death rates from a large prospective epidemiological study of 265,118 men and women in Japan. This investigation was the first of its kind to be conducted in an Asian population. During the followup period, 11,858 deaths occurred during 1,269,382 person years of observation. Male and female cigarette smokers experienced higher mortality rates from arteriosclerotic heart disease than did nonsmokers. Among cigarette smokers, the mortality ratios for arteriosclerotic heart disease were 1.56 ($P < 0.001$) for men and 1.44 ($P < 0.05$) for women. Dose-response relationships were found for both men and women as measured by the number of cigarettes smoked per day and age at initiation of smoking (fig. 3).

Figure 3.—Standardized mortality ratios for arteriosclerotic heart disease for males and females by age at initiation of cigarette smoking (Prospective study 1966–1970).



SOURCE: Hirayama, T. (27).

Gordon, et al. (22, 57), in a further analysis of the Framingham data, considered both by univariate and multivariate analysis the relation of certain key characteristics to the development of coronary heart disease. The characteristics were: High blood pressure, elevated serum cholesterol, cigarette smoking, left ventricular hypertrophy diagnosed by electrocardiogram, and glucose intolerance. Cigarette smoking emerged as one of the important risk factors for the development of coronary heart disease. There was a strong association between cigarette smoking and CHD other than angina pectoris, particularly among young male and female smokers. The relative role of cigarette smoking as a risk factor was emphasized by multivariate analysis. Cigarette smoking was not as strongly related to CHD in women as it was in men. This may have been in part due to the fact that there are fewer heavy smokers among women, and women tend to inhale smoke less than men.

Kagan, et al. (31) reported preliminary findings from the Honolulu Heart Study. The effect of migration on dietary patterns and the incidence of cardiovascular diseases in a cohort of men of Japanese ancestry born between 1900 and 1919, who were residents of Oahu in 1965, was examined in this prospective study. During the 2 years of followup, 101 men developed CHD in the population of 8,006 men ini-

tially examined. A significant relationship to CHD was found for the following risk factors: Cigarette smoking, elevated systolic and diastolic blood pressure, increased serum cholesterol, triglycerides or uric acid, and various measures of obesity.

Using data from the International Cooperative Study on Cardiovascular Epidemiology, Keys, et al. (34) calculate the probabilities for men aged 40 to 59 to develop coronary heart disease in 5 years. The authors noted "* * * that the relative CHD risk of different men within a given population is well predicted from the results of the multivariate analysis of the experience of men in other far-distant populations differing in socioeconomic circumstances, language, and ethnic background." Although the CHD incidence rate of European men was about half that of the Americans, the fact still remained that investigation of the four variables (cigarette smoking, age, systolic blood pressure, and cholesterol) was sufficient to identify men whose likelihood of dying of CHD or having a definite myocardial infarction within 5 years was greatly above the average.

Punsar (51) reported 10-year followup data on the cohort of men in Finland who were part of the seven-country study of coronary heart disease, confirming that cigarette smoking was a major risk factor for CHD. The authors reported a 1.7-fold increase in CHD mortality among cigarette smokers. They estimated that 1,700 excess CHD deaths occur each year among cigarette smoking men in Finland.

Kozarevic, et al. (38) reported the results of the initial prevalence survey and the 2-year incidence data from the Yugoslavian study of cardiovascular disease. A total of 11,121 men between the ages of 35 and 62 were examined in the towns of Tuzla and Remetinec. Criteria for the diagnosis of CHD were based on objective electrocardiographic findings of myocardial infarction, left bundle branch block, or sudden death. A very low prevalence of myocardial infarction was initially found, and only 36 new cases of CHD developed over the 2-year period. The subjects who developed CHD smoked cigarettes at about the same level as the total study population. The annual average incidence rate of acute coronary heart disease was about 1.6 per 1,000 among both the smokers and nonsmokers. The CHD incidence rates found in this Yugoslavian study are appreciably below those found in the United States.

Comstock (16) examined the association between water hardness, various other environmental factors including cigarette smoking, and death from CHD. A total of 189 deaths from CHD occurred in the population of Washington County, Md., in the 3-year period following a census in 1963. For each case, two controls were randomly selected from the census lists and matched for race, sex, and year of birth. The relative risk of CHD for all smokers was 1.5 compared to nonsmokers ($P < 0.05$). This relative risk among cigarette smokers was dose-

related; persons smoking more than two packs a day had the highest risk of CHD. No significant association was found between CHD and water hardness.

Casciu, et al. (12), reported the prevalence of cardiovascular disease among 4,668 miners on Sardinia. Smoking and drinking habits, blood pressure, and heart rates were recorded. Smokers had higher rates of CHD than nonsmokers, and a dose-response was noted with the number of cigarettes smoked per day. The prevalence of myocardial infarction was 0.9 percent for nonsmokers, 1.62 percent for smokers of 10 or less cigarettes, 2.34 percent for smokers of 11 to 20 cigarettes, 9.9 percent for smokers of 20 or more cigarettes a day, and 1.42 percent for cigar or pipe smokers. When cigarette smokers were grouped by alcohol consumption, no significant difference was found in the prevalence of myocardial infarction between drinkers and nondrinkers.

Kornitzer, et al. (35, 36, 37) examined the prevalence of CHD in 566 male bank employees aged 40 to 59 in Brussels. They determined an individual's smoking history, blood lipids, ECG, peak flow rates, relative weight, skinfold thickness, and blood pressure. The prevalence of possible CHD as determined by ECG and CHD history was 7.1 percent in nonsmokers, 11.6 percent in cigarette smokers who inhaled, 6.9 percent in cigarette smokers who did not inhale, 10.6 percent in smokers of pipes and cigars, and 15.5 percent in the ex-smokers. Among the various risk factors examined, the strongest association was found for elevations in the serum cholesterol and the other blood lipids examined. Weaker associations were found for increased relative weight, high blood pressure, and tobacco use.

Agnese, et al. (2) examined 265 patients in Italy aged 20 to 65 years who had myocardial ischemia. Patients were matched with an equal number of controls by age. A number of risk factors for CHD were measured in both groups. Cigarette smoking and elevated serum cholesterol were identified as major risk factors for CHD, particularly for individuals under the age of 50.

Boudik (10) found the prevalence of myocardial infarction to be significantly ($P < 0.001$) higher in cigarette smokers than in nonsmokers in a population of 8,292 Czechoslovakian men between the ages of 52 and 67.

Storch, et al. (60), Estandia Cano, et al. (17), and Jakuszewska (30), in studies in Germany, Mexico, and Poland of CHD in individuals under the age of 40, reported that cigarette smoking was the dominant factor in the development of CHD in these patients.

Golovchiner (21) found cigarette smoking to be a significant factor in the development of myocardial infarction in a study of 530 patients with CHD in Leningrad hospitals.

Three studies without control groups from New Zealand (59), Nepal (47), and India (58) reviewed the prevalence of various risk factors, including cigarette smoking in populations with documented CHD.

BLOOD LIPIDS

In most of the following studies where the effect of cigarette smoking on blood lipids was examined, there was no control for dietary factors that may independently affect serum lipid levels. Schwartz, et al. (56) examined serum lipids in relation to smoking habits and relative weight in 7,972 male employees of the Parisian Civil Service in the city of Paris. Cigarette smoking was associated with a slight but significant ($P < 0.001$) increase in serum cholesterol. The authors found a positive correlation between increased relative weight and serum cholesterol levels, and a negative correlation between relative weight and smoking habits. These factors would operate in such a way as to reduce the apparent effect of cigarette smoking on the cholesterol levels. After controlling for relative weight, however, the investigators found a significant ($P < 0.001$) positive relationship between smoking and serum cholesterol.

In a study of various factors in relation to the mean serum cholesterol, Pincherle (48) examined the following parameters: blood pressure, height, weight, and skinfold thickness, X-ray findings of the chest and abdomen, the electrocardiogram, and smoking history; 10,000 British business executives between the ages of 25 and 65 were examined. A significant association was found between elevated serum cholesterol, obesity, elevated systolic blood pressure, inadequate exercise, radiographic evidence of arterial calcification of the iliac arteries, and certain other factors. The increase observed in mean serum cholesterol with increasing number of cigarettes smoked was not statistically significant.

Romslo (53) studied the distribution of serum lipids in 324 Norwegian military recruits. Cigarette smokers had a small but insignificant increase in serum triglycerides. No elevation was found for serum cholesterol. The subjects were young, and most smokers had only smoked for a few years.

Burney and Enslein (11) investigated changes in clinical laboratory tests as related to aging and smoking in a 5-year study of 502 healthy male veterans. It was found that five variables were needed to predict age-related changes in those over 50. These were: fasting blood glu-

cose, 2-hour post-glucose blood sugar, total serum protein, hemoglobin, and cholesterol esters. No significant differences in the laboratory data between smoking and nonsmoking subgroups were found.

Vlaicu, et al. (70) examined the interaction of cigarette smoking with blood pressure and serum lipids in 100 patients with angina pectoris who were between the ages of 40 and 59. Half the patients were smokers using more than 25 cigarettes a day. The smokers had lower serum lipids and lower blood pressure than the 50 nonsmoking patients with angina pectoris.

Miturzynska-Stryjecka, et al. (43) found that cigarette smoking immediately following a fatty meal did not significantly alter the serum free fatty acid, esterified fatty acid, cholesterol, or plasma turbidity levels over control values.

Ciampolini, et al. (15) examined the effects of cigarette smoking on blood lipid values in 10 healthy volunteers between the ages of 20 and 40. Cigarette smoking resulted in a prompt rise in free fatty acids and a delayed rise in serum triglycerides.

The relationship between cigarette smoking and changes in various serum lipid levels has not been clearly determined. Studies in this area continue to present conflicting results.

ELECTROCARDIOGRAM

Wysokinski (76) examined the effect of smoking on certain parameters of cardiovascular function in 100 healthy nonsmokers and 100 healthy smokers who were military recruits 19 to 25 years of age in Poland. Significant prolongation of the QRS interval ($P < 0.001$), flattening of the T wave, and ST segment depression following exercise were seen more frequently in the smokers than in the nonsmokers.

Van Buchem, et al. (69) examined the occurrence and significance of extrasystoles and conduction disorders in 760 healthy Dutch men between the ages of 40 and 67 who were followed for 7 years. The presence of extrasystoles was not correlated with cigarette smoking or elevated serum cholesterol and was not associated with the development of CHD over the 7-year period.

Kattus, et al. (33) tested 314 healthy males 23 to 82 years of age for ischemic ST segment depression on the ECG during or after submaximal exercise. The abnormal ST segment depression identified in 30 subjects was correlated significantly with elevated serum cholesterol, abnormal resting ECG, and a history of cardiac symptoms but not with smoking, high blood pressure, physical inactivity, or family history of coronary disease.

Van Buchem, et al. (68) found no significant association between cigarette smoking and ischemic ST segment depression on ECG in 120 apparently healthy men who demonstrated this abnormality among a population of 760 men 50 to 70 years of age.

Experimental Studies

CIGARETTE SMOKE

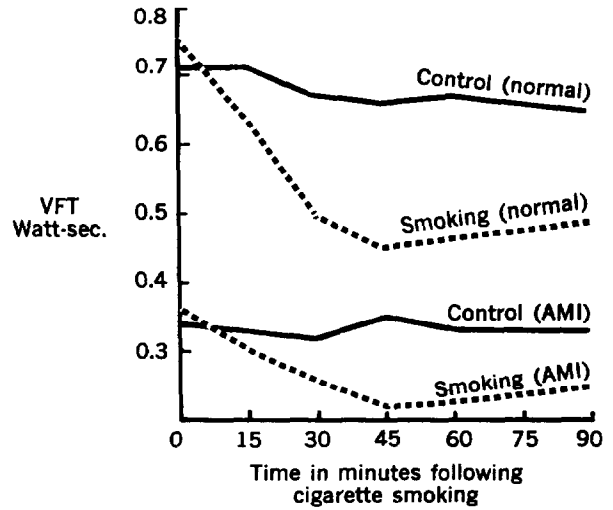
Studies in Man

Summers, et al. (61) examined the effect of cigarette smoking on cardiac lactate metabolism in 15 patients with severe angina pectoris who had at least 75 percent obstruction in each of two or three major coronary vessels. All patients had been long-term cigarette smokers. Cigarette smoking produced increases in heart rate, systolic aortic pressure, the systolic ejection period per minute, and the tension-time index per minute, but lactate production was not induced by smoking in any patient who did not also have lactate production in the control state. In three patients with lactate abnormalities prior to smoking, inhalation of cigarette smoke sustained and slightly aggravated this condition.

Studies in Animals

The effect of inhalation of cigarette smoke on ventricular fibrillation threshold (VFT) in normal dogs and dogs with experimentally produced acute myocardial infarction was studied by Bellet, et al. (6). Mongrel dogs weighing 25 to 30 kilograms were anesthetized with sodium pentobarbital, and respiration was maintained using a Harvard ventilator attached to an endotracheal tube. In one group the electrical impulses used to precipitate ventricular fibrillation were delivered through the chest wall, and in another group the impulses were delivered directly to the heart through electrodes implanted in the myocardium. The experimental group of dogs were exposed to the smoke of three cigarettes over a 10-minute period. Each cigarette contained approximately 2 mg. of nicotine. With acute myocardial infarction, the VFT was significantly ($P < 0.001$) decreased, but in both the normal and myocardial infarction groups cigarette smoking resulted in a decrease in VFT that averaged 30 to 40 percent of the control value (fig. 4). These findings are of interest in view of the increased incidence of sudden death observed among coronary patients who are heavy cigarette smokers (65).

Figure 4.—The effect of cigarette smoke inhalation on the ventricular fibrillation threshold (VFT) of normal dogs and dogs with experimentally produced acute myocardial infarction (AMI).



SOURCE: Bellet, S., et al. (6).

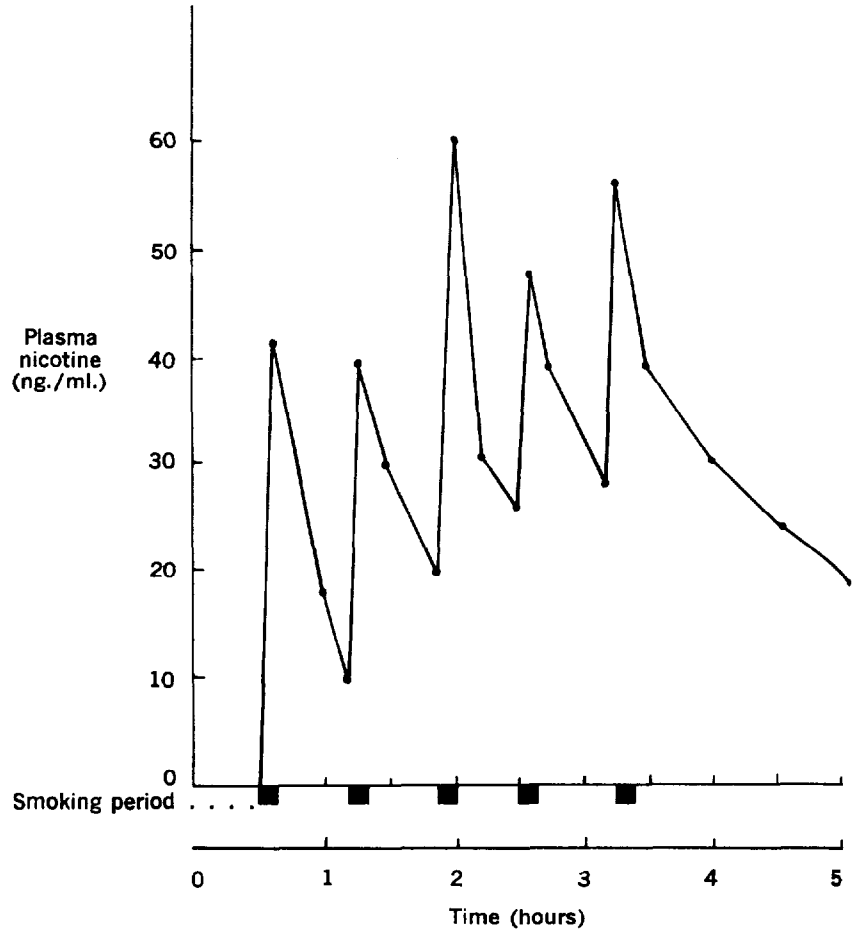
The effects of passively inhaled cigarette smoke on several measures of cardiovascular function in treadmill-exercised dogs were examined by Reece and Ball (52). The experimental dogs were trained on the treadmill for approximately 1 year before exposure to cigarette smoke began. Each dog was passively exposed to the smoke of 36 cigarettes over a 3-hour period 5 days a week in a 2.2 m.³ chamber ventilated at the rate of seven exchanges per hour. The dogs were exposed to this cigarette smoke and were continued on their exercise program for an additional year. Exposure to cigarette smoke was associated with cardiac enlargement, ST segment depression, and an increase in post-exercise serum lactate concentrations.

NICOTINE

Studies in Man

Isaac and Rand (28) have recently described a method for the assay of plasma nicotine. An alkali flame ionization detector was used with a gas-liquid chromatograph. The test is sensitive to 1 ng./ml. of nicotine in a 2.5 ml. sample; 30 minutes elapsed between end of one cigarette and start of next. Blood samples were taken before smoking and at 5, 10, and 30 minutes after the last puff of each cigarette. Plasma nicotine levels increased rapidly during cigarette smoking (fig. 5). The post-smoking decay curve consisted of two components: an initial rapid phase which may be due to the uptake of nicotine from the blood by various tissues, and a slower phase which may represent metabolism and excretion of nicotine. Some accumulation of plasma nicotine occurred during a day of smoking, but the background level never approached the peaks attained during and immediately following active cigarette smoking. The rate of elimination was rapid enough to prevent any appreciable accumulation of nicotine from 1 day to the next. The development of sensitive tests of plasma nicotine levels will allow a greater understanding of various dynamics of smoking. Inhalation patterns can be objectively measured, and the role of nicotine in habituation to cigarettes can be evaluated.

Figure 5.—Effects of smoking five consecutive cigarettes on plasma nicotine concentration.



SOURCE: Isaac, P. F., Rand, M. J. (28).

Studies in Animals

The effect of nicotine on regional blood flow in the canine heart was examined by Mathes and Rival (41). The effects of nicotine were examined in normal hearts and after partial coronary artery occlusion. Under normal circumstances, as well as after infusion of nicotine in normal hearts, the subendocardial portion of the myocardium had a 9.5-percent greater capillary flow than the subepicardial fraction. Partial ligation of the coronary arteries resulted in a 22.8-percent reduction in left ventricular blood flow; however, the subendocardial portion remained 8.6 percent higher than in the epicardium. After

coronary artery ligation, an infusion of nicotine resulted in a significant ($P < 0.001$) reduction in the capillary flow of the inner portion of the myocardium relative to the outer part.

Bhagat, et al. (7) examined the effect of cigarette smoking on the cardiovascular system of dogs, various pharmacological agents; e.g., tyramine hydrochloride, propranolol, and chlorisondamine, were used to modify the evoked response to tobacco smoke in order to clarify the mechanisms producing the observed effects. The authors concluded that the more important actions of nicotine include a stimulation of sympathetic ganglia and the adrenal medulla and the release of catecholamines from sympathetic nerve endings and chromaffin tissue.

Bing, Hellberg, and associates (8, 25) studied the microcirculation of the left atrium of anesthetized cats by direct visualization using high-speed cinematography. Nicotine injections produced a slight but insignificant increase in red cell velocity in the capillary circulation during both systole and diastole.

The effects of nicotine on the biosynthesis of various lipid fractions in the aorta of dogs were studied by Kupke (40). After nicotine administration, significant reduction occurred in the formation of free (^{14}C)-sterols, while elevated levels of unesterified fatty acids were formed in the media and intima of these in vitro specimens. The author suggested that nicotine may impair oxidative enzyme systems possibly by damaging the mitochondrial structures, thereby leading to lipid accumulation in the aorta.

Schievelbein and Eberhardt (54) reviewed the cardiovascular actions of nicotine and smoking.

CARBON MONOXIDE

Studies in Man

Numerous articles have recently been published on the various effects of carbon monoxide on man and animals and are of particular interest because of the relatively high levels of carbon monoxide found in the main and sidestream smoke of cigarettes. Only those articles are discussed here which contain data on the cardiovascular effects of carbon monoxide.

Aronow and Rokaw (3) examined the effects of smoking-induced carboxyhemoglobin levels on angina pectoris in 10 patients with CHD. The time to the onset of angina after smoking a nonnicotine cigarette was measured. Each patient had smoked more than a pack of cigarettes a day for at least 19 years and had a classical history of exertional dyspnea. Smoking nonnicotine cigarettes failed to result in an elevation of the blood pressure or the heart rate; however, there was a

significant ($P < 0.01$) increase in COHb levels to about 8 percent. This resulted in a significant decrease in exercise performance compared to the nonsmoking state ($P < 0.01$). This confirms that carbon monoxide can compromise oxygen delivery independently of the effect of nicotine.

Maximal oxygen consumption under conditions of carbon monoxide intoxication were studied in human volunteers by several authors (40, 71, 72). COHb levels of 15 or 20 percent resulted in a proportionate reduction in maximal O_2 consumption. The volunteers responded to the decrease in oxygen-carrying capacity of the blood with a tachycardia and relative hyperventilation during moderate exercise. Carbon monoxide produces a limitation of an individual's maximal oxygen consumption by decreasing the availability of oxygen supplied under conditions of increased oxygen demand.

Heistad and Wheeler (24) reported that the hypoxia induced by carbon monoxide inhalation caused an inhibition of reflex vasoconstrictor responses despite the presence of normal arterial oxygen tension.

Studies in Animals

The effects of carbon monoxide on coronary hemodynamics and left ventricular function in six unanesthetized dogs were studied by Adams, et al. (1). The animals reacted to a 5-percent carboxyhemoglobin level with a 14-percent increase in coronary blood flow. Twenty percent COHb resulted in a 57-percent increase in coronary flow and slight increases in heart rate and stroke volume.

Birnstingl, et al. (9) exposed young adult rabbits to 400 p.p.m. CO for periods that varied from 6 to 14 hours. The mean COHb level after a series of 22 exposures was 17 percent. A qualitative increase in platelet stickiness, as measured by the bead-column method, developed during the 24-hour period following CO exposure. The authors observed that this " * * " provides a possible mechanism for intimal deposition and a further link in the association between habitual smoking and peripheral vascular disease." Astrup (5) found the cholesterol level in the aorta of rabbits exposed to a low level of carbon monoxide for 10 weeks to be, on the average, 2.5 times higher than in the control rabbits. Both the experimental and control groups were maintained on a high-cholesterol diet.

Gibbons and Mitropoulos (20) reported that CO inhibited cholesterol biosynthesis with accumulation of lanosterol and 24,25-dihydrolanosterol in an in vitro system of rat liver homogenates exposed to a 90-percent CO atmosphere. It was felt that CO may have influenced an early step in the oxidative elimination of the 14 α -methyl group of lanosterol.

SMOKING AND THROMBOSIS

Previous reports of the Surgeon General on smoking and health (62, 63, 64, 65, 66) have reviewed the effects of smoking on thrombosis. Recent reviews and studies have not thus far yielded a unifying concept of the effect of smoking on thrombosis (4, 18, 19, 32, 45).

Cerebrovascular Disease

Paffenbarger and Wing (46) examined several precursors of non-fatal stroke in 102 patients with this disease in a population of 10,327 men who had attended Harvard University between the years of 1916 and 1940 and also returned a self-administered questionnaire in 1966. Examination of university medical records of these former students revealed four characteristics present in youth that predisposed those individuals who were more likely to experience a nonfatal stroke in later life. These factors were: cigarette smoking, elevated blood pressure, increased weight for height, and short body stature. The age and interval-adjusted incidence rates per 1,000 were 10.1 for nonsmokers, 15.3 for smokers of one to nine cigarettes, and 17.9 for smokers of 10 or more cigarettes a day. The relative morbidity ratios for the four factors cited above increased from 1.1 for patients with only one risk factor to 1.7 for those with any two risk factors, and to 3.2 for patients with any three or four risk factors.

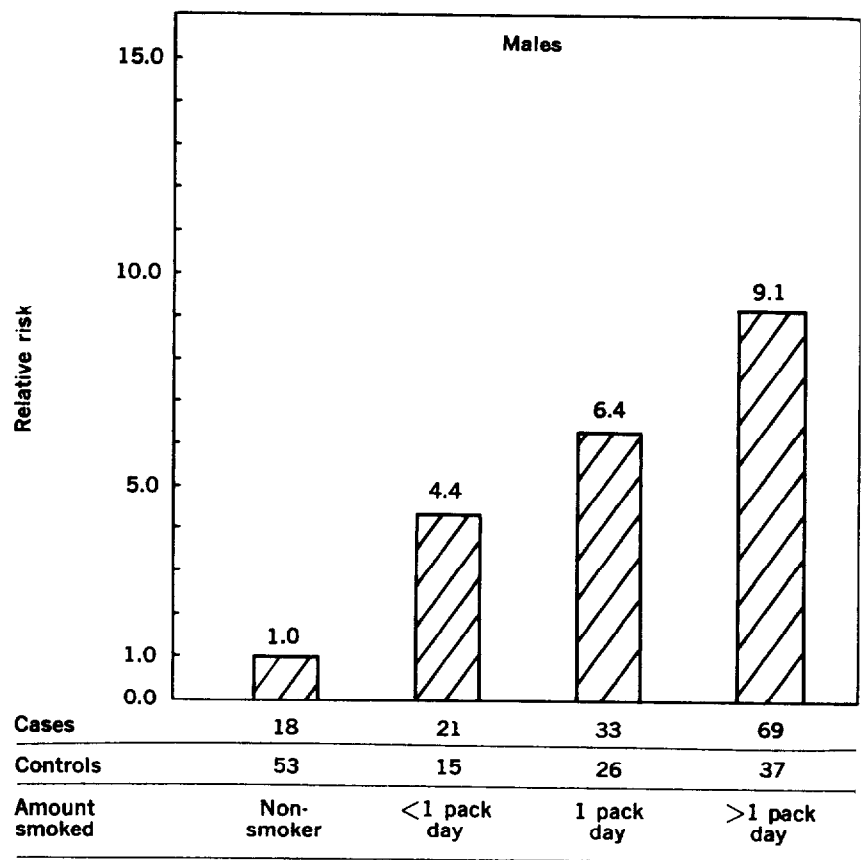
Miyazaki (44) studied blood flow in the internal carotid artery using ultra sound techniques. Internal carotid blood flow was examined under a variety of experimental conditions. Inhalation of cigarette smoke in three individuals aged 27, 67, and 69 resulted in an increased blood flow due to decreased vascular resistance. This effect lasted for 10 to 20 minutes following smoking.

Peripheral Vascular Disease

The association between cigarette smoking and arteriosclerosis obliterans (ASO) was investigated by Weiss (73). Patients were considered to have ASO if both the dorsalis pedis and posterior tibial pulses were absent in one lower extremity and the examining physician made a diagnosis of ASO. Patients were asked the age of initiation of smoking; the daily number of cigarettes smoked; the amounts smoked at ages 30, 50, and 70; the age at which they stopped smoking;

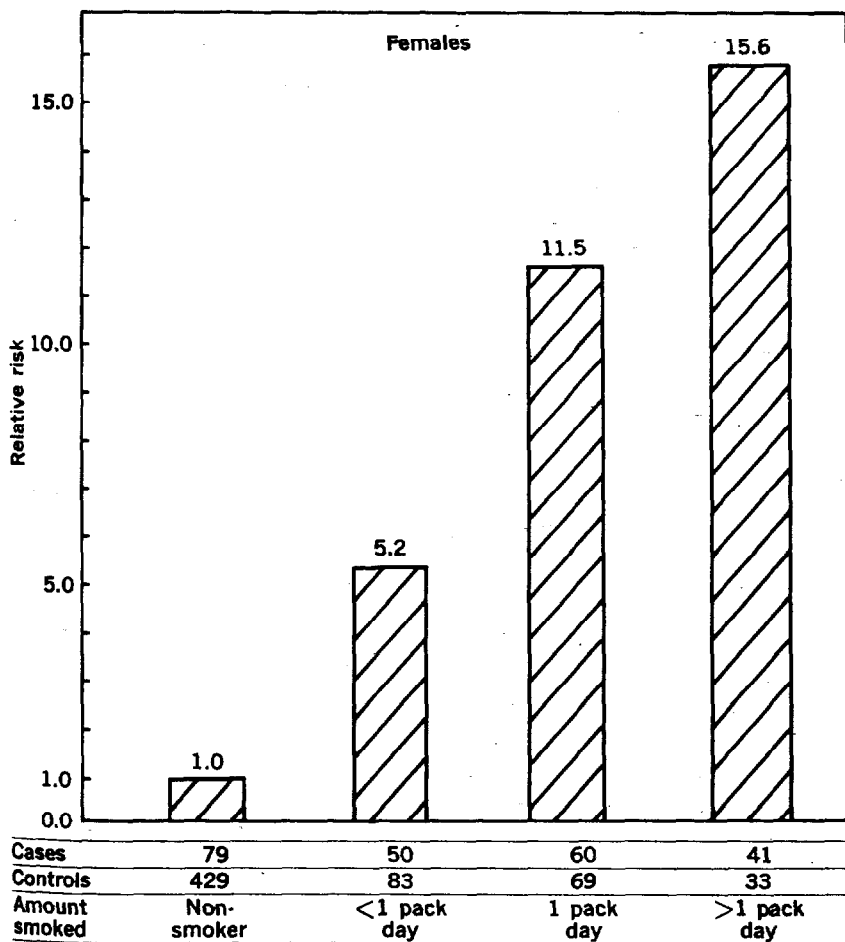
and, for males, whether they smoked cigars or a pipe, A total of 214 male cases, 206 male controls, 390 female cases, and 913 female controls were studied. The control group was composed of patients with peripheral vascular problems other than ASO but who had dorsalis pedis pulses present on initial examination. In each age and sex group, cigarette smoking was more prevalent among cases than controls. In both sexes, risks were high for smokers of less than one pack a day, and increased with the amount smoked (figs. 6 and 7). It was estimated that 70 percent of nondiabetic ASO in the United States is related to the use of cigarettes. Diabetes mellitus is a major risk factor for the development of ASO; however, cigarette smoking appeared to act independently of diabetes.

Figure 6.—Relative risk of developing arteriosclerosis obliterans (ASO) for males by amount of cigarettes smoked.



SOURCE: Weiss, N. S. (73).

Figure 7.—Relative risk of developing arteriosclerosis obliterans (ASO) for females by amount of cigarettes smoked.



SOURCE: Weiss, N. S. (73).

Preuss, et al. (50) examined the relationship between several factors including cigarette smoking, blood pressure, weight, and history of diabetes and the development of occlusive disease of the peripheral arteries in a population of 300 patients in Germany. Group I consisted of 150 patients with a mean age of 59 years who had intermittent claudication. Most of these patients were ambulatory. The 150 patients in group II had a mean age of 60 years and had far advanced peripheral arteriosclerosis with ischemic pain at rest or evidence of gangrene. There was no control group of patients free of vascular disease. There were few nonsmokers in either group of patients, but the group with

the more severe disease had a higher average daily consumption of cigarettes than did group I.

The influence of cigarette smoking on late occlusion of aortofemoral bypass grafts was examined by Wray, et al. (75). A series of 100 patients who had aortic reconstruction for aneurysmal or aortoiliac occlusive disease between 1965 and 1968 were studied. Of the patients who had bypass grafts for occlusive disease, 30 patients smoked cigarettes and 16 did not. Late occlusions from thrombosis occurred in nine patients, each of whom was smoking more than a pack of cigarettes a day at the time the thrombosis occurred ($P < 0.5$). The authors recommend cessation of cigarette smoking to all patients undergoing vascular reconstruction.

Schmauss and Arlt (55), Wilbert (74), and Kradjian, et al. (39) reported a greater than 93 percent prevalence of cigarette smoking in three separate series of patients with severe peripheral vascular disease.

Isacsson (29) performed venous occlusion plethysmography in 684 men aged 55 in Malmö, Sweden. In addition to a detailed smoking history, a number of other factors were studied, including blood pressure, pulse, height, weight, ECG, heart volume, and blood lipids. The plethysmograms were taken on both legs simultaneously with the patient in the recumbent position. Measurements were taken at rest and during reactive hyperemia produced by obstructing arterial inflow to the legs for 3 minutes with a blood pressure cuff applied to the thigh. Smokers had a significantly lower mean flow capacity (MFC) than did nonsmokers. The MFC in the legs was reduced in direct proportion to the amount of tobacco consumed per day regardless of the mode of smoking. The MFC was significantly lower with inhalation ($P < 0.001$) and with increasing amount smoked ($P < 0.001$).

Matsubara and Sano (42) studied the effect of cigarette smoking on human precapillary sphincters of the leg using a pressure plethysmograph applied to the calf. Precapillary sphincter tone was estimated using the capillary filtration coefficient, which is the product of "functional capillary service area" and the filtration constant of the capillary wall. Four healthy male subjects were tested. All were regular smokers of cigarettes who had not smoked for the previous 24 hours. When cigarette smoke was inhaled deeply at 30-second intervals over a 12- to 15-minute period, there was a 19-percent decrease in the capillary filtration coefficient, indicating closure of precapillary sphincters. Cigarette smoking also resulted in a 31-percent decrease in calf blood flow, indicating some degree of constriction of the arterioles in the leg. The pressure volume curves of the venous system were not affected by cigarette smoking.

Heistad and Wheeler (24) examined the effect of carbon monoxide on vascular resistance and reflex vasoconstriction in the forearms of 12

healthy men 19 to 23 years old. After control measurements were taken, the subjects were exposed to enough carbon monoxide to produce carboxyhemoglobin levels of 18 to 20 or 25 percent. Carbon monoxide did not cause a change in alveolar PO_2 or PCO_2 . The arterial oxygen saturation was less than 75 percent, but this decrease did not result in altered resting arterial pressure nor was there much evidence of sympathetic stimulation. Carbon monoxide hypoxia did result in a significant decrease in vascular resistance in the resting forearm ($P < 0.05$). Carbon monoxide exposure also resulted in a significant depression of the vasoconstrictor responses of the forearm following the application of negative pressure to the lower body ($P < 0.001$) and of ice on the forehead. It appears that the hypoxia induced by carbon monoxide causes an inhibition of reflex of vasoconstrictor responses despite the presence of normal arterial oxygen tension.

Summary of Recent Cardiovascular Findings

In addition to the summary presented in the introduction to this chapter based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field :

1. Recently conducted epidemiological studies from several countries continue to confirm that cigarette smoking is one of the major risk factors contributing to the development of coronary heart disease.
2. Epidemiological evidence suggests that black men in the rural South respond to the same risk factors for coronary heart disease, including cigarette smoking, as white men do but apparently at lower disease rates, which appears to be in part due to differences in physical activity.
3. Data from several epidemiological and experimental studies suggest that cigarette smoking is a major risk factor in the development of peripheral vascular disease. This may in part be due to the decreased blood flow in arterioles and capillaries associated with cigarette smoking. Smoking may complicate the surgical intervention in this disease by contributing to late occlusion of the treated vessel.
4. A laboratory test has been developed which accurately measures nicotine levels in blood. This test will be useful in understanding nicotine metabolism and can be used as an objective measure of cigarette smoke inhalation.

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CHAPTER 2

Nonneoplastic Bronchopulmonary Diseases

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Introduction

The term chronic obstructive bronchopulmonary disease (COPD), as used within this report, refers to chronic bronchitis and pulmonary emphysema. The following is a brief summary of the major relationships between smoking and nonneoplastic bronchopulmonary disease which have been presented in previous reports of the health consequences of smoking (91, 92, 93, 94, 95, 96).

Epidemiological and clinical studies have established cigarette smoking as the most important cause of COPD in the United States. Cigarette smokers have higher death rates from pulmonary emphysema and chronic bronchitis and more frequently have impaired pulmonary function and symptoms of pulmonary disease than nonsmokers. Respiratory infections are more prevalent and more severe among cigarette smokers, particularly heavy smokers, than among nonsmokers. Cigarette smokers appear to develop postoperative pulmonary complications more frequently than nonsmokers. The risk of developing or dying from COPD among pipe or cigar smokers is higher than that of nonsmokers, but it is clearly lower than that among cigarette smokers. Ex-smokers have lower death rates from COPD than do continuing smokers. Cessation of smoking is associated with improved ventilatory function and decreased pulmonary symptom prevalence. Young cigarette smokers of high school age have impaired ventilatory function compared to nonsmoking peers.

For most of the United States population, cigarette smoking is a much greater factor in the development of COPD than air pollution or occupational exposure. Cigarette smoking may, however, act conjointly with atmospheric pollution or occupational exposure to produce greater mortality and morbidity from COPD than would occur from one exposure factor alone.

A genetic error, homozygous alpha₁-antitrypsin deficiency, present in approximately 1 in 3,600 people in the United States, has been associated with the early development of severe panacinar emphysema. Available evidence does not permit a firm conclusion about the nature of the interaction between smoking and this condition.

Autopsy studies have demonstrated that smokers who die of diseases other than COPD have histologic changes characteristic of COPD more frequently than do nonsmokers.

Experiments in both animals and humans have demonstrated that the inhalation of cigarette smoke is associated with acute and chronic changes in ventilatory function and pulmonary histology. Cigarette smoking exerts an adverse effect on the pulmonary clearance mechanisms including ciliary and macrophage function.

The effect of cigarette smoking on nonneoplastic bronchopulmonary disease has been examined in detail in a number of recently published epidemiological, pathological, and experimental studies.

COPD Mortality and Morbidity

Reid (70) reported that age-adjusted mortality rates from chronic nonspecific lung disease (ICD 502, 526, 527) among British citizens varied with migration patterns. British males living in the United Kingdom had a death rate of 125 per 100,000, whereas migrants to the United States experienced a mortality rate of only 24 per 100,000, which is similar to the mortality rate from chronic nonspecific lung disease found in the U.S. population. The possibility that this variation was due to significant differences in diagnostic criteria was in part ruled out by the finding that standardized morbidity surveys of both populations demonstrated differences in morbidity rates that were similar to the observed differences in mortality rates. The prevalence of respiratory symptoms increased in proportion to the number of cigarettes smoked per day. Cigarette smoking and air pollution were identified as the major factors contributing to the real excess in bronchitis morbidity experienced by the British in the United Kingdom.

Freour and Coudray (23) investigated the prevalence of respiratory symptoms and chronic bronchitis among a random sample of 4,000 men and women between the ages of 30 and 70 who were residents of Bordeaux, France. A standardized questionnaire was administered and measurements of pulmonary function taken. The prevalence of chronic bronchitis increased with age and cigarette smoking. In each age category, smokers had more chronic bronchitis than did nonsmokers. The greater the number of cigarettes smoked per day and the greater the lifetime number of cigarettes smoked, the higher was the prevalence of chronic bronchitis. Coudray, et al. (13), in a study of 1,357 women in the Bordeaux Study, reported a prevalence of morning cough of 1.12 percent among nonsmoking women and 8.91 percent among women who smoked.

Racoveanu, et al. (66) studied the prevalence of chronic bronchitis in 300 residents of a mountainous region and a low-lying delta area in

Romania. Both areas were free of air pollution. The prevalence of chronic bronchitis was higher in the mountains than in the lowlands, and although a definite association between chronic bronchitis and smoking was found in both areas, smoking patterns could not completely account for the differences observed.

Several papers have been recently published (24, 25, 26, 37, 55, 100) comparing respiratory symptoms, such as cough and sputum production, among smokers and nonsmokers in different populations. In each study, respiratory symptoms and disease were more common among cigarette smokers than nonsmokers. Most of these studies (24, 26, 37, 100) demonstrated a dose-response relationship between smoking and symptoms for the amount smoked as measured by the number of cigarettes smoked per day, the lifetime number of cigarettes, or the degree of inhalation.

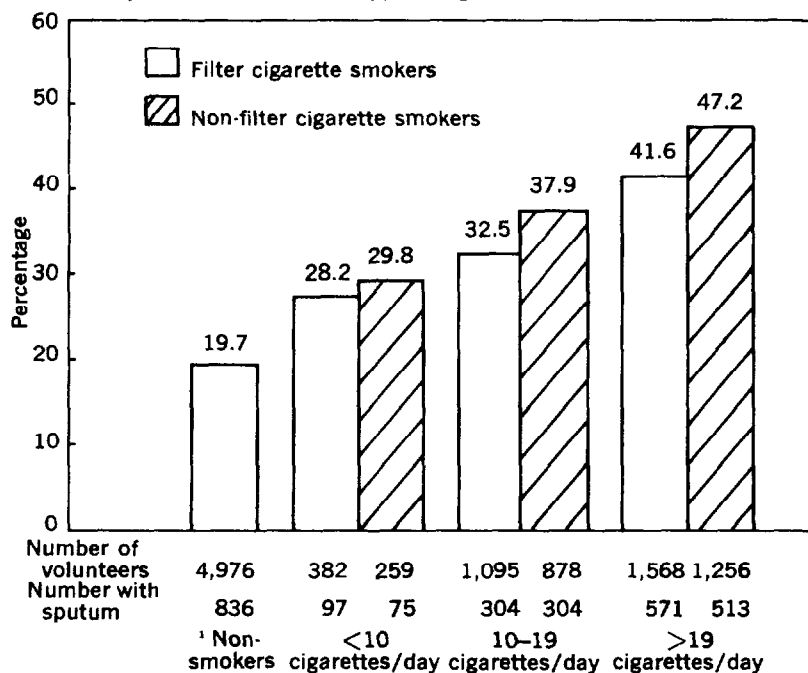
The spontaneous development of a pneumothorax with the resultant collapse of a lung is often produced by rupture of an emphysematous bleb on the pleural surface. Fournier and Zivy (21) reviewed 61 cases of spontaneous pneumothorax. The smoking habits of these patients were compared with those of matched controls. Spontaneous pneumothorax after the age of 25, was strongly associated with cigarette smoking. Zivy (101) further characterized 40 of these cases.

FILTER CIGARETTES

The effect of smoking plain and filtered cigarettes on the prevalence of sputum production was examined by Rimington (71). A total of 10,414 volunteers aged 40 and older were studied by questionnaire and chest X-ray. Of this group, 3,045 smoked filter cigarettes and 2,393 smoked nonfilter cigarettes. The rate of persistent daily sputum production was 31.9 percent in filter cigarette smokers and 37.2 percent in smokers of nonfilter cigarettes. The difference is significant ($P < 0.001$). Although there was an increase in sputum production with the amount smoked in both groups, the difference between filter and nonfilter smokers was maintained irrespective of the amount smoked (fig. 1). The author observed, "While there is no doubt that smokers of any type of cigarette are liable to develop chronic bronchitic symptoms such as persistent phlegm, it seems likely that those plain cigarette smokers who are unable to stop smoking cigarettes would suffer less if they smoked filter brands of comparable size."

The effect of smoking modified cigarettes on respiratory symptoms and ventilatory capacity was examined by Freedman, et al. (22). Six hundred men between the ages of 25 and 54 who smoked at least 10 cigarettes a day and had symptoms of chronic bronchitis were divided into three equal groups matched by age, pulmonary function, cigarette consumption, and cough frequency. The individuals were provided

Figure 1.—Age-standardized percentage of chronic sputum production in males by amount smoked and type of cigarette.



¹ Includes ex-smokers and non-cigarette smokers.

SOURCE: Rimington, J. (71).

with test cigarettes "A," "B," or "C." All the test cigarettes contained 1.65 mg. of nicotine. "A" delivered 22 mg. of tar, and "B" and "C" 17 mg. of tar. In addition, "C" had approximately a 50 percent reduction in the vapor phase constituents. Those provided with cigarette "C" increased the average number of cigarettes smoked by about 10 percent, where consumption eventually leveled off. After 4 months, men smoking cigarette "C" began to have lower average cough frequency scores than the others. Significant changes did not occur in sputum production or pulmonary function. The authors observed that, " * * * modification of the composition of cigarettes and their filters can reduce smokers' cough, an important and early symptom of bronchitis."

PULMONARY FUNCTION

Results of studies of pulmonary function and smoking from several countries, including India (65), Turkey (2), Germany (7, 34, 38), and Great Britain (41) indicate that cigarette smokers have diminished average pulmonary function compared to nonsmokers. The various measures of pulmonary function used included vital capacity, expiratory reserve volume, residual volume, residual functional capacity, maximum voluntary ventilation, forced expiratory volume in 1 second, and peak expiratory flow rate.

Other studies in which both pulmonary function and respiratory symptoms are considered (27, 30, 36, 43, 59, 69) have again confirmed that smoking is associated with an increase in pulmonary symptoms and a decrease in pulmonary function.

Ex-smokers experience a decrease in the prevalence of respiratory symptoms and an improvement in pulmonary function compared to continuing smokers. These effects have been noted in several recent studies (36, 37, 43).

Ulmer (87) conducted a survey of respiratory symptoms in a random sample of 2,444 individuals between the ages of 10 and 70 years in Duisburg, Germany. The prevalence of chronic bronchitis as measured by cough and/or sputum production in the morning or throughout the day increased with advancing age and with increasing cigarette consumption ($P < 0.001$).

Latimer, et al. (48) studied the ventilatory patterns and pulmonary complications of 46 patients following elective upper abdominal surgery. Factors that favored the development of postoperative macroatelectasis included smoking, obesity, and prolonged anesthesia.

Teculescu and Stanescu (84) examined several measures of pulmonary function in 44 asymptomatic young men between the ages of 18 and 29 in Romania. No significant differences were found between the smokers and nonsmokers. This may have been due to the selection of asymptomatic subjects for examination and relatively insensitive measures of early airway obstruction.

Occupational Hazards

BYSSINOSIS

Byssinosis is a respiratory disease found in cotton, flax, and hemp workers. The earliest manifestations of this disease are shortness of breath, cough, and chest tightness. Initially, symptoms occur only upon reexposure to cotton dust at the beginning of the work week. In more advanced form, byssinosis is associated with permanent and occasionally severe airway obstruction, which may force the worker to change his occupation (31). Abnormalities in pulmonary function tests reflect the severity of the symptoms; however, chest films of workers with byssinosis reveal no characteristic findings. McKerrow and Schilling (54) first suggested that byssinosis may occur more frequently among smokers than nonsmokers. Several relatively recent studies have clarified the relationship between smoking and byssinosis. Bouhuys, et al. (8) found 61 cases of byssinosis in 214 male workers in the carding and spinning rooms of a cotton mill. The prevalence of

byssinosis symptoms was higher among cigarette smokers than in nonsmokers ($P < 0.025$).

Szymczykiewicz, et al. (82) found a higher prevalence of chronic nonspecific pulmonary symptoms among smokers than nonsmokers in a study of 3,167 cotton mill workers in Poland.

An examination of 500 cotton textile workers by Schrag and Gullett (75) disclosed 63 individuals with byssinosis; 57 percent (36 workers) of those with byssinosis smoked more than a pack of cigarettes a day, whereas only 34 percent (152 workers) of those without byssinosis smoked this amount ($P < 0.001$).

Merchant, et al. (58) conducted a study of byssinosis in a yarn mill in North Carolina; 25 employees with byssinosis were identified in a population of 441 workers. A scale of 0 to 3 (based on 5 weighted questions concerning cough, breathlessness, and chest tightness on Monday mornings) was used to indicate the degree of severity of byssinosis among the working population. The effect of cigarette smoking on this byssinosis index is apparent (table 1). Among the employees with high exposure to cotton dust, no nonsmokers had a byssinosis index rating over 1, but nearly 18 percent of those currently smoking had ratings of 2 or 3. The effect of smoking alone on the byssinosis index is significant ($P < 0.01$). Also, the interaction between current smoking and current exposure-risk on the byssinosis index is highly significant ($P < 0.005$). Women in this study were exposed to lower levels of respirable cotton dust, and among them no age, smoking, or exposure-risk effects were demonstrated. Smoking among males also had a significant effect on the bronchitis index ($P < 0.002$). Spirometry results on 134 males and 100 females were categorized by sex, age, and smoking history. Among men, the greatest impairment

TABLE 1.—Percent prevalence of byssinosis for men by index of severity and smoking habits (numbers in parentheses indicate number of cases in exposure-risk group)

	Index rating (see text)	Percentage of subject		
		Never smoked (23)	Current smokers (85)	Ex-smokers (21)
Severe.....	3	0	14	5
Moderate.....	2	0	4	5
Mild.....	1	22	26	29
None.....	0	78	57	62
Total.....		100	100	100

Source: Merchant, J. A., et al. (58).

was observed among the smokers who worked in the high exposure-risk areas. The mean FEV₁ for 66 men in this category was only 76 percent of predicted, and their FVC was 90 percent of predicted. Nonsmoking men in both the high- and low-exposure areas had better pulmonary function than their smoking coworkers.

EXPOSURE TO ASBESTOS

Langlands, et al. (45) surveyed respiratory symptoms, pulmonary function, and radiological findings among 252 asbestos insulation workers in Belfast, Ireland. Respiratory symptoms of cough, sputum production, and wheezing were much more frequent in smokers. Of the tests for pulmonary function, the peak flow rate and forced expiratory volume at 1 second were most impaired in cigarette smokers. Although little difference was reported in the X-ray findings of smokers and nonsmokers, smokers of more than 25 cigarettes a day had a 20-percent reduction in pulmonary function as measured by these tests.

Lung function and pulmonary symptoms in 1,015 chrysotile asbestos mine and mill workers in Quebec were studied by Becklake, et al. (6) and McDonald, et al. (53). An analysis of respiratory symptoms indicated that shortness of breath was more closely related to dust exposure than to smoking. However, cough, wheezing, and sputum production were much more frequent in smokers than nonsmokers. Pulmonary function was assessed by measuring lung volumes, flow rates, and diffusing capacity. The best pulmonary function was found in nonsmokers with low dust exposure while smokers with high dust exposure had lower pulmonary function values.

In a survey of 201 asbestos workers, Regan, et al. (67) investigated the relative power of 16 clinical, radiological, and pulmonary function variables including smoking for differentiating between asbestosis and chronic obstructive airway disease. Cigarette smoking was not a characteristic that could be used to separate these conditions.

EXPOSURE TO COAL DUST

The spectrum of pulmonary reactions to coal dust was reviewed in a volume edited by Key, et al. (40). Hunter (33) noted that coal miners who smoked experienced a higher prevalence of respiratory symptoms (cough, sputum production, breathlessness, and wheezing) and developed them earlier than nonsmoking miners. Their pulmonary function tests also tended to show greater impairment than those of nonsmokers. Lainhart and Morgan (44) reported that coal miners had an increase in persistent productive cough with increasing years of exposure to coal dust. This effect was magnified by cigarette smoking independent of age or years of underground work. In an autopsy

study, Naeye (62) observed more right ventricular hypertrophy and a higher emphysema index in smoking miners than in nonsmoking miners. In commenting on the etiology of pulmonary reactions in coal miners, Lee (49) felt that smoking in coal miners probably facilitated the development of bronchitis and emphysema, rather than participating in the genesis of the characteristic lesion of coal workers' pneumoconiosis.

The prevalence of chronic bronchitis in 3,012 ex-coal miners and 9,361 nonminers of similar age and social class was examined by Lowe and Khosla (51). All were employed at the time of the investigation in two steel works in South Wales. The ex-miners had substantially more chronic bronchitis and more impaired ventilatory capacity than the nonminers irrespective of age and smoking habits. The prevalence of chronic bronchitis was 24.9 percent in smoking ex-miners and 12.0 percent in nonsmoking ex-miners. The prevalence was 18.6 percent and 7.7 percent in smoking and nonsmoking nonminers, respectively. In this study, smoking appeared to be a more important factor for the development of chronic bronchitis than coal mining or age.

Haber, et al. (29) studied cigarette smoking, dust inhalation, and sputum production as factors in the etiology of chronic bronchitis among 479 coal miners and 166 farmers in Hungary. In both the miners and the farmers, there was a significantly higher proportion of chronic bronchitis cases among smokers than among nonsmokers, and the proportion of bronchitics increased with the number of cigarettes smoked. Cigarette smoking was found to be a more important factor in the etiology of bronchitis than dust inhalation.

Lapp, et al. (46) examined changes in several measures of ventilatory capacity in 93 coal miners and 42 nonminers before and after a work shift. Following the shift, small but significant decreases in ventilatory capacity occurred among the miners ($P < 0.05$), while significant increases in ventilatory capacity occurred among the nonminers ($P < 0.05$). Decreases in pulmonary function tests were related to the dust exposure of the miners; however, the greatest decreases in pulmonary function occurred among the smokers.

Seaton, et al. (76) examined several measures of pulmonary function in 214 coal workers who had radiologic evidence of CWP with lung opacities that ranged in size from less than 1.5 mm. to 3 mm. in diameter. They found no significant difference in pulmonary function between the 102 smokers and 112 nonsmokers with coal workers' pneumoconiosis. Similar results were reported by Lyons, et al. (52).

Hyperinflation of the lungs in coal miners was studied by Morgan, et al. (61). Residual volumes, total lung capacities, and chest X-rays of 1,455 working Pennsylvania coal miners were examined. The relationship between radiographic evidence of coal workers' pneumoconiosis and lung volumes was investigated. The residual volume in-

creased with radiographic category, obstruction to air flow, and cigarette smoking. Each of these factors had a separate and additive effect that resulted in an increased residual volume.

Ulmer (86) examined a random sample of the working population in the Ruhr area of West Germany. Measurements were made of the total lung capacity, airway resistance, and arterial oxygen saturation. All coal miners had larger total lung capacities than workers without dust exposure. Smokers had significantly larger volumes than nonsmokers ($P < 0.05$).

Lapp, et al. (47) examined pulmonary hemodynamics in 47 asymptomatic coal miners. They were divided into two groups depending upon the absence or presence of airway obstruction. Pulmonary hypertension was more frequent in the group with obstruction. The group of 23 men (mean age 51 years) without airway obstruction, had an average cigarette consumption of 17 pack-years per miner, whereas the group of 24 men (mean age 56 years) with airway obstruction averaged 31 pack-years per miner.

From the work of several investigators it can be concluded that cigarette smoking is an important factor in the development of respiratory disease other than pneumoconiosis, among coal miners (29, 40, 46, 47, 51, 61, 86). There is no consensus in recent publications on what role cigarette smoking may play in the development of coal workers' pneumoconiosis (40, 61, 76).

MISCELLANEOUS EXPOSURES

The effect of cigarette smoking on pulmonary function in jet fighter pilots and crew members was examined by Browning (9). At high altitudes, 100-percent oxygen is delivered under low pressure to the aircrew members in order to maintain adequate blood oxygen levels. The vital capacity was acutely compromised in flight on the 100-percent oxygen mixture. This was especially true under high G (gravity) conditions. Smokers had a significant inflight volume loss that was three and one-half times that noted among the nonsmokers under these conditions ($P < 0.05$). Recovery of normal vital capacity following flight was also delayed in the smokers.

Gregory (28) reviewed 340 cases of chronic bronchitis that occurred among the employees of the Sheffield steelworks in England. Smoking was associated with a high prevalence of chronic bronchitis, but of particular interest was the effect of cigarette smoking on disability. The interval between the onset of chronic bronchitis and disability from this disease was significantly less ($P < 0.02$) for those smoking more than 20 cigarettes a day than for nonsmokers and for those smoking less than this amount ($P < 0.02$).

Batawi (5) examined the prevalence of several diseases including

respiratory illnesses in 4,643 employees in Egypt, comprising a 5.3 percent sample of 92,000 employees in 17 major industries. Respiratory illnesses occurred more frequently in all segments of the cotton industry, as well as leather, printing, and glass industries; 40 percent of all employees were smokers, and they experienced higher rates of respiratory symptoms and illnesses than nonsmokers. Smokers with occupational exposure to dust were particularly affected.

The effect of cigarette smoking and occupational exposure to dust on the prevalence of chronic bronchitis was examined by Golli (25) in Romania. There were 2,942 individuals examined of whom 142 were employed in dusty occupations. Chronic bronchitis was present in 24.6 percent of the 457 smokers and 4.4 percent of the 2,343 nonsmokers ($P < 0.001$). Increasing age, cigarette smoking, and occupational exposure to dust each independently contributed to an increased prevalence of chronic bronchitis.

Recent studies in metal casting, plaster, coke, baking, agricultural, and chemical industries have documented a higher incidence of respiratory symptoms and/or diminished pulmonary function among cigarette smoking workers than nonsmoking workers (42, 64, 89, 97, 99).

Air Pollution

Reichel and Ulmer (68, 88) examined the effect of air pollution on the prevalence of respiratory disease among 8,162 men and women in West Germany. The three areas chosen for study had widely different atmospheric levels of sulphur oxides and particulate matter. The frequencies of cough and sputum production were the same within the nonsmoking groups in all three areas. No differences were found in pulmonary function or arterial blood gases between subjects of the three districts. Smokers in each area had a higher prevalence of respiratory symptoms than nonsmokers. The authors concluded, "There is no doubt that the influence of air pollution is less important than that of age, sex, and smoking habits."

Tsunetoshi, et al. (85) examined the prevalence of chronic bronchitis in Osaka, Japan. The independent contributions of age, smoking habits, and air pollution were examined. In male cigarette smokers using more than a pack a day, chronic bronchitis was three to four times more prevalent than in nonsmokers. In female smokers using half a pack or more a day, chronic bronchitis was five to six times more prevalent than in nonsmokers. The standardized prevalence of chronic bronchitis increased with the degree of air pollution, particularly sulphur dioxide pollution, but not with increasing levels of suspended particulate matter.

The Federal Aviation Administration, Department of Transportation, and the National Institute for Occupational Safety and Health jointly conducted a study of the levels of certain combustion byproducts of tobacco on military and civilian aircraft produced by passengers' smoking and also asked the passengers for their subjective reaction to tobacco smoke (90). Levels of carbon monoxide, particulate matter, polycyclic hydrocarbons, ammonia, and ozone were measured on 20 military and eight domestic flights. On all aircraft the measured level of each substance was much lower than recommended occupational and environmental air quality standards. This was probably the result of the efficient ventilation systems required on all aircraft (20 exchanges of cabin air each hour).

More than 60 percent of the passengers reported that they were bothered by tobacco smoke and suggested that corrective action such as segregation of smokers and nonsmokers be taken. More than 70 percent of the nonsmokers who had a history of respiratory conditions were annoyed by tobacco smoke. The discomfort attributed to tobacco smoke in spite of the efficient ventilation system might have reflected crowded seating conditions or drying of the respiratory membranes which results from the very low humidity found on most aircraft.

Autopsy Studies

Auerbach, et al. (4) 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. Table 2 and figure 2 show these relationships.

Fingerland, et al. (19) investigated the prevalence of various pathological conditions including emphysema and chronic bronchitis in an autopsy population comprising all persons over the age of 20 who came to autopsy over a 2-year period at the Institute of Pathological Anatomy in Czechoslovakia; 765 males and 573 females were included

in the study. Smoking histories were obtained from patients before death, medical records, or relatives. The smokers were divided into three groups based upon the number of cigarettes smoked during their lifetime; 26 percent of the male nonsmokers showed some evidence of emphysema, whereas 70 percent of male smokers of more than 500,000 lifetime cigarettes showed these changes (fig. 3). Similar relationships were demonstrated for chronic bronchitis.

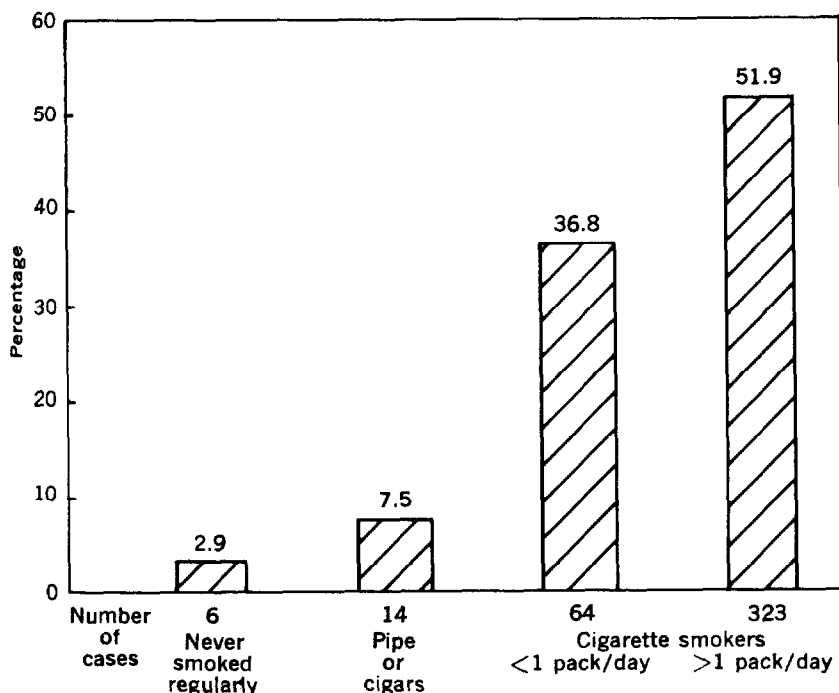
TABLE 2.—*Degrees of emphysema in current¹ smokers and in nonsmokers according to age groups*

Age group and degree of emphysema (see text)	Subjects who never smoked regularly	Current pipe or cigar	Packages smoked per day			
			<½	½ to 1	1 to 2	>2
<60:						
0 to 0.75.....	53	18	12	3	2	0
1 to 1.75.....	2	11	4	9	24	5
2 to 2.75.....	0	1	2	17	130	56
3 to 3.75.....	0	1	5	12	50	38
4 to 4.75.....	0	0	0	4	8	7
5 to 6.75.....	0	0	0	0	4	5
7 to 9.00.....	0	0	0	0	3	1
Totals.....	55	31	23	45	221	112
Mean.....	.10	.83	1.29	2.37	2.56	2.86
SD.....	.04	.13	.26	.16	.07	.10
60 to 69:						
0 to 0.75.....	35	17	4	0	0	0
1 to 1.75.....	1	8	1	0	4	1
2 to 2.75.....	2	3	4	5	37	23
3 to 3.75.....	2	2	2	9	42	24
4 to 4.75.....	0	0	1	3	11	9
5 to 6.75.....	0	0	0	1	8	1
7 to 9.00.....	0	0	0	1	5	4
Totals.....	40	30	12	19	107	62
Mean.....	.39	.95	1.90	3.59	3.39	3.37
SD.....	.13	.16	.34	.35	.15	.20
70 or older:						
0 to 0.75.....	68	21	2	0	0	0
1 to 1.75.....	4	28	10	8	2	2
2 to 2.75.....	5	22	13	23	40	9
3 to 3.75.....	4	8	5	10	38	18
4 to 4.75.....	0	2	1	7	11	7
5 to 6.75.....	0	1	0	2	9	3
7 to 9.00.....	0	0	0	1	12	5
Totals.....	81	82	31	51	112	44
Mean.....	.50	1.66	2.15	2.98	3.68	3.91
SD.....	.39	.11	.17	.20	.17	.27

¹ Subjects who smoked regularly up to time of terminal illness.

Source: Auerbach, O., et al. (4).

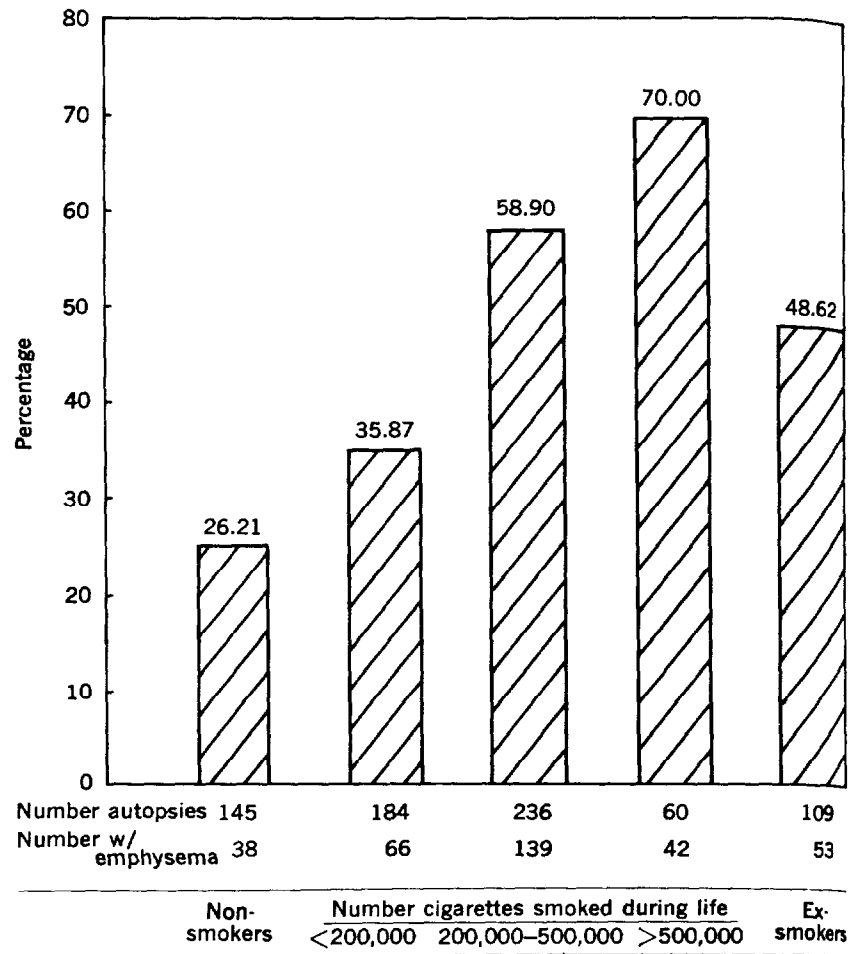
Figure 2.—Age-standardized percentage distribution of whole lung sections of males with moderate to far-advanced emphysema (score 3–9) by smoking category.



SOURCE: Auerbach, O., et al. (4).

Mitchell, et al. (60) conducted a study to determine the accuracy of the recorded cause of death on death certificates of adults; 578 autopsies were performed on patients 40 years of age and older at two large hospitals in Colorado. In addition, 409 patients with COPD were enrolled in an emphysema registry. Autopsies were performed on the 56 patients who died during the study period. Death certificates were obtained from the State Health Department, and the recorded cause of death was compared with the autopsy findings. In 211 of the 634 autopsies performed, the cause of death was found to be COPD; however, in only 160 of these cases (76 percent) was COPD listed as the cause of death on the death certificate; 3 percent of death certificates incorrectly listed emphysema as a cause of death when this was not supported by autopsy evidence. The authors concluded their study by suggesting “* * * that national statistics, which are based on non-autopsy confirmed diagnoses, might understate deaths from chronic bronchitis and ‘emphysema.’”

Figure 3.—Prevalence of emphysema in adult males at autopsy by smoking category.



SOURCE: Fingerland, A., et al. (19).

Experimental and Histopathological Studies

Histopathological Studies

Studies in Man

Naeye and Dellinger (63) examined the small pulmonary arteries of 126 male cigarette smokers and 67 nonsmokers for quantitative changes in collagen, elastic tissue, and circularly and longitudinally oriented smooth muscle. They found a progressive increase in collagen

and longitudinally oriented smooth muscle fibers and a progressive decrease in circularly oriented muscle fibers with age. These changes were more advanced at each age in smokers than in nonsmokers ($P < 0.01$).

Sobonya and Kleinerman (78) quantified the smooth muscle and mucous glands in the bronchi of 13 male cigarette smokers and 11 male nonsmokers from Ohio who were 18 to 46 years old and had died of nonrespiratory causes. The smokers averaged 24 pack-years of exposure. Although the smokers had a history of more respiratory symptoms and colds than the nonsmokers, no difference was found in the percentages of smooth muscle or bronchial glands between smokers and nonsmokers. Five of the 13 smokers showed evidence of squamous metaplasia.

Ellefsen and Tos (17) determined the goblet cell density in tracheal biopsies from 50 patients with respiratory symptoms or disease. Goblet cell density increased with symptoms of tracheobronchitis and history of exposure to dust. A slight increase was also noted in mean goblet cell density with increasing consumption of cigarettes from 136 in symptomatic nonsmokers to 154 in smokers of more than a pack a day.

Studies in Animals

Syzganov, et al. (81) exposed 55 dogs to cigarette smoke inhaled through tracheostomas for periods of up to a year or longer. An additional 15 dogs served as nonsmoking controls. The smoking animals developed bronchitis, bronchopneumonia, interstitial pneumonia, and hyperplasia of the bronchial epithelium. Later histologic changes included squamous metaplasia and papilloma formation not found in controls.

The effect of sulphur dioxide (SO_2) and cigarette smoke on the mucous glands of rats and the bronchial glands of lambs was studied by Mawdesley-Thomas, et al. (57). There was a slight increase in the goblet cell count of rats with the inhalation of SO_2 and cigarette smoke. Exposure of lambs to cigarette smoke inhaled through a tracheostoma resulted in hypertrophy of the bronchial glands.

Jones, et al. (39) found that the addition of phenylmethyloxadiazole (PMO) to tobacco protects rats against some of the adverse effects of exposure to cigarette smoke. Two groups of 15 Sprague-Dawley rats were exposed to 25 cigarettes a day, 4 days a week for 6 weeks. The group exposed to cigarettes containing PMO showed less immediate distress after exposure and had a lower tracheal goblet cell count, less thickening of the tracheal epithelium, and fewer cells in mitosis than those exposed to the regular cigarettes.

The response of the rat lung to low levels of nitrogen dioxide (NO_2), a constituent of cigarette smoke, was studied by Stephens, Evans, and

their associates (18, 80). Young male rats were continuously exposed to NO₂ at concentrations of 2 p.p.m. and 17 p.p.m. for 1 year. Animals were sacrificed after a short exposure and also at regular intervals over the 12-month period. At the level of 17 p.p.m., destructive changes occurred in the respiratory epithelium within 4 hours. These changes included cell hypertrophy, loss of cilia, and increased mitotic activity. After 24 hours of exposure at this level some repair began, but cuboidal cells replaced the normal respiratory epithelium. At 2 p.p.m. the acute damage was less severe, and complete recovery occurred over a period of several weeks.

Sherwin, et al. (77) studied the effect of low doses of NO₂ on the alveolar wall cells of the guinea pig. They found that continuous exposure of 2 p.p.m. NO₂ produced a significant increase ($P < 0.05$) in the lactate dehydrogenase (LDH) index of the lower lobes of the lung, suggesting that the ultrathin type 1 (LDH positive) alveolar wall cells were being replaced by relatively thick type 2 cells resulting in a physiologically significant blood-gas barrier.

Pulmonary Function

Ingram and O'Cain (35) studied dynamic compliance in nine smokers and nine nonsmokers under the age of 30 who were in good health. Both groups were identical with respect to airway resistances, lung volumes, maximal expiratory flow rates, and static compliance values. Dynamic compliance fell more rapidly in the smokers than in the nonsmokers above a frequency of 40 breaths a minute. The difference was statistically significant ($P < 0.0001$). Isoproterenol produced no significant increase in dynamic compliance in either the smokers or the nonsmokers. In six of the smokers who stopped smoking, the dynamic compliance curves gradually approached the values of the nonsmokers over an 8-week period. Changes over this relatively long period of time indicate that the decrease in dynamic compliance observed in smokers was more likely caused by inflammatory changes or some other mechanism rather than muscular constriction in the bronchioles. The authors concluded that peripheral airway abnormalities are regularly present in young asymptomatic smokers.

The effect of cigarette smoking on pulmonary diffusing capacity was studied by Van Ganse, et al. (98). Diffusing capacity is dependent upon: A membrane component, which is the resistance offered by the lung tissues, and the volume of blood in the lung capillaries. Studies were conducted on 142 randomly selected residents of Berlin, N.H., over the age of 25. In both men and women, there was a decrease in diffusing capacity for carbon monoxide with an increase in age and

with increases in cigarette smoking. Ex-cigarette smokers tended to have results similar to those of nonsmokers. The authors found that the membrane component did not show any consistent change with increased current cigarette smoking, whereas the volume of blood in the lung capillaries decreased markedly with increased cigarette consumption, and slightly with age. The value of this vascular component in male nonsmokers was 75.5. This decreased to 49.1 in males who smoked 25 or more cigarettes a day ($P < 0.01$). The figures for women were 77.2 and 50.7 for nonsmokers and smokers, respectively ($P < 0.05$).

Acetaldehyde is found in cigarette smoke and is a known ciliotoxic agent. The single-breath retention of acetaldehyde vapor by the respiratory tract of human subjects was measured by Egle (16) who found a direct relationship between the volume inhaled and the percent taken up. Up to 90 percent of the inhaled acetaldehyde was removed in a single breath.

Stanescu (79) studied the single-breath oxygen test in 38 male smokers and 68 male nonsmokers who were in excellent health. A significant difference ($P < 0.001$) in the slope of the nitrogen gradient between smokers and nonsmokers was found.

Teculescu (83) performed single-breath determinations of total lung capacity in 89 males aged 19 through 67 who had normal chest X-rays and no history of respiratory disease. No significant differences were found with age or smoking habits.

Pulmonary Clearance

Studies in Man

Tracheobronchial clearance rates were studied in nine pairs of monozygotic and nine pairs of dizygotic twins by Camner, et al. (12). A test aerosol of radioactively tagged teflon particles 6 to 7 microns in diameter was inhaled and external measurements of radioactivity in the lungs were made. The clearance patterns within pairs of monozygotic twins were similar, more so than clearance patterns within pairs of dizygotic twins, indicating that tracheobronchial clearance rates may to some extent be constitutionally determined. Only one individual had been a regular cigarette smoker.

Camner and Philipson (10) also studied tracheobronchial clearance in smoking-discordant twins, using the same techniques as in the previous study: 10 pairs of monozygotic twins discordant with regard to cigarette smoking were studied. All the smokers had used 10 to 20 cigarettes a day for more than 20 years. Tracheobronchial clearance was, on the average, significantly ($P < 0.02$) slower in the smokers

than in the nonsmokers. Although the basic rate of mucociliary transport may be constitutionally determined, it is evident that cigarette-smoking decreases the effectiveness of this physiologic mechanism.

The regional deposition of inhaled aerosols in man was studied by Lippmann, et al. (50), who used a monodisperse ferric oxide aerosol tagged with a radioisotope. Particles were deposited in the pharynx, trachea, bronchi, and alveoli. Measurements were made in 65 adults including 14 nonsmokers, 29 current cigarette smokers, six elderly bronchitic patients, and one young asthmatic. Larger particles were deposited in the upper airways by turbulent precipitation with only the small particles of one to five micron size reaching the lower airways. The cigarette smokers, bronchitics, and the asthmatic had a higher proportion of particles deposited in the tracheobronchial area than nonsmokers. As a result, fewer particles reached the alveoli in these patients. These findings may be the result of a decrease in the diameter of the small bronchioles due to inflammation, mucus, or bronchoconstriction.

Albert, et al. (3) studied the effects of cigarette smoking on the kinetics of bronchial clearance in a group of volunteers most of whom also participated in the previous study. A two-phase clearance pattern was described for many subjects. The first, a short, rapid clearance phase, was completed within a few hours and probably represented clearance of the upper airways. The second phase varied in duration from a few hours to 1 day and represented clearance of particles deposited in the distal portions of the bronchial tree. The average clearance time was 126 minutes in 18 nonsmokers, 170 minutes in 19 of the smokers, and 238 minutes in the six patients with bronchitis, most of whom had been heavy cigarette smokers for many years. Much variation in clearance rates was found among smokers. Cigarette smoking resulted in diminished pulmonary clearance in the upper airways first. As a result, mucus cleared from the lower airways accumulated in the larger airways where stasis occurred. In severe cases, stasis was more generalized throughout the bronchial tree.

Sanchis, et al. (74) also studied lung clearance mechanisms in nine adult females who had smoked more than 15 cigarettes a day for more than 5 years and who had no evidence of bronchitis or respiratory disease. A group of nonsmoking females matched for age served as controls. A heterodisperse aerosol of I^{131} tagged human albumin was inhaled by the volunteers, and measurements of radioactivity were made over three crescentic areas of the right lung which corresponded to large ciliated airways, intermediate bronchi, and nonciliated peripheral airways and alveoli. Cigarette smokers exhibited a slowing of the rapid clearance phase of the large ciliated airways and also a relative acceleration in the second clearance phase resulting in an accumulation of activity at the hilar area. Comparing the clearance among

smokers and nonsmokers, the authors found that the nonsmokers retained twice as much activity in the lung at the end of 24 hours as did the smokers. This finding resulted from the deposition of much more of the aerosol distal to the ciliated airways in nonsmokers than in smokers suggesting that seemingly healthy smokers may have obstruction of the small airways.

Camner, et al. (11) examined the short-term effects of heavy cigarette smoking on mucociliary transport using the same methods as in his previous studies (10, 12). The subjects were 13 men aged 27 to 38 who had been habitual smokers for several years. Baseline clearance rates were measured after refraining from cigarette smoking for 1 hour. The subjects then repeated the test but were instructed to "chain smoke" by inhaling the smoke as deeply and as frequently as possible, but without coughing. Subjects smoked much more intensely than under normal circumstances. The speed of mucociliary transport was significantly higher during intensive cigarette smoking than when they were not smoking ($P < 0.01$). These results differ from the results of other investigators. The effect of the deep regular inhalation patterns used during the period of heavy smoking on clearance rates remains uncertain.

Studies in Animals

Rylander (73) studied the effect of cigarette smoke on the clearance of radioactively tagged particles and viable bacteria in the lungs of 114 experimental and control guinea pigs. The clearance of particles measures mucus transport whereas the clearance of viable bacteria is a partial indicator of phagocytic activity. Inhalation of smoke from cigarettes with varying levels of "tar" resulted in similar decreases in both the mechanical and bactericidal clearance. In each case, the mechanical clearance appeared to be affected earlier than the bactericidal clearance. When phenylmethyloxadiazole (PMO) was added to the tobacco, neither the mechanical nor bactericidal clearance was affected by cigarette smoke.

Dalhamn and Rylander (14) also reported that phenylvinylloxadiazole (PVO) and phenylmethyloxadiazole (PMO), when added to tobacco, were effective in reducing the ciliotoxic effects of cigarette smoke in in vivo cat trachea preparations.

Phagocytosis

Rylander (72) studied the effect of acute and chronic exposure to cigarette smoke on the number of alveolar macrophages in the guinea pig. Acute exposure to the smoke of five or more cigarettes, resulted in

a significant ($P < 0.05$) reduction in the number of alveolar macrophages. With more prolonged exposure to cigarette smoke, an increase occurred in the number of alveolar macrophages over control values.

The effect of nitrogen dioxide (NO_2), a compound found in cigarette smoke, on alveolar macrophages in rabbits was studied by Acton and Myrvik (1). Phagocytic activity and virus-induced resistance to rabbitpox virus were suppressed by exposure to 15 p.p.m. of NO_2 over a 3-hour period.

Bacterial and Mycological Studies

The prevalence of fungi in the throat was examined by Martin, et al. (56) in a population of 365 male and 103 female European patients in South Africa who were hospitalized for a variety of conditions. Throat swabs were taken shortly after admission and plated on appropriate culture media. The yeasts isolated were *Rhodotorula mucilaginosa*, *Torulopsis glabrata*, and seven species of *Candida*. A seasonal variation in prevalence was noted with a decline in the winter and with peaks in the spring and summer. Smokers of more than 30 cigarettes a day had a higher prevalence of pharyngeal fungi than nonsmokers or those smoking less than this amount. No effect of age or disease category on the prevalence of pharyngeal fungi was found.

The bacterial flora in respiratory tree secretions obtained at bronchoscopy from 207 patients with chronic lung disease and 48 controls were characterized by Dobisova, et al. in a study from Germany (15). No relationship was found between smoking or severity of respiratory symptoms and the composition of the bacterial flora. They also reported that smokers comprised 84.6 percent of those with chronic cough but only 58.3 percent of the controls.

The effects of nitrogen dioxide and cigarette smoke on the retention of inhaled bacteria were investigated by Henry, et al. (32). Male golden hamsters were exposed to an aerosol of *Klebsiella pneumoniae* following exposure to NO_2 and/or cigarette smoke. A control group was exposed to the pathogen without pretreatment. Acute exposure to either NO_2 or cigarette smoke resulted in an increased mortality and decreased survival time from *Klebsiella* infections. Exposure to both NO_2 and cigarette smoke reduced the rate of clearance of viable bacteria from the lungs to a greater extent than exposure to either substance alone. The increase in lethal effects of *Klebsiella* exposure may have resulted from inhibition of the mucociliary transport system or reduction of phagocytic capacity of the alveolar macrophages.

The Surfactant System

Finley and Ladman (20) measured pulmonary surfactant in cigarette smokers and nonsmokers. The surfactant was recovered after endobronchial lavage. The lipid content of surfactant in smokers and nonsmokers was qualitatively similar; however smokers had on the average only 14.3 percent of the surfactant levels found in nonsmokers. Their levels of surfactant returned promptly to levels found in nonsmokers following cessation of smoking. Cigarette smoking may reduce the quantity of surface active material lining the alveolar walls through either decreased production, an increased removal, or a dilution with mucus from the airways.

Summary of Recent Nonneoplastic Bronchopulmonary Findings

In addition to the summary presented in the introduction of this chapter, based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field:

1. Epidemiological and clinical studies from several countries confirm that cigarette smoking by both men and women is associated with an increased prevalence of respiratory symptoms and decreased pulmonary function compared to nonsmokers.
2. The regular use of filter cigarettes is associated with less cough and sputum production compared with the regular use of non-filter cigarettes.
3. Cigarette smoking in combination with certain occupational exposures is associated with a higher prevalence of respiratory symptoms and COPD than is observed with either cigarette smoking or occupational exposure alone. Byssinosis is found more frequently in cotton mill employees who smoke cigarettes than in nonsmoking workers.
4. Recent autopsy studies confirm that pulmonary emphysema is much more frequent and severe in cigarette smokers than in nonsmokers.
5. Several recent investigations have confirmed that cigarette smoking exerts adverse effects on pulmonary clearance and macrophage function.

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CHAPTER 3

Cancer

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Introduction

This introduction is a brief summary of the major relationships between smoking and cancer which have been established in previous reports on the health consequences of smoking (91, 92, 93, 94, 95, 96).

Cigarette smoking has been clearly identified as the major cause of lung cancer in the United States. This conclusion is based on detailed epidemiological, clinical, autopsy, and experimental data which have accumulated over a period of more than 20 years. For both men and women, the risk of developing lung cancer is directly related to total exposure to cigarette smoke as measured by the number of cigarettes smoked per day, the total lifetime number of cigarettes smoked, the duration of smoking in years, the age at initiation of smoking, the depth of inhalation of tobacco smoke, and the "tar" and nicotine levels in the cigarettes smoked. Lung cancer death rates, however, are lower for women than they are for men, a finding due, in part, to a difference in exposure. Women smokers use fewer cigarettes a day, choose filtered cigarettes with lower "tar" and nicotine values, and also tend to inhale less. However, even when women experience comparable levels of exposure to cigarette smoke as men, their mortality rates for lung cancer still remain somewhat lower.

Those who stop smoking experience a decline in the risk of developing lung cancer relative to continuing smokers. The air pollution commonly found in an urban setting appears to result in elevated lung cancer death rates; however, this effect is relatively small compared to the overriding effect of cigarette smoking.

Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with many of these exposures to produce much higher death rates from lung cancer than would result from one exposure alone. Interacting exposure factors may be experienced simultaneously or at different times. The uranium mining and asbestos industries are examples of occupations in which this interaction occurs.

The bronchial epithelium of smokers often shows premalignant changes including squamous metaplasia, atypical squamous metaplasia, and carcinoma in situ.

Pipe and/or cigar smokers experience a risk of developing lung cancer that is higher than the risk of nonsmokers; however, it remains

significantly lower than the risk of cigarette smokers. A more complete discussion of the risks from pipe and cigar smoking is found in another chapter of this report.

Epidemiological, experimental, and autopsy data have demonstrated that cigarette smoking is a significant factor in the development of cancer of the larynx, oral cavity, esophagus, and urinary bladder. B-naphthylamine, a carcinogen known to cause cancer of the urinary bladder in humans, has been identified in cigarette smoke. There is also an association between cigarette smoking and cancer of the pancreas. Experimental studies with animals in which cigarette smoke or one of its constituent compounds is administered in a variety of assays have confirmed the presence of complete carcinogens, cocarcinogens such as tumor initiators and tumor promoters, and tumor accelerators in cigarette smoke.

Recently, additional epidemiological, autopsy, and experimental studies have added to our understanding of these relationships.

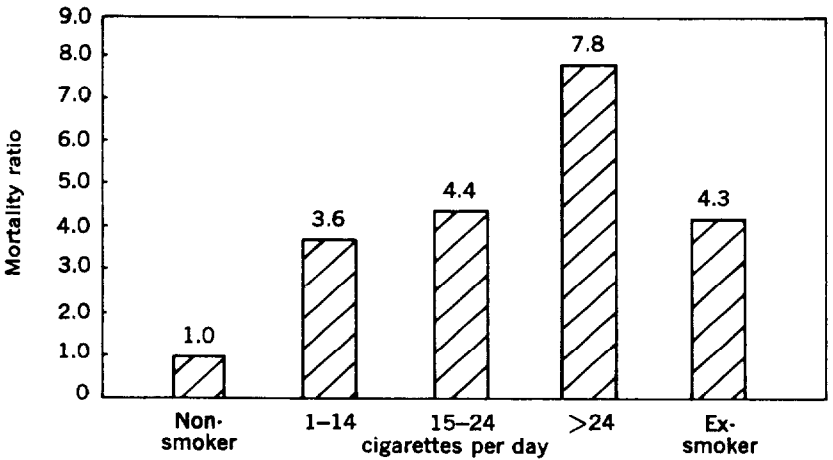
Lung Cancer

Epidemiological Studies

An ongoing prospective epidemiological study conducted in Japan 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. Hirayama (37) has now reported 5-year followup data on 265,118 men and women aged 40 years and older. This represented 91 to 99 percent of the total population in the area of the 29 health districts where the study was conducted. A total of 11,858 deaths occurred during the 5-year period which included a total of 1,269,382 person-years of observation. Both men and women who smoked cigarettes experienced higher death rates from lung cancer than nonsmokers. Among smokers, the lung cancer mortality ratio was 3.85 for men and 2.44 for women as compared to nonsmokers ($P < 0.001$). Dose-response relationships were demonstrated for the number of cigarettes smoked per day and the age at initiation of smoking (figs. 1 and 2). These mortality ratios are considerably lower than those reported for the United States, Canada, and Great Britain, and may reflect a lower average number of cigarettes smoked a 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, are similar to the results of all the other major

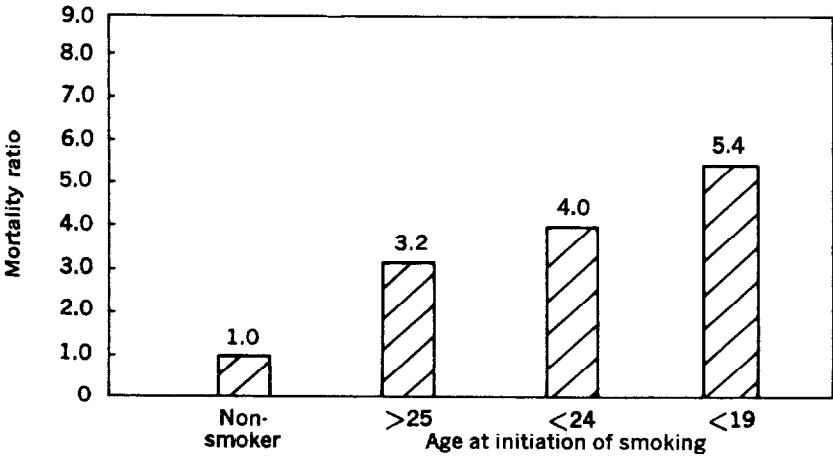
epidemiological investigations. Thus, the reliability and accuracy of the methods of population selection and analysis used in previous studies based on population samples, and the conclusion that cigarette smoking is the major cause of lung cancer are again confirmed.

Figure 1.—Standardized lung cancer mortality ratios of Japanese by number of cigarettes smoked (1966–1970).



SOURCE: Hirayama, T. (37).

Figure 2.—Lung cancer mortality ratios of Japanese by age at initiation of cigarette smoking (1966–1970).



SOURCE: Hirayama, T. (37).

TABLE 1.—Age-standardized lung cancer death rates of British physicians and the population of England and Wales at various time periods

Lung cancer standardized death rate per 1,000 men per year in—						
Years.....	Doctors			England and Wales		
	1953-57	1957-61	1961-65	1954-57	1958-61	1962-65
Death rate per 1,000.....	1.10	0.85	0.83	1.49	1.71	1.88

Source: Doll, R., Pike, M. C. (22).

Kennedy (45) studied primary lung cancer in 29 men and 11 women diagnosed before the age of 40 and found a strong association between cigarette smoking and the development of this disease.

Boucot, et al. (11) further characterized the 121 cases of lung cancer detected in the population of the Philadelphia pulmonary neoplasm research project. The risk of developing lung cancer increased with age, was higher in nonwhites than in whites, and increased sharply with increased cigarette consumption.

The relationship between cigarette smoking and lung cancer was investigated in a retrospective study by Ferrara (25) in La Plata, Argentina. The smoking habits of 144 lung cancer patients were contrasted with those of 386 controls. A dose-response relationship was found between cigarette usage measured by the number of cigarettes smoked per day and the duration of smoking and the risk of developing lung cancer.

A high incidence of lung cancer is reported from the island of Jersey in the Channel Isles compared to England and Wales. The island has no heavy industry and only minimal levels of air pollution. Cragg (16) studied 144 patients who developed lung cancer on Jersey during a 4-year study period. Only three nonsmokers were found among the 113 patients for whom histories were available.

Fingerland, et al. (26) determined the prevalence of lung cancer and certain other diseases in an autopsy series of 1,338 adults in Czechoslovakia. Some 198 cases of primary lung cancer were identified. In the autopsy population, 1.4 percent of the nonsmokers, 14.1 percent of those smoking less than 200,000 lifetime cigarettes, and 33.3 percent of those smoking more than 500,000 lifetime cigarettes had lung cancer.

Rickard and Sampson (71) studied 94 Negro patients with lung cancer in Washington, D.C., and found that 57 (92 percent) of 63 patients whose smoking history was available were regular smokers.

Epidemiological studies conducted in Italy (10), Sweden (48), Poland (46), Russia (42), Cuba (73), Mexico (13), and the Netherlands (98) demonstrate an association between cigarette smoking and lung cancer.

Berg, et al. (5) examined the incidence of recurrent primary cancers following initial primary cancers of the respiratory and upper digestive systems in New York. During 23,802 man-years of observation in 9,415 patients with an initial squamous cell cancer, 518 second cancers developed at other sites. Patients whose first primary cancer was in the lung had an observed to expected relative risk ratio of 5.7 ($P < 0.05$) for subsequent cancers of the respiratory or upper GI system. Patients with the first cancer in the oral cavity or larynx frequently developed a second cancer in the lung. Medical records confirmed long smoking histories among almost all of these patients who developed second cancers.

Cancer of the lung, oral cavity, larynx, and esophagus were reported by Schmidt and De Lint (79) to be common causes of death among 6,578 men and women who had received treatment for alcoholism in Toronto. The authors attributed this finding to the strong association that exists between alcohol and tobacco use and not to the effect of alcohol alone.

Carcinoma of the trachea is a relatively rare condition with only about 400 cases having been reported in the literature. In a study of 41 patients with carcinoma of the trachea, Hajdu, et al. (31) found an apparent association between cigarette smoking and the development of epidermoid cancers of this structure.

An association between cigarette smoking and the development of bronchiolo-alveolar carcinoma in 74 patients was described by Delarue, et al. (18).

Ex-smokers

Those who stop smoking experience a decline in the risk of developing lung cancer relative to continuing smokers. Doll and Pike (22) conducted a study of the smoking habits and causes of death of 40,000 British physicians. Smoking habits were surveyed in 1951, 1957, and 1966. During the study period, more than 3,500 physicians became ex-smokers. The age-standardized percentage of ex-smokers among physicians 35 to 64 years of age rose from 18.1 percent in 1951 to 26.5 percent in 1957 and 29.5 percent in 1966. Concurrently, the percentage of physicians smoking cigarettes fell from 44.1 percent to 22.0 percent, while over the same period estimates of the per capita cigarette consumption for the adult male population in the United Kingdom suggested a slight increase in cigarette consumption. Over this 15-year period, the mortality from lung cancer among physicians dropped considerably while lung cancer death rates among the male population in England and Wales increased to some extent (table 1). Although cer-

tain limitations apply to the interpretations derived from secular data, analysis of the study design and the magnitude of the results indicate that this study constitutes important evidence of some of the benefits that result from the cessation of cigarette smoking.

Uranium Mining and Exposure to Radioactivity

Epidemiological evidence supported by autopsy studies has established that airborne radiation, particularly in synergistic combination with cigarette smoking, is the major cause of the excess of respiratory cancers among uranium miners.

Lundin, et al. (53) considered quantitative and temporal aspects of radon daughter exposure and respiratory cancer in a report from the Epidemiological Study of United States Uranium Miners. They observed a statistically significant excess of respiratory cancer among white uranium miners at each cumulative radiation exposure category down to and including 120-359 WLM (working level months). The authors noted that although cigarette smoking alone entailed a risk of the development of cancer of the respiratory tract in miners just as it does in nonminers, cigarette smoking in combination with radon daughter exposure appeared to result in an even greater risk.

Several authors (30, 44, 63, 84, 104) continue to report the presence of polonium-210 or one of the thorium isotopes in tobacco leaf, tobacco smoke, or the lungs of smokers.

Air Pollution

Data standardized for cigarette smoking indicate the existence of an urban factor in the development of lung cancer; it is likely that air pollution, frequently part of the city environment, is a component of the urban factor.

The National Academy of Sciences published a review (61) of the biological effects of atmospheric pollution by particulate polycyclic organic matter. Detailed epidemiological, experimental, physical, and chemical data were reviewed. It was concluded that air pollution, as commonly found in urban settings, was found to be associated with increased lung cancer mortality in cities. An examination of the data presented, however, indicates that cigarette smoking is, in most cases, the overriding factor in the development of lung cancer. Polycyclic hydrocarbons and related compounds which are known to cause cancer of the lung and other organs in experimental animals were found to

be present in relatively high concentrations in cigarette smoke, in large quantities in the air of industries in which workers have high-lung cancer rates, and also in the air of urban communities.

Sterling and Pollack (86) reviewed the effects of air pollution on death rates from lung cancer. They suggested that particles resulting from the combustion of organic fuels may be more strongly related to the incidence of lung cancer in the population than cigarette smoking. The cumulated epidemiological data regarding cigarette smoking and lung cancer were not considered by the authors in this report.

Asbestos

Cigarette smoking asbestos workers have markedly elevated lung cancer death rates compared to nonsmoking asbestos workers. Berry (6) examined the combined effect of asbestos exposure and smoking on mortality from lung cancer among 1,300 male and 480 female asbestos factory workers over a 10-year period. There was no significant increase in lung cancer mortality among smoking or nonsmoking workers with a low-to-moderate exposure to asbestos. However, among smokers who had heavy exposure to asbestos, 32 lung cancer deaths occurred among 663 men (9.9 expected), and there were 18 deaths among 292 women (1.4 expected). This confirms the greatly increased risk of developing lung cancer among asbestos workers who smoke cigarettes.

Autopsy and Cytological Studies

The respiratory tract of cigarette smokers examined at autopsy frequently demonstrates epithelial changes considered to be precursors of bronchogenic carcinoma. Such changes include squamous metaplasia, atypical squamous metaplasia, and carcinoma in situ. Herrold (35) studied histologic types of primary lung cancer in U.S. veterans who were subjects of the Dorn study. Of a total of 2,241 white male veterans who died of lung cancer over an 8-year period, histologic material was available for review in 1,477 patients. Histologic types were grouped according to the Kreyberg classification of Groups I and II tumors. Group I tumors, epidermoid and oat-cell carcinomas, were present in 27.3 percent of the 55 nonsmokers and were present in 57.8 percent of the 472 "current smokers of cigarettes only." The difference was statistically significant ($P < 0.001$), confirming the strong association between cigarette smoking and Kreyberg Group I tumors.

Auerbach et al. (2) examined epithelial changes in the bronchial tree of 456 men and 302 women who had died of a cancer other than lung cancer. There were 72 ex-smokers among the men, all of whom had smoked for 10 years or more but had quit smoking for at least 5 years prior to death. Atypical cells were present in 93.2 percent of the current smokers, 6.0 percent of the ex-smokers, and 1.2 percent of the non-smokers. Areas of epithelium composed entirely of atypical cells devoid of cilia were found in the bronchial tree of 8 percent of the current smokers, 0.2 percent of the ex-smokers, and none of the nonsmokers. Unusual cells with disintegrating or fading nuclei were found exclusively in 15 percent of the ex-smokers.

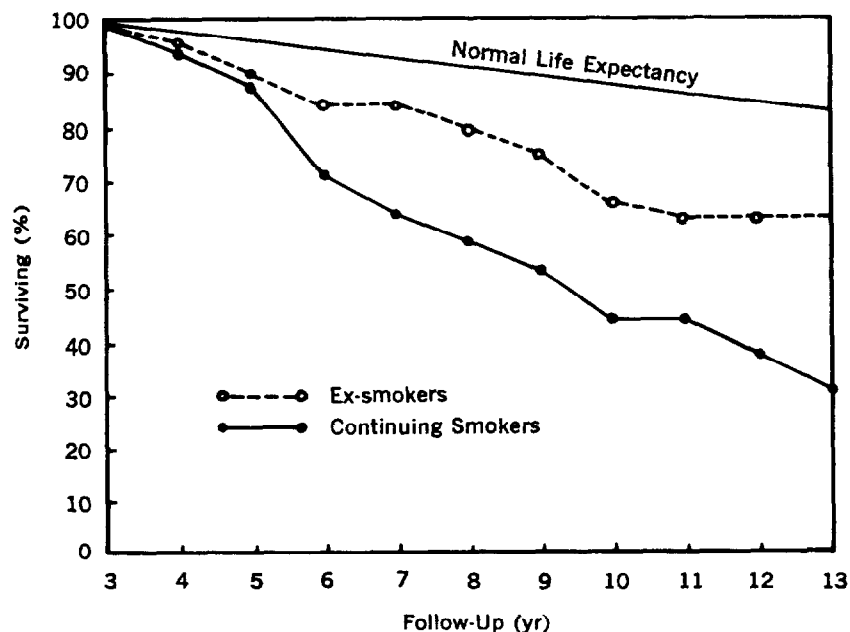
The prevalence of atypical cells (hyperplastic and metaplastic) in the sputum of 122 male and 128 female workers was examined by Robins (72). These smokers, all under the age of 19, were matched with a control group drawn from a population of college students. Atypical cells were found in 14 percent of the smokers and 5 percent of the non-smokers.

Oral Cancer

Data from the large Japanese prospective study by Hirayama (37) indicate that mortality rates from cancer of the oral cavity among males are higher in smokers than nonsmokers. A dose-response relationship was demonstrated for the age at initiation of smoking. The standardized mortality ratio among cigarette smokers was 10.0 for men ($P < 0.001$) and 1.22 for women compared to nonsmokers. These ratios are not stable due to the few deaths that occurred from oral cancer in this study.

Certain relationships between cigarette smoking and cancer of the oral cavity, pharynx, and larynx were investigated by Moore (59). Over a 15-year period, 1,000 patients with invasive squamous carcinoma at these sites were treated in Kentucky. Of these patients, 203 had a history of cigarette smoking and had had no recurrence of cancer for a period of 3 years or more. This group was further divided on the basis of current smoking habits. Of the 122 who continued to smoke, 48 (40 percent) eventually developed a second cancer at these sites, whereas only five (6 percent) of the 81 who stopped smoking developed a second malignancy. This sixfold difference is statistically significant ($P < 0.001$). The survival curves for these two groups are presented in figure 3.

Figure 3.—The survival of ex-smokers and continuing smokers who were treated for a primary cancer of the oral cavity, pharynx, or larynx.



SOURCE: Moore, C. (59).

Martinez (57) studied the relationship between smoking in various forms and cancer of the oral cavity in a retrospective study of 153 patients with this disease. Dose-response relationships were demonstrated for the amount smoked; the amount of alcohol consumed, and the development of cancer of the oral cavity.

Tyldesley (90) examined the prevalence of leukoplakia among 402 English coal miners of whom 280 smoked and chewed tobacco. Tobacco chewing was commonly found to be a substitute for smoking in underground conditions where smoking was impossible. Leukoplakia was found in 3.6 percent of the chewers, whereas no leukoplakia was found among the nonchewers.

Nelson and Ship (62) determined the relative influence of eight variable factors on the development of oral cancer in relation to age at the onset of disease in a population of 191 patients with a confirmed diagnosis of a primary squamous cell carcinoma of the oral cavity. The factors considered included age, sex, race, consumption of alcohol and tobacco, certain systemic diseases, and oral trauma. The prevalence of heavy tobacco use was more common among the younger patients. While 91 percent of the cancer patients under the age of 45 smoked more than 20 cigarettes a day, only 59 percent of the patients over 65 smoked this heavily.

Reverse smoking is a common practice in some parts of India, whereby the lighted end of a homemade cigar is held inside the mouth. Pindborg, et al. (64) conducted an epidemiological survey of 10,169 villagers in the Srikakulam district of south India and found that 43.8 percent of those interviewed practiced reverse smoking. Leukoplakia was found in 8.8 percent of reverse smokers compared to 0.1 percent in nonsmokers. The 10 patients found to have oral cancer were all reverse smokers. Reddy, et al. (68) found that reverse smoking was practiced by 73 of 100 patients with oral cancer. Reddy, et al. (66, 67) reported characteristic histologic findings of the oral cavity in biopsies obtained from reverse smokers. In two other studies from India, changes in the ultrastructure of the oral mucosa of chewers (54) and smokers (65) are described.

Cancer of the Esophagus

In the Japanese prospective study, Hirayama (37) reported that male smokers had a mortality ratio for cancer of the esophagus of 2.24 compared to nonsmokers ($P < 0.001$). Martinez (57) studied the relationship between smoking in various forms and the development of cancer of the esophagus in a retrospective study of 179 patients. Dose-response relationships were demonstrated for the amount smoked and alcohol consumption and the development of cancer of the esophagus.

Cancer of the Larynx

The mortality ratios for cancer of the larynx in the large Japanese prospective study were reported by Hirayama (37) to be 11.0 for male cigarette smokers and 9.0 for female cigarette smokers compared to nonsmokers ($P < 0.001$).

Stell (85) conducted a retrospective study of 190 patients with carcinoma of the larynx. Only 13 percent of the patients were nonsmokers or ex-smokers compared with 41 percent of the controls. The relative risk ratio for heavy cigarette smokers was 3.48 compared to nonsmokers. The relative risk was 1.34 for smokers of pipes and cigars.

Moore (59) reported the occurrence of second primary cancers in 203 smokers who had been surgically treated for cancer of the oral cavity, pharynx, or larynx, without recurrence for a period of 3 years.

Within an average followup period of 7 years, 40 percent of the 122 patients who continued to smoke developed second primary cancers of the upper respiratory or digestive tract, but only 6 percent of the patients who stopped smoking developed second cancers. A total of 50 patients with cancer of the larynx underwent laryngectomy. Of the 16 who continued to smoke, three developed a second cancer, whereas none of the 34 ex-smokers without a larynx developed a second primary malignancy.

Cancer of the Pancreas

Hirayama (37) reported a significant association between cigarette smoking and the development of cancer of the pancreas. The mortality ratios were 2.05 ($P < 0.001$) for men and 1.9 ($P < 0.05$) for women.

Krain (47) reviewed a number of environmental factors that may be associated with the 15 percent annual increase in the death rate from cancer of the pancreas found in the United States. The strongest associations appeared to be with cigarette smoking and certain occupational exposures.

Cancer of the Kidney and Urinary Bladder

Hirayama (37) reported a mortality ratio of 2.71 for cancer of the kidney and bladder in women who smoke cigarettes ($P < 0.001$). The mortality ratio of 1.07 for men who smoked compared to non-smokers was not significant; however, the few deaths from this cancer among men in the Japanese study did not allow conclusions to be drawn.

Hoover and Cole (39) examined the strength of the association between cigarette smoking and the development of bladder cancer in successive birth cohorts of men and women in the United States, Denmark, England, and Wales. 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 consistent for different nationalities and urban and rural groups. These findings suggest a causal role for cigarette smoking in the development of bladder cancer.

In a retrospective study from Germany, Fischer (27) examined the smoking habits of 162 men with bladder cancer and a control group of 198 men who had benign prostatic hypertrophy. The relative risk

ratio was 6.4 for smokers of fewer than 15 cigarettes a day, and 27.5 for smokers using more than this amount. Only 3 percent of the men with bladder cancer were nonsmokers.

Xipell (103) studied renal nodules in 250 patients in Australia who came to autopsy. Benign adenomas were the most common lesions and were found in 22 percent of the patients. The remaining nodules were cysts, thrombosed veins, abscesses, granulomas, and metastatic lesions. A statistically significant difference between the smoking habits of those with adenomas and those with the miscellaneous lesions was reported ($P < 0.012$). All the adenomas were found in smokers.

Cole, et al. (14) conducted a retrospective study of 461 persons with transitional or squamous cell carcinoma of the lower urinary tract. After the data were controlled for cigarette smoking, occupational exposure appeared to contribute to 18 percent of the lower urinary tract cancer among men aged 20 to 89 compared to the 39 percent attributed to cigarette smoking in men in a previous report (15).

Werf-Messing and Kaa'len (100) examined the association of occupational exposure and smoking in the development of bladder cancer in 346 males in the Netherlands who had this disease. The smoking habits of cancer and control patients in each group were nearly identical; however, patients with bladder cancer had a longer exposure to hazardous working conditions than did controls.

Experimental Carcinogenesis

Experimental studies, mainly in animals, have added to an understanding of many of the processes involved in tobacco carcinogenesis. Possible mechanisms of chemical carcinogenesis were reviewed by Miller and Miller (58), Ryser (76), and Leone (51). Electron spin resonance studies of carcinogenesis were reviewed by Swartz (87). Franke (28) discussed the possible role of hydrophobic interactions of polycyclic aromatic hydrocarbons with protein in chemical carcinogenesis. Chemical carcinogenesis in Syrian hamsters was reviewed by Shubik (82) and Homburger (38).

Respiratory Tract Carcinogenesis

Epidemiological, clinical, and autopsy data from studies of humans have established cigarette smoking as the major cause of lung cancer in the United States. One of the reasons it has not been possible to

characterize fully the mechanisms responsible for this causal relationship is the lack of an ideal animal model in which to study respiratory tract carcinogenesis in the laboratory. Exposing animals to cigarette smoke in a closed chamber does not replicate the kinds of exposure smoking humans receive, although some recently developed smoking chambers provide conditions similar to the exposure experienced by human smokers. Many animals are obligatory nose breathers and, in them, a large portion of the particulate phase of cigarette smoke may be removed by turbulent precipitation in the nasal passages or larynx before reaching the sites in the lung most commonly exposed in humans. Auerbach, et al. (3) first demonstrated that malignant lung tumors could be produced in smoking dogs who were taught to smoke through a tracheostoma. Several investigators have recently examined respiratory tract carcinogenesis in animals using intratracheal instillations of chemical carcinogens found in cigarette smoke, including benzo(a)pyrene and 7H-dibenz(d,g)carbazole. Tumors resulting from this type of treatment are frequently similar to lung tumors found in humans (24, 32, 33, 36, 77, 80).

Harris, et al. (33) examined the acute ultrastructural effects of benzo(a)pyrene carried on ferric oxide particles on the tracheo-bronchial epithelium of the Syrian Golden hamster. Test substances were administered by intratracheal instillation. Ferric oxide alone resulted in some focal replacement of columnar epithelium with polygonal basal cells. This effect was reversed by termination of the treatment. After treatment with benzo(a)pyrene and ferric oxide, focal replacement of the columnar cells with pleomorphic cells occurred. These pleomorphic cells had the ultrastructural features of atypical squamous cells and were similar to the hyperplastic epithelial cells described in the bronchi of smoking dogs and the neoplastic squamous cells found in human bronchogenic carcinoma.

In an extension of this study, Harris, et al. (32) reported that vitamin A deficiency or the application of benzo(a)pyrene-ferric oxide through intratracheal instillation resulted in squamous metaplasia of the trachea. Both lesions appeared to be morphologically similar by light microscopy, but at the ultrastructural level significant differences were observed. Squamous metaplasia induced by benzo(a)pyrene-ferric oxide was characterized by defects in the basement membrane, enlarged nuclei with cytoplasmic invaginations, and pleomorphic nucleoli not seen following vitamin A deficiency.

Sellakumar and Shubik (80) treated Golden Syrian hamsters with weekly intratracheal instillations of 7H-dibenz(c,g)carbazole (7H-DBC) suspended with equal amounts of ferric oxide in a saline solution. One group of 35 hamsters was treated with 45 mg. of the carcinogen and a second group was treated with 15 mg. More than 85 percent of the animals in each group developed respiratory tract

tumors. Most of the tumors occurred in the major airways and were squamous cell carcinomas. Adenocarcinomas and anaplastic carcinomas were found less frequently.

Saffiotti, et al. (77) examined the carcinogenic effects of benzo(a)pyrene prepared as a suspension of fine crystalline particles attached to ferric oxide in a physiologic saline solution and administered by intratracheal applications to Syrian Golden hamsters. Various concentrations of benzo(a)pyrene and ferric oxide were used in single and multiple applications. A single administration of 37.5 mg. of benzo(a)pyrene with 12.5 mg. of ferric oxide resulted in five bronchogenic carcinomas and five histologically benign respiratory tumors in a total of 61 hamsters. Following multiple administrations, bronchogenic carcinomas including anaplastic and squamous cell types were induced in all dosage groups and a positive dose-response relationship was demonstrated.

Feron (24) studied respiratory tract tumors in Syrian Golden hamsters following tracheal instillations of furfural and/or benzo(a)pyrene. Of the 62 hamsters, 41 developed respiratory tract tumors of which squamous cell carcinoma of the trachea was the most frequent type observed. Furfural in combination with benzo(a)pyrene resulted in a higher yield of tumors than was seen with benzo(a)pyrene alone. Furfural alone possessed no carcinogenic activity.

Shabad (81) and one of his collaborators, Yanysheva, produced benign and malignant epidermoid lung tumors in rats following single and multiple administrations of benzo(a)pyrene by intratracheal instillation. Dose-response relationships were demonstrated.

Experiments in Mice

Cigarette smoke condensate (CSC), various fractions of CSC, and many chemical compounds identified in CSC have been tested for tumorigenic activity in mice by a variety of methods, including skin painting and subcutaneous injections. Complete carcinogens and incomplete carcinogens, which include tumor initiators, tumor promoters, and tumor accelerators have been described. Several recent studies have been conducted using mice as the experimental animal which examine further the mechanisms involved in tobacco carcinogenesis.

Lee and O'Neill (50) measured the effect of duration and dosage of benzo(a)pyrene applications on the rate of development of benign and malignant skin tumors in mice. The incidence rate for tumor formation was directly proportional to both time and dose. These data conformed quite closely to postulated mathematical models of the rate of tumor development.

Davies and Whitehead (17) studied the effect of altering the "tar" and nicotine ratio of cigarettes on experimental carcinogenesis. No significant difference in tumor yield was found between condensates obtained from the smoke of cigarettes containing 16.6 mg. "tar" and 1.79 mg. nicotine and other cigarettes containing 10.0 mg. "tar" and 1.94 mg. nicotine.

Several studies by Bock, et al. (7, 8, 9) have examined the tumor promoting activity of a number of fractions of cigarette smoke condensate (CSC). A number of subfractions of the neutral fraction of CSC were tested for tumor promoting activity in mice pretreated with 7,12-dimethylbenz(a)anthracene as a tumor initiator (8). The most polar subfractions and the fraction containing benzo(a)pyrene were the most active tumor promoting fractions. In another study (9), the weak acid fraction of CSC was found to be a very weak complete carcinogen which probably acts primarily as a tumor promoting agent. The promoting activity depended primarily on the nonvolatile constituents of this fraction. More recently, Bock, et al. (7) reviewed the tumor promoting effects of CSC and extracts of tobacco leaves. A combination of two subfractions of the tobacco extracts, as well as five major fractions of CSC, were found to have tumor promoting activity. The fraction containing the polynuclear aromatic hydrocarbons was found to be a complete carcinogen. Two subfractions were found to be strongly synergistic in their tumor promoting activity when applied simultaneously to mouse skin.

Lazar, et al. (49) found that hydroquinone applied to mouse skin in conjunction with the active fractions of CSC accelerated the early histologic changes that result from the application of "tar" or its fractions.

Van Duuren, et al. (97) have suggested that "cocarcinogenesis" be differentiated from "tumor promotion" defining "cocarcinogenesis" as the production of malignant tumors by two or more agents applied simultaneously or alternately in single or repeated doses to mouse skin and "tumor promotion" as a single treatment with one agent followed by single or repeated treatment with a second agent. Using these definitions, the authors found several tumor promoting agents to possess cocarcinogenic activity.

Roe, et al. (74) studied mechanisms of mouse skin carcinogenesis using benzo(a)pyrene and a neutral fraction of CSC applied singly or in various combinations with each other. Skin tumor incidence rates increased with the dose of applied material for both the neutral fraction and benzo(a)pyrene. Mixtures of the neutral fraction with benzo(a)pyrene did not act independently in the production of malignant skin tumors but synergistically, suggesting that some of the components of the neutral fraction act as cocarcinogens rather than as complete carcinogens.

Schmähl (78) found a direct relationship between the dosage and duration of subcutaneous injections of tobacco smoke condensates and the development of sarcomas in rats.

Maenza, et al. (56) studied the effects of a combination of nickel subsulfide (Ni_3S_2) and benzo(a)pyrene on sarcoma induction in rats. The interval between administration of the carcinogen and the development of sarcomas was significantly shorter ($P < 0.001$) in male Fischer rats given injections of a combination of 10 mg. of Ni_3S_2 and 5 mg. of benzo(a)pyrene than in rats given either ingredient alone. There appeared to be a synergistic interaction between nickel compounds and the polycyclic aromatic hydrocarbons.

Healey, et al. (34) added further refinements to a technique for measuring the nonspecific esterase activity of mouse skin following applications of various chemical compounds. With few exceptions, changes in esterase activity reflected the known tumor producing activity of a number of polycyclic hydrocarbons and tobacco condensates.

Sydnor, et al. (89) examined the effect of an aqueous extract of cigarette smoke condensate on benzo(a)pyrene-induced sarcoma in female Sprague-Dawley rats. Benzo(a)pyrene was injected subcutaneously in various concentrations of 12.5 μg . to 400 μg . per dose dissolved in sesame oil. Injections were given on alternate days for 30 doses. The mean tumor induction time was accelerated in five of seven groups given the aqueous extract of CSC in their drinking water. Animals given any benzo(a)pyrene eventually developed sarcomas at the site of injection. Dose-response relationships were demonstrated for the concentration of benzo(a)pyrene administered. It appeared that aqueous extracts of CSC contained one or more components which functioned as cocarcinogens.

Aryl Hydrocarbon Hydroxylase (AHH)

Certain of the chemical compounds found in the gas and particulate phase of cigarette smoke are absorbed through the lung or oral cavity into the general circulation. Possibly through such absorption some chemical carcinogens are carried to target organs not directly exposed to cigarette smoke. Some of these chemical compounds are probably excreted unchanged while others are metabolized to various degrees by enzyme systems present in the liver and many other tissues. The microsomal mixed-function oxidases are key enzyme systems for the metabolism of a wide variety of chemical compounds including the

chemical carcinogens found in cigarette smoke. Aryl hydrocarbon hydroxylase (AHH) is a part of the cytochrome P-450 containing microsomal enzyme system that is present in several tissues of humans and many animal species. The activity of this enzyme system is induced following exposure to the appropriate chemical stimulus. The hydroxylation of polycyclic hydrocarbons results in the detoxification of some and the activation of others to reactive carcinogenic forms. An understanding of the role of AHH in the metabolism of chemical carcinogens in man may help clarify some of the mechanisms involved in tobacco carcinogenesis. Recently, several studies examined AHH activity in animals and man.

Studies in Animals

Sydnor, et al. (88) found that an aqueous extract of CSC administered in the drinking water of rats potentiated benzo(a)pyrene-induced AHH activity in the liver. The liver AHH activity was slightly increased by the aqueous extract of OSC alone.

Rondia and Gielen (75) reported that rats exposed to various levels of carbon monoxide developed a decrease in AHH activity in liver homogenates. The reduction in AHH activity developed after 120 hours exposure to levels of carbon monoxide which produced carboxy-hemoglobin levels below 15 percent.

Welch, et al. (99) reported that the administration of benzo(a)pyrene to pregnant rats resulted in an increase of the in vitro AHH activity of maternal liver, placenta, and fetal liver. A twentyfold higher dose of benzo(a)pyrene was necessary for stimulation of AHH activity in fetal liver than in the placenta or maternal liver.

Studies in Man

Levin, et al. (52) studied the induction of AHH activity in human skin. Human foreskin obtained from circumcised children was maintained in tissue culture medium. Exposure to 10 μ /M. of benzo(a)pyrene for 16 hours led to a twofold to fivefold increase in the activity of AHH in the exposed skin over control values.

Whitlock, et al. (101) reported the presence of AHH in human lymphocytes. The AHH activity of lymphocytes compared to rat liver or hamster embryo cells is relatively low. Treatment with pokeweed mitogen alone increased AHH activity about twofold. However, a threefold to eightfold greater AHH activity was found in cells treated with the mitogen and benz(a)anthracene than in resting cells.

In studies of tobacco carcinogenesis, cigarette smoke condensate (CSC), subfractions of CSC, and individual chemical compounds found in CSC have been administered to a variety of animals using several routes of administration. Tests on living animals are frequently complicated and time consuming. Cell and tissue culture systems offer an alternate tool for the study of carcinogenesis which, in some instances, is relatively more rapid than animal testing. Specific enzyme systems and other cellular functions can often be studied in greater detail using these systems. Cells obtained from a variety of tissues and animals can be grown or maintained in culture bottles when nourished with an appropriate nutritive medium in a supportive atmosphere. When these cultures are exposed to various chemical compounds, changes can occur which may range from minor morphologic variations to malignant transformation or cell death. Toxic effects on cell cultures must be differentiated from malignant transformation. Several studies have recently examined the effect of cigarette smoke condensate or individual polycyclic hydrocarbons found in CSC on various cell and tissue culture systems.

Benedict, et al. (4) studied polycyclic hydrocarbon produced cytotoxicity, malignant transformation, and chromosome deformity in a variety of cell lines derived from rats, hamsters, and human tumor cells. The cytotoxic effect of benzo(a)pyrene was found to be related to the aryl hydrocarbon hydroxylase activity (AHH) of the given cell culture. Benzo(a)pyrene was cytotoxic to fetal rat hepatocytes, but this effect was probably related to the action of the hydroxylated metabolite, 3-hydroxybenzo(a)pyrene, since the cytotoxicity was blocked when the AHH system was overloaded with phenobarbital. Cell strains not possessing AHH activity showed no cytotoxic effects from benzo(a)pyrene alone; however, in the presence of fetal rat hepatocytes possessing AHH activity, enough benzo(a)pyrene metabolites were secreted into the medium to induce cytotoxic effects in the normally resistant cell lines. In hamster secondary cultures, at the chromosome level cytotoxicity was associated with chromatid breaks, whereas malignant transformation was more closely related to aneuploidy.

Diamond (19) studied the metabolism of benzo(a) pyrene and 7,12-dimethylbenz(a)anthracene (DMBA) in mouse, hamster, rat, monkey, and human cell cultures. Metabolism of hydrocarbons to "alkali soluble" and "water soluble" derivatives was measured. The results suggested that the parent compounds were first metabolized to "alkali extractable" derivatives and then to "water soluble" derivatives. All the cell cultures tested which were sensitive to the growth-inhibitory effects of benzo(a)pyrene or DMBA were able to metabolize these

carcinogenic hydrocarbons to "water soluble" derivatives. The data are consistent with the hypothesis that metabolism of the carcinogen is required for growth-inhibitory or cytotoxic effects.

Several authors have examined malignant transformation in cell cultures. Inui and Takayama (41) cultured hamster lung fibroblasts and then exposed them to crude cigarette "tar" for a period of 3 hours. Between 2 to 48 hours following this exposure, toxic effects of the "tar", including cell necrosis, swelling, vacuolization, and disintegration of cytoplasm were observed. The death of 40 to 70 percent of the cells within 72 hours was followed by the appearance of transformed cells which grew at rapid rates. These transformed cells produced malignant tumors when inoculated in the cheek pouch of hamsters. Control cell lines produced no changes when inoculated in a similar fashion.

In a similar study by Di Paolo, et al. (21), transformation of primary hamster cell cultures was induced by benzo(a)pyrene, 3-methylcholanthrene, or 7,12-dimethylbenz(a)anthracene. Transformed cell lines were established and subsequently inoculated in hamsters producing malignant tumors at various sites. Characteristic chromosomal changes in the transformed cells were also described.

An increase in proliferation and tumor production rate of L-Strain cells produced by treatment with cigarette "tar" was studied by Inui and Takayama (40). L-Strain cell cultures not exposed to "tar" did not produce tumors when inoculated in C3H mice. After an exposure to low concentrations of cigarette "tar" significant changes occurred in the cultures characterized by enlarged cells with vacuolated cytoplasm, giant cell formation, and accelerated growth rates. These transformed cells produced tumors in 70 percent of injected C3H mice.

Nagata (60) treated cell cultures obtained from kidneys of newborn mice with 20-methylcholanthrene in various concentrations. Control cultures could not be maintained for long; however, the treated cells formed two permanent cell lines which had a transformed morphology and altered karyotypes. Epithelial carcinomas were produced after the subcutaneous injection of these transformed cells into unconditioned newborn mice.

Freeman, et al. (29) isolated hamster-specific C-type RNA viruses from tumors induced by cell cultures transformed by chemical carcinogens. Cell cultures were prepared from early passage hamster embryo cells and treated for 7 days with 3-methylcholanthrene or certain fractions of cigarette smoke condensate. Following treatment, morphologically transformed cell lines were isolated and maintained. Subsequent inoculation in newborn hamsters produced malignant tumors at the site of inoculation. New cell lines were established from some of the resulting tumors. No infectious viruses were isolated from cell lines prior to inoculation; however, C-type RNA viruses were iso-

lated from tumors and from cell lines derived from tumors. The authors concluded that the chemical treatment and activation of viruses appeared to be related events.

Sivak and Van Duuren (83) developed a cell culture system that responded with characteristic changes in cell morphology to the application of various fractions of tobacco leaf extracts. Certain dose-response characteristics were demonstrated, suggesting a mechanism whereby various tobacco fractions might be rapidly screened for tumor-promoting activity.

Dietz and Flaxman (20) studied the toxicity of aromatic hydrocarbons on normal human epidermal cells in vitro. Pieces of adult human abdominal skin were maintained in tissue culture medium and exposed to 3-methylcholanthrene and benzo(a)pyrene at a concentration of 1 $\mu\text{g./ml.}$ for a period of 4 days. The cultures were then kept for an additional 3 months following exposure. No malignant transformation occurred; however, giant cells and a more disorderly pattern of growth were observed in the treated cultures weeks earlier than similar changes in control cultures.

Binding of Polycyclic Hydrocarbons to DNA and RNA

There is evidence that some chemical carcinogens including certain of the polycyclic hydrocarbons found in cigarette smoke condensate are active because of the reaction of the carcinogen or a reactive metabolite with cellular macromolecules. Duncan, et al. (23) studied a series of radioactive polycyclic hydrocarbons with respect to their metabolism and tendency to bind with cellular DNA and RNA in monolayer cultures of primary mouse embryo cells. All the tested hydrocarbons were metabolized to "water soluble" metabolites at approximately equal rates. A "binding index" was calculated to determine the binding of various hydrocarbons to cellular DNA and RNA. The group of hydrocarbons with a high "binding index" consisted of potent carcinogens, while another group with much lower values for the "binding index" were with but one exception non-carcinogens.

Carlassare, et al. (12) studied the in vivo binding of benzo(a)pyrene to DNA. Benzo(a)pyrene- ^3H was fed to male and female NCL mice which were sacrificed after 15 hours. The DNA was extracted and purified from the skin, spleen, and liver. The binding of benzo(a)pyrene was greatest in the liver and somewhat less in the spleen and skin. It was calculated that the average molecular weight of DNA was 6 million and that 1 molecule of benzo(a)pyrene was bound to every 46.8 molecules of DNA in the liver, suggesting covalent binding of benzo(a)pyrene to DNA.

Alexandrov and Vendrely (1) found that cigarette smoke condensate, the hexane-extracted fraction of CSC, and benzo(a)pyrene all inhibited RNA synthesis in mouse skin.

N-Nitrosamines in Tobacco Smoke

The largest number of chemical carcinogens which have been identified in cigarette smoke condensate are polycyclic hydrocarbons. N-nitrosamine compounds known for many years to be potent carcinogens have produced malignant tumors in a number of organ systems of a wide variety of animals. These compounds were recently identified in cigarette smoke. Only recently has an association been found between exposure to N-nitrosamines and malignant tumors in humans (55). N-nitrosamines are formed chemically by a reaction of NO and NO₂ or nitrites with secondary amines. The chemical precursors of the N-nitrosamines have been identified in cigarette smoke condensate (CSC) by a number of investigators. These studies were reviewed by Wynder and Hoffmann (102). More recently, Rhoades and Johnson (69) developed a method for the determination of N-nitrosamines in tobacco smoke condensate using gas chromatography. Two N-nitrosamines were found in CSC: one was identified as N-dimethylnitrosamine (DMNA) and the other was believed to be N-methylethylnitrosamine (MENA) (43, 70). The concentration of DMNA per cigarette in nanograms was determined in condensates from experimental cigarettes made from single tobacco varieties rather than a tobacco blend. Each tobacco tested was grown in both a low- and high-nitrogen soil. High-nitrogen soil conditions resulted in a considerable increase in nitrosamines. A popular brand of nonfilter cigarettes was also tested. These results are presented in table 2.

TABLE 2.—*N*-dimethylnitrosamine (DMNA) content of condensates obtained from several tobaccos grown in both "high" and "low" nitrogen soils

Tobacco type	Soil nitrogen	DMNA (nanograms per cigarette)
Robinson	Low nitrogen	0
Catterton	do	5
Burley	do	3
Robinson	High nitrogen	27
Catterton	do	60
Burley	do	140
U.S. nonfilter		8

Source: Johnson, D. E., Rhoades, J. W. (45).

Summary of Recent Cancer Findings

In addition to the summary presented in the introduction of this chapter, based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field:

1. Recent epidemiological and autopsy studies from several countries confirm that cigarette smoking is the major cause of lung cancer.
2. Continued cigarette smoking by patients following successful surgical removal of a cancer of the oral cavity, pharynx, or larynx without tumor recurrence for a period of 3 years is associated with a significant increase ($P < 0.001$) in the risk of developing a second primary cancer of the upper respiratory or digestive tract compared to similar patients who discontinue smoking at the time of their surgery.
3. The intratracheal administration of certain polycyclic hydrocarbons found in cigarette smoke condensate results in the formation of anaplastic and squamous cell cancers of the lung and respiratory tract in hamsters and rats. Many of these tumors are histologically similar to the lung cancers found most frequently in cigarette smokers.
4. The application of cigarette smoke condensate or polycyclic hydrocarbons to various cell cultures often results in transformation to cells with a more rapid and disorderly growth pattern. Transformed cell lines frequently produce benign or malignant tumors when transplanted to experimental animals.
5. N-nitrosamines have been identified in cigarette smoke. These compounds are known to be potent cancer causing chemicals for a variety of animals. They appear to be formed in higher concentrations from tobaccos raised under high-nitrogen soil conditions.

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CHAPTER 4

Pregnancy

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Introduction

Cigarette smoking is a common habit among women of child-bearing age in the United States. In 1970, approximately one-third of American women of child-bearing age were cigarette smokers. The percentage of U.S. women who smoked throughout pregnancy is not definitely known, but is presumably lower, probably in the neighborhood of 20 to 25 percent. With a large fetal population at potential, but preventable, risk, the relationship between cigarette smoking and the outcome of pregnancy has been the focus of considerable and continuing research.

Every investigator who has examined the relationship has confirmed that the infants of women who smoke during pregnancy have a lower average birth weight than the infants of women who do not smoke during pregnancy. Much evidence indicates that cigarette smoking during pregnancy causes this reduction in infant birth weight. Several investigators have demonstrated that the fetal and neonatal mortality rate is significantly higher for the infants of smokers than for the infants of nonsmokers; other investigators have not found higher mortality for smokers' infants. Studies of the association between maternal cigarette smoking and congenital malformations have produced conflicting results.

The following is a review of work previously reported and recent studies which bear on the relationships between cigarette smoking and different outcomes of pregnancy. In addition, the chapter includes a review of the relationship between cigarette smoking and lactation.

Smoking and Birth Weight

Epidemiological Studies

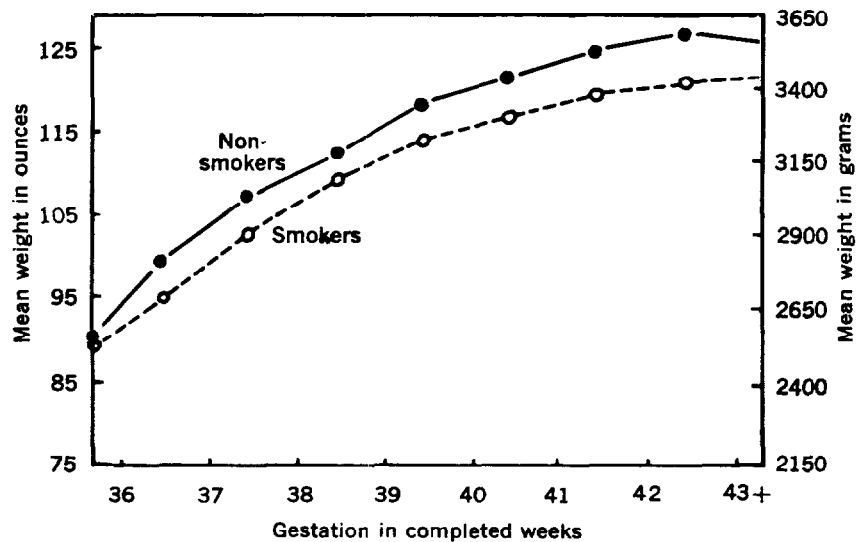
CIGARETTE SMOKING AND THE LOW-BIRTH-WEIGHT INFANT

In 1957, Simpson (90), using a retrospective study design, determined that among 7,499 women in San Bernardino County, Calif., the delivery of infants weighing less than 2,500 grams was nearly twice as

frequent among cigarette smokers as among nonsmokers. Subsequently, Lowe (46) studied 2,042 women in Birmingham, England, and demonstrated in his retrospective study that the infants of smoking mothers were delivered only slightly earlier (1.4 days on the average) than those of nonsmokers. He further noted that for gestations of 260 days and over, the infants of smokers were consistently lighter in weight during each week of gestation than those of the nonsmokers. This finding has been confirmed since, and figure 1 from the British Perinatal Mortality Study (13) provides illustration of this relationship.

Given the nearly constant disparity present between the birth weights of the infants of smokers and nonsmokers for gestations of 260 days and over, but absent prior to that time, and given the similar birth weights of infants of nonsmokers and of women who gave up smoking early in pregnancy and did not begin to smoke again, Lowe inferred that the influence of smoking upon birth weight might lie mainly in the later months of pregnancy. He emphasized the tentative nature of this conclusion, since the number of infants with a gestation of less than 260 days and the number of women who gave up smoking early in the pregnancy and did not begin to smoke again were both small.

Figure 1.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons.¹



¹ This term refers to singleton births in England, Scotland, and Wales occurring during the week of March 3-9, 1958, which are included in the Perinatal Mortality Survey. These comprise 97 percent of all births notified in England and Wales or registered in Scotland during this week.

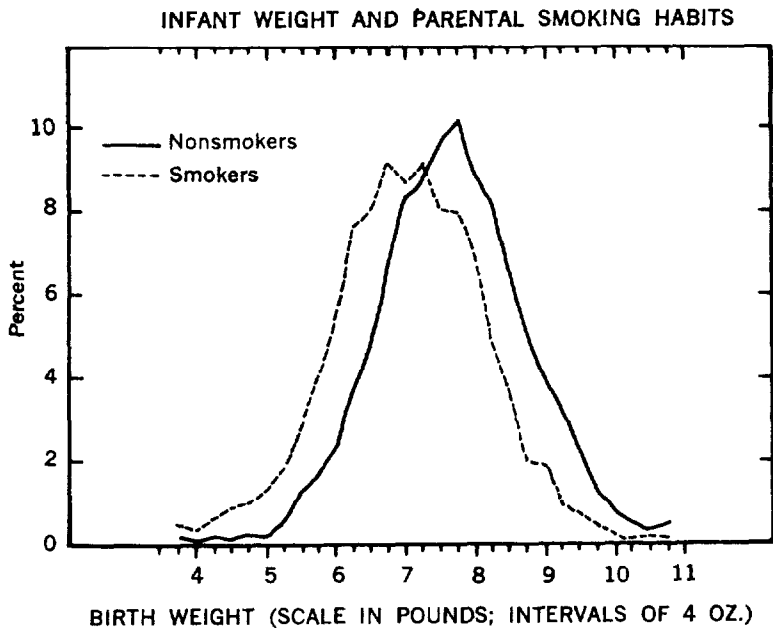
SOURCE: Butler, N. R., Alberman, E. D. (13).

Lowe found that the infants whose mothers smoked throughout pregnancy weighed, on the average, 170 grams less than those whose mothers did not smoke. In addition, he noted that the entire distribution of weights of infants of smokers was shifted to the left (toward lower weights) relative to that for the infants of nonsmokers. This finding, too, has been confirmed by other investigators. Figure 2 offers an illustration from MacMahon, et al. (49).

Given that the infants of smokers and nonsmokers differed only slightly with respect to the duration of gestation, Lowe concluded that the lower birth weight of smokers' infants must be attributed to a direct retardation of fetal growth. In other words, on the basis of his data, the infants of smokers were small-for-dates rather than truly premature.

Many investigators have subsequently confirmed this point (12, 14, 25, 35, 65, 78, 85, 113). Buncher (12), in a study of 49,897 births among U.S. naval wives, in the same population studied by Underwood, et al. (100), found that the infants of smokers were, on the average, delivered only 1 day earlier than those of nonsmokers. This finding accounted for only 10 percent of the discrepancy in birth weight between the two groups of infants. The remainder of the studies resulted in the detection of either similar variations in gestational length or no average difference. In a recent study, Mulcahy and Murphy (56),

Figure 2.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked 1 pack of cigarettes or more per day.



SOURCE: MacMahon, et al. (49).

in a sample of 5,099 Irish mothers, concluded that although the babies born to cigarette smokers were delivered slightly earlier than those of nonsmokers, independent of age and parity, the direct effect of smoking in retarding fetal growth was more significant.

The following points, based upon the results from many different studies, can be made about the relationship between cigarette smoking during pregnancy and lower infant birth weight :

1. Women who smoke cigarettes during pregnancy have a higher proportion of low-birth-weight infants than do nonsmokers. This excess of low-birth-weight infants among cigarette smokers predominantly consists of infants who are small-for-gestational age rather than gestationally premature.
2. The entire distribution of birth weights of the infants of cigarette smokers is shifted toward lower weights compared to the birth weights of the infants of nonsmokers.
3. The birth weights of the infants of cigarette smokers are consistently lighter than those of the infants of nonsmokers when the birth weights of the two sets of infants are compared within groups of similar gestational age beyond the 36th week of gestation.

The results of the studies which have been considered so far identify a relationship between cigarette smoking and lower infant birth weight and illustrate some aspects of that relationship, but do not indicate whether the association is causal or indirect. The succeeding two sections of this chapter contain evaluations of the available evidence which bears upon the nature of the association between cigarette smoking during pregnancy and the incidence of small-for-dates infants.

EVIDENCE FOR A CAUSAL ASSOCIATION BETWEEN CIGARETTE SMOKING AND SMALL-FOR-DATES INFANTS

Evidence previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) suggests that cigarette smoking is causally associated with the delivery of small-for-dates infants. The following is a summary of this evidence :

1. The results from all 30 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between maternal cigarette smoking and delivery of low-birth-weight infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker

(3, 13, 17, 20, 25, 29, 35, 42, 43, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 78, 80, 83, 85, 90, 95, 99, 100, 113, 118).

2. The strong association between cigarette smoking and the delivery of small-for-dates infants first demonstrated with results from studies of retrospective design (3, 13, 17, 35, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 80, 85, 90, 95, 99, 100, 118) has been repeatedly confirmed subsequently by data from studies of prospective design (20, 25, 29, 42, 43, 78, 83, 113).

3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants (25, 43, 46, 49, 100, 113).

4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has always been shown to be independently related to low birth weight (1, 13, 25, 43, 46, 73, 78, 83).

5. The association has been demonstrated in many different countries, among different races and cultures, and in different geographical settings (13, 17, 25, 29, 36, 42, 43, 59, 73, 78, 80, 113).

6. Previous smoking does not appear to influence birth weight if the mother gives up the habit prior to the start of her pregnancy (25, 46, 49, 113).

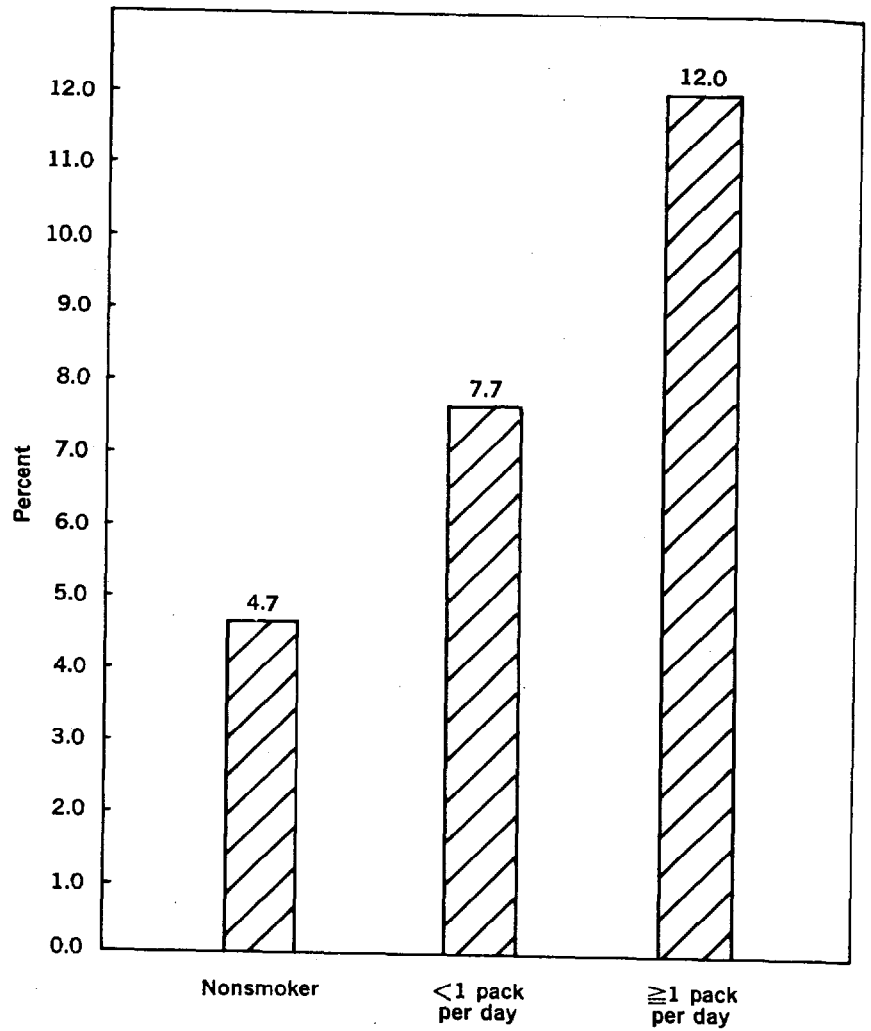
7. The infants of smokers experience an accelerated growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence (83).

8. Data from experiments in animals have documented that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight offspring (7, 8, 9, 23, 40, 87, 117).

Several recently published studies have provided additional supporting evidence for a causal relationship between cigarette smoking and small-for-dates infants. The Ontario Perinatal Mortality Study (66) was conducted among 10 teaching hospitals during 1960 and 1961. The authors of this retrospective study of 50,267 births demonstrated a significant excess of infants weighing less than 2,500 grams among cigarette smokers as compared with nonsmokers ($P < 0.001$). Smoking was significantly dose-related to the percentage of pregnancies terminating in the delivery of a low-birth-weight infant (fig. 3).

Niswander and Gordon (63) have recently reported data from the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. In this prospective study of 39,200 pregnancies, which were nearly equally divided among black and white women, the authors found a significant dose-related excess of low-birth-weight infants among smokers of both groups, compared to nonsmokers of the same race.

Figure 3.—Percentage of pregnancies with infant weighing less than 2,500 grams, by cigarette smoking category.



	Nonsmoker	<1 pack per day	≥1 pack per day
Number of infants weighing <2,500 grams:	1,322	1,186	793
Total births:	28,358	15,328	6,581
		(P < 0.001)	

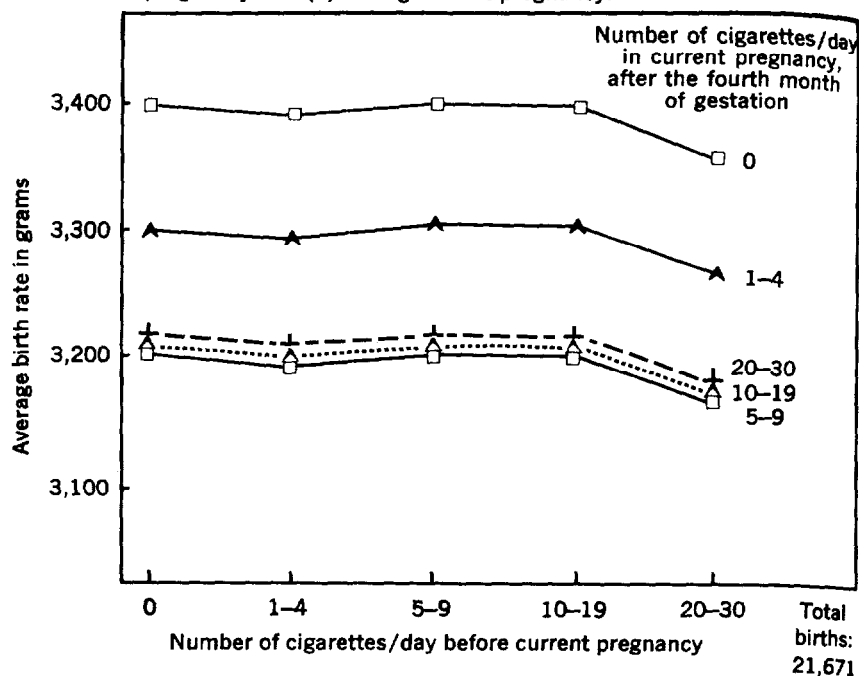
SOURCE: Ontario Department of Health (66).

Rantakallio (76) carried out a prospective study of 11,905 single births in Finland. Cigarette smoking mothers had significantly more infants weighing less than 2,500 grams than did nonsmokers ($P < 0.001$).

Rush and Kass (82), in a prospective study of 1,040 pregnancies in Boston, Massachusetts; Domagala, et al. (19), in a retrospective study of 1,832 pregnancies in Poland; and Mukherjee and Mukherjee (54), in a retrospective study of 2,886 pregnancies in India, each found a significantly higher incidence of low-birth-weight infants among cigarette smokers.

Butler, et al. (15) have further analyzed the British Perinatal Mortality Study data. Analysis of the 16,994 questionnaires revealed that 40.8 percent of the women were cigarette smokers before pregnancy. After the fourth month, this percentage had decreased to 27.4 percent. Given the large number of women in the study, and the significant changes in smoking behavior which occurred, Butler, et al. found it possible to consider the effect of a change in smoking behavior on birth weight between the beginning of the pregnancy and the fourth month (after which smoking behavior was reportedly stable). The authors stated, "If smoking itself (rather than the type of woman who smokes) has a deleterious effect on the fetus, it would be reasonable to expect the mothers who gave up smoking during pregnancy to show differences in the birth weight and perinatal mortality of their offspring compared with those who continued to smoke." Their results are presented in figure 4. The birth weights by smoking categories were estimated by using a main effect model without mediating variables. However, the authors reported that when the mediating variables (social class, maternal age, parity, maternal height, sex of infant, gestational age, and perinatal mortality) were allowed for, the results of the analysis were very similar. The effect of cigarette smoking before pregnancy was insignificant compared to that of smoking regularly after the fourth month of gestation. The authors concluded, "The finding that a change in maternal smoking habits during pregnancy had the effect of putting the baby into a birth weight and perinatal mortality category associated with the new smoking habits points toward some kind of cause-effect relationship. * * * This finding is further strengthened by the birth weight analysis which shows that the diminution in birth weight of the offspring of smoking mothers persists and is indeed little changed when allowance has been made for a number of other social and obstetric mediating factors."

Figure 4.—Average birth weight by maternal smoking habit (a) before current pregnancy and (b) during current pregnancy.



SOURCE: Adapted from Butler, et al. (15).

EVIDENCE FOR AN INDIRECT ASSOCIATION BETWEEN CIGARETTE SMOKING AND SMALL-FOR-DATES INFANTS

Yerushalmy (113, 114, 115) has suggested that smoking is an index to a particular type of reproductive outcome and thus does not play a causal role in the production of small-for-dates infants. He has developed several lines of support for this hypothesis, from an analysis of data from the prospective investigation of 13,083 mothers in the Oakland Child Health and Development Study. He has emphasized that ineffective randomization and the phenomenon of self-selection complicate the development of appropriate inferences with regard to causality. Such difficulties do not prevent the identification of causal associations, but they demand careful and critical analysis of the data. Yerushalmy has questioned the causal nature of the relationship between cigarette smoking and small-for-dates infants because of: (a) The relationship between the smoking habit of the father and low birth weight of the infant, (b) behavioral differences between smokers and nonsmokers, and (c) comparison of the birth weights

of a woman's infants born during the periods when she smoked cigarettes and when she did not.

Yerushalmy (114) has stated that the smoking habit of the father could not reasonably be related to the birth weight of the infant. From preliminary data derived from the study, however, he determined that there was an increased incidence of low-birth-weight infants when the fathers smoked and, moreover, there was an apparent dose-response relationship as found for maternal smoking. However, he noted that only when both the husband and the wife smoked was the incidence of low-birth-weight babies increased. He felt that these findings supported the conclusion that smoking was a marker of types of individuals and not a causal factor for low birth weight. Other investigators have since examined this relationship (49, 100), but none has confirmed an independent association for paternal smoking. The association between paternal smoking and birth weight appears to be an indirect one. Paternal and maternal smoking behavior are highly correlated and maternal smoking is strongly related to infant birth weight. Underwood, et al. (100) studied 48,505 women, their husbands' smoking behavior, and the relation with birth weight (table 1). If the mother was a nonsmoker, then the father's smoking had no influence on the birth weight of the infant.

TABLE 1.—*Infant birth weight by maternal and paternal smoking habits*

Cigarettes per day	Mothers			Fathers (nonsmoking mothers)		
	Number	Birthweight (grams)		Number	Birthweight (grams)	
		Mean	Difference ¹		Mean	Difference ¹
None.....	24, 865	3, 395	0	9, 547	3, 396	0
1 to 10.....	7, 609	3, 286	109	3, 493	3, 389	7
11 to 30.....	14, 450	3, 196	199	10, 403	3, 391	5
>30.....	1, 570	3, 182	213	1, 330	3, 393	3

¹ Nonsmoker minus smoker.

Source: Underwood, et al. (100).

Yerushalmy (115) pointed out that other investigators had found marked differences between smokers and nonsmokers. In his own study, he found that nonsmokers used contraceptives significantly more frequently than did smokers. Moreover, a significantly higher proportion of smokers drank coffee, beer, and whiskey. However, he did not adjust for these variables in his analysis of the association between cigarette smoking and lower infant birth weight. Other investigators have also found differences between smokers and nonsmokers. For example, Frazier, et al. (25) found significant differences in the distribution of parity, work history, education, and psycho-

somatic complaint score between smokers and nonsmokers. However, when smokers were compared with nonsmokers of the same parity, education, work history, and psychosomatic complaint score, cigarette smokers still had a significantly higher proportion of small infants than did nonsmokers. As previously mentioned, whenever other factors known or suspected to influence birth weight have been controlled, cigarette smoking has always been demonstrated to have an independent and significant effect.

Ounsted (69) offered evidence that the best predictor of the birth weight of a mother's future offspring was the birth weight of her previous children. Herriott, et al. (35) found prematurity rates for previous pregnancies among smokers to be markedly higher than among nonsmokers, independent of parity, height, and social class. Evidently a woman whose previous infants have been small tends to continue to have relatively smaller than average infants in subsequent pregnancies. The question is, will those infants be even smaller than expected if she smokes?

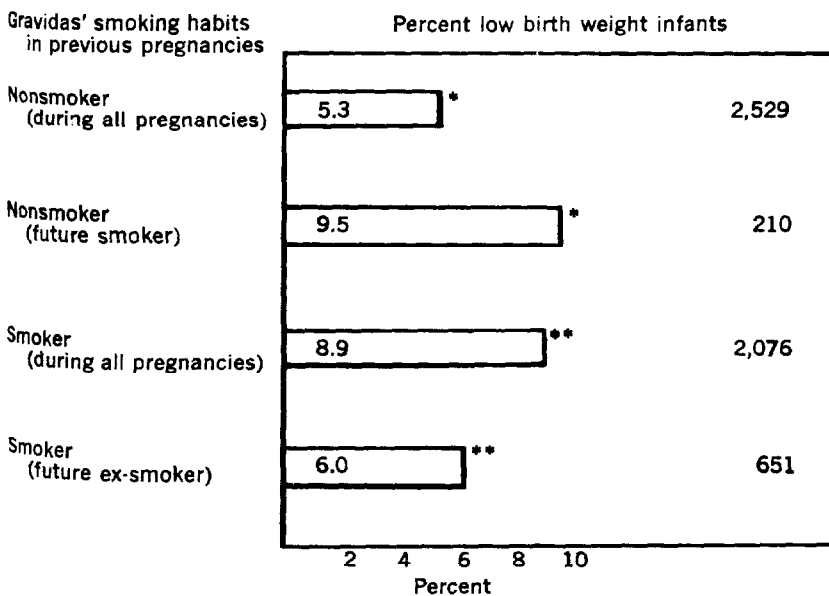
Goldstein, et al. (28), in a comprehensive review, proposed a research design in which a woman would serve as her own control to compare outcomes of pregnancies during which she smoked with those during which she did not with consideration of the effect of parity on the outcome. Yerushalmy (112) has recently tested this type of research design, using data from his Oakland Growth Study. With information on the age at which a woman began to smoke cigarettes, her smoking status during the pregnancy actually studied, her prior reproductive experience, and the outcome of her present pregnancy, the author compared the outcomes of pregnancy during periods of smoking and nonsmoking using the woman as her own control. As the author noted, "If smoking *causes* the increase in low-birth-weight infants, then the incidence of low birth weight for infants born to smoking mothers during the period before they acquired the smoking habit, should be relatively low. If, on the other hand, the high incidence of low birth weight is due to the *smoker*, then it should be high for infants of future smokers also when they were born before their mothers started to smoke."

Yerushalmy then proceeded to compare the reproductive experiences of four groups of women: (a) Those who smoked in none of their pregnancies, (b) those who smoked in all of their pregnancies, (c) those who were smoking now but previously had not smoked during some pregnancies (future smokers), and (d) those who were ex-smokers now but had previously smoked during some pregnancies. These outcomes are shown in figure 5. The incidence of low-birth-weight infants in the pregnancies of the future smokers, before they started to smoke, was similar to that for women who smoked in every pregnancy, which was significantly higher than that of infants from

mothers who had never smoked. He also noted that ex-smokers, during the period before they quit, gave birth to relatively few low-birth-weight infants; the incidence was significantly lower than for mothers who smoked during all of their pregnancies. He concluded that the findings cannot be easily reconciled with a cause-effect basis for smoking and birth weight. He said, "Rather the evidence appears to support the hypothesis that the higher incidence of low-birth-weight infants is due to the *smoker*, not the *smoking*."

There are several considerations which limit the interpretations which can be drawn from this study. The information on smoking behavior of the women during past pregnancies was apparently derived from the woman's age when she began to smoke, her smoking behavior early in the study pregnancy, and the age at which she had her prior pregnancies. Thus, if the woman reported that she began smoking at a certain age, and that she was still smoking at the time of the study, it was apparently inferred that she had smoked during all of her pregnancies. Since no questions were specifically asked about actual smoking behavior during each previous pregnancy, it is possible that the woman indeed had not smoked during every pregnancy or that the amount or way she smoked had differed from current smoking

Figure 5.—Percent of low birth weight white infants by smoking status of their mothers.



*Difference is statistically significant ($P < 0.01$).

**Difference is statistically significant ($P < 0.02$).

SOURCE: Adapted from Yerushalmy, J. (112).

habits. This would be important to know given the strong dose-response relationship which has been established between cigarette smoking and low birth weight, and would tend to make the reproductive outcomes for ex-smokers similar to those of nonsmokers, and different from those of women who smoked in all pregnancies.

For ex-smokers, the age at which smoking began was not elicited. Hence, some of the infants of ex-smokers may have been born before their mothers acquired the smoking habit. This would also tend to make the reproductive experiences of ex-smokers more like those of nonsmokers and different from those of women who smoked in all pregnancies.

No direct adjustment for age, parity, and other variables was reported, although Yerushalmy stated that the study population was limited to the births that occurred to women at age 25 years or less. He noted that, "In order to adjust for parity, the same comparisons were performed for firstborn infants only. The numbers were reduced considerably, but the same tendencies as found above were noted." However, no data were presented. Primiparous births and births in teenagers are strongly associated with the delivery of low-birth-weight infants. If the pregnancies which occurred among future smokers included a predominance of very young women and primiparous births, the reproductive experiences of future smokers would tend to be similar to those of women who smoked during all pregnancies, and different from those of nonsmokers. In the absence of more precise information on actual smoking behavior during pregnancy and more rigorous adjustment for maternal age, this study does not provide a critical test of the hypothesis that it is the smoking during pregnancy which is responsible for the high proportion of small-for-dates infants born to women who smoke.

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 (23, 87, 117). Younoszai, et al. (117) 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. The authors suggested that carbon monoxide might also not be responsible for the retardation of

fetal growth; however, the evidence presented was inadequate to support a firm conclusion.

Haworth and Ford (33) recently extended the experiments of Younoszai. A group of pregnant rats was exposed to cigarette 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, and suggests that the exposure to tobacco smoke either inhibited cellular proliferation or accelerated cellular destruction.

Nicotine

Several workers have demonstrated that chronic injections of large doses of nicotine into pregnant rats resulted in a reduction of birth weight of the offspring (7, 8, 9, 23, 40). Other investigators have determined that tritium-labelled nicotine injected into pregnant rabbits and C¹⁴-labelled nicotine injected into pregnant mice crossed the placenta to the developing embryo and fetus (89, 98). Kirschbaum, et al. (41) found no significant acute effects of small doses of nicotine, injected intravenously into near-term sheep, on blood gas composition, pH, blood pressure, or heart rate in either the ewes or their fetuses. The authors concluded that the influence of maternal smoking upon the fetus must result from chronic effects or through the effects of other variables which they did not study.

Recently, Suzuki, et al. (94) evaluated the short-term effects of injected nicotine on the cardiovascular performance, acid-base status, and oxygenation of pregnant female Rhesus monkeys and their infants during the second half of gestation using the mothers as their own controls. Nicotine was administered either as a single intravenous dose of 0.5 to 1.0 mg. or as a continuous infusion of 100 μ g./kg. over

a 20-minute period. The injection of nicotine in the larger, single dose into the mother produced a rise in maternal blood pressure and a fall in maternal heart rate, and an immediate fall in both fetal blood pressure and fetal heart rate followed by persistent hypotension and tachycardia in the fetus. Subsequent to the injection of 1.0 mg./kg. of nicotine into pregnant monkeys, in a single dose, significant changes in the arterial blood of the older fetuses included a fall in pH, a rise in base deficit, and a fall in oxygen tension. Carbon dioxide tension remained unchanged. Nicotine injected directly into the fetus prompted an immediate rise in fetal blood pressure and a fall in fetal heart rate. These responses were similar to those previously seen in the mothers following a direct injection of nicotine. The changes were more prominent in older rather than in younger fetuses. The authors summarized their findings by stating that: (a) fetuses in different gestational stages are differentially responsive to a given dose of nicotine, probably because of the different stages of development of the autonomic nervous system; (b) diminished intervillous space perfusion resulting from vasoconstriction in the uterine circulation appears to be mainly responsible for the fetal asphyxia following the injection into the mother, because fetal hypotension and bradycardia were not preceded by the transient hypertension seen following the direct administration of nicotine to the fetus; (c) the differences between the results obtained by Kirschbaum and by Suzuki, et al. may reflect either the considerable dosage differences or species differences; and (d) the doses which the authors employed were much larger than those which a human mother would absorb from usual cigarette smoking, but that differences in tolerance to nicotine between the Rhesus monkey and humans would imply that the dosages were, in fact, comparable and that, "Hence, it can be envisaged that the concentration of nicotine which could be reached in the organism of a smoking mother would reduce oxygen availability to the fetus."

Carbon Monoxide

Longo (45) has reviewed the work of several investigators which has demonstrated the transplacental passage of carbon monoxide from mother to fetus in animals. A recent study which related CO to birth weight was published by Astrup (?). He found that continuous exposure throughout gestation of pregnant rabbits to different levels of ambient carbon monoxide resulted in a statistically significant dose-related reduction in birth weight (table 2). The actual significance level was not reported.

TABLE 2.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits.....	17	14	17
Total number of babies.....	116	81	123
Average weight of babies in grams.....	53.7	51.0	44.7

SOURCE: Astrup, P. (2).

Polycyclic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene (BAP) are constituents of cigarette smoke which have been implicated in the generation of cancers in many animal species (111). 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. (108) 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-labelled 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.

Schlede and Merker (86) 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 24 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 on 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.

STUDIES IN HUMANS

Carbon Monoxide

Smokers and their newborn infants have significantly elevated levels of carbon monoxide as compared with nonsmokers and their infants (31, 34, 88, 116). Recently, Baribaud, et al. (5) studied 50 nonsmokers and 27 cigarette smokers and their newborns. All smokers inhaled. The authors found that the mean level of CO content in the blood of nonsmokers was 0.211 volumes percent compared with 0.672 volumes percent in the blood of smokers. The values for blood samples from the umbilical cords of their newborns were 0.352 and 0.949 volumes percent, respectively. Moreover, a definite dose relationship was found between CO levels and number of cigarettes smoked.

Younoszai, et al. (116) found, in addition to elevated carboxyhemoglobin levels among the infants of smoking mothers, significant elevation of mean capillary hemotocrits and significant reduction of standard bicarbonate levels, as compared to the infants of nonsmoking mothers. Since no evidence for nicotine effects upon blood glucose, serum FFA levels, or urinary catecholamines, or for 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.

Longo (45) pointed out that a level of 9 percent carboxyhemoglobin in the fetus is the equivalent of a 41 percent decrease in fetal blood flow or fetal hemoglobin concentration. In reviewing the studies of CO levels in human mothers and their newborns, he made the follow-

ing comments: "These samples were obtained at the time of vaginal delivery or Cesarean section and may not accurately reflect the normal values of $(\text{COHb})_F$ for several reasons. The number of cigarettes smoked by the mothers during labor may be less than their normal consumption and was not specified in these studies. The blood samples were collected at varying time periods following the cessation of smoking. In addition, many of the samples were probably taken early in the day before COHb levels had built up to the levels reached after prolonged periods of smoking. Thus actual levels of $(\text{COHb})_M$ and $(\text{COHb})_F$ may be higher than the reported values."

Polycyclic Hydrocarbons

The results of several studies concur that cigarette smoking is strongly associated with the induction of aryl hydrocarbon hydroxylase in the human placenta (18, 38, 61, 99, 109). This finding implies that benzo(a)pyrene or other polycyclic hydrocarbons reach the placenta. To date, evidence to support the passage of polycyclic hydrocarbons through the placenta to the human fetus has not been published.

Vitamin B₁₂ and Cyanide Detoxification

McGarry and Andrews (48) determined serum vitamin B₁₂ 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 B₁₂. They also found a direct, statistically significant dose-response relationship between cigarettes smoked and serum vitamin B₁₂ level. They again confirmed the relationship between smoking and low birth weight. The authors suggested that the lowered vitamin B₁₂ levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (39, 60, 62, 64, 68, 74, 91).

Vitamin C

Venulet (105, 106, 107) has 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.

Possible Mechanisms

The following mechanisms have been proposed for the production of low birth weight and other unfavorable outcomes of pregnancy following exposure to cigarette smoke:

1. A direct toxic influence of constituents of cigarette smoke upon the fetus (2, 45, 50, 51, 117).
2. Decreased placental perfusion (94).
3. Decreased maternal appetite and diminished maternal weight gain with secondary effects upon the fetus (6, 33, 36, 65, 75, 99, 117).
4. A direct effect upon the placenta (36, 57, 65, 110).
5. An oxytocic effect on uterine activity (44).
6. A disturbance of vitamin B₁₂ metabolism (48).
7. A disturbance of vitamin C metabolism (105, 106, 107).

Of the potential mechanisms, available evidence suggests that neither decreased maternal appetite and decreased maternal weight gain nor a direct effect upon the placenta are responsible for a significant reduction in birth weight. Existing evidence does not permit firm conclusions concerning the relative significance of the remaining mechanisms.

Timing of the Influence of Cigarette Smoking on Birth Weight

Several investigators have published results which bear on the time period during which exposure to cigarette smoke most affects fetal growth. Lowe (46) and Zabriskie (118) have offered evidence which suggests that cigarette smoking influences fetal growth most during the second half of pregnancy. Butler, et al. (15) found that the birth weights of infants of women who did not smoke after the fourth month of pregnancy were essentially the same as those of the infants of nonsmokers. This implies that the influence is most probably exerted after the fourth month of pregnancy. Herriott, et al. (35), however, found that women in lower socioeconomic classes who gave up smoking early in pregnancy tended to have intermediate weight babies as compared with nonsmokers and persistent smokers, but his numbers of women were small and the results were not statistically significant. Underwood, et al. (100) found that cigarette smoking in any single trimester was associated with a lower birth weight of the infant, although the difference between the birth weights of infants of women who smoked only during a single trimester and infants of nonsmokers was not statistically significant because of small numbers. Several investigators have detected a nearly constant difference between the birth weights of the infants of smokers and nonsmokers, delivered during the last month of pregnancy, following gestations of comparable length [fig. 1, (11)]. Although this observation is

compatible with the suggestion that the influence of cigarette smoking upon the fetus occurs prior to the last month of pregnancy, it is based upon data derived from cross-sectional rather than longitudinal studies. The results of many human epidemiological studies suggest that maternal smoking prior to pregnancy does not influence fetal weight gain (15, 25, 46, 49, 113).

Site of Action at the Tissue and Cellular Level

The use of labelled nicotine (98) and the preparations of autoradiograms have permitted the localization of nicotine within the tissues of the fetus and mother. Tjalve, et al. (98) found high levels of nicotine in the respiratory tract, adrenal, kidney, and intestine of 16- to 18-day mice fetuses. The use of other labelled constituents during various parts of gestation might further the understanding of how certain ingredients in cigarette smoke produce an impact upon birth weight. Haworth and Ford (33) have reported data which suggest that the reduction of birth weight of rat fetuses caused by the action of the ingredient(s) of tobacco smoke results from a reduction in cell number, but not in cell size.

Significance of the Association

Among all women in the United States, cigarette smokers are nearly twice as likely to deliver low-birth-weight infants as are non-smokers. Assuming that 20 percent of pregnant women in the United States smoked cigarettes through the entire pregnancy (extrapolated from data on changes in smoking behavior during pregnancy collected for the British Perinatal Mortality Study), taking into account the apparently different risks of delivering a small-for-dates infant for Caucasian and non-Caucasian women who smoke during pregnancy, and considering the number of infants with a birth weight less than 2,500 grams born to Caucasian and non-Caucasian women, an excess of nearly 43,000 occurred in the 286,000 low-birth-weight infants among the 3,500,000 infants born in the United States in 1968, because of the increased risk among women who smoke of having small-for-dates infants.

Since neonatal mortality is higher for low-birth-weight infants, with gestational age held constant, the excess of small-for-dates infants among smoking mothers would imply a significant excess mortality risk as well.

Birth Weight Summary

A causal association between cigarette smoking and fetal growth retardation is supported by the following evidence:

1. The results of all 42 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between cigarette smoking and delivery of small-for-dates infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker.
2. This association has been confirmed by both retrospective and prospective study designs.
3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants. Available evidence suggests that the effect of smoking upon fetal growth reflects the number of cigarettes smoked daily during a pregnancy, and not the cumulative effect of cigarette smoking which occurred before the pregnancy began.
4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has consistently been shown to be independently related to low birth weight.
5. The association has been found in many different countries, among different populations, and in a variety of geographical settings.
6. New evidence suggests that if a woman gives up smoking by the fourth month of pregnancy, her risk of delivering a low-birth-weight infant is similar to that of a nonsmoker.
7. The infants of smokers experience a transient acceleration of growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence.
8. The results of experiments in animals have shown that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight offspring. New evidence demonstrates that chronic exposure of rabbits to carbon monoxide during gestation results in a dose-related reduction in the birth weight of their offspring.
9. Data from studies in humans have demonstrated that smokers' fetuses are exposed directly to agents within tobacco smoke, such as carbon monoxide, at levels comparable to those which have been shown to produce low-birth-weight offspring in animals.

Cigarette Smoking and Fetal and Infant Mortality

Introduction

Several previous studies of the relationship between cigarette smoking and higher fetal and infant mortality among the infants of smokers have been reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102). In many of these studies, the authors combined two or more categories of fetal and infant mortality. Different mortality outcomes, such as spontaneous abortion, stillbirth, and neonatal death, are influenced by different sets of factors. Among other factors, the frequency of abortion is influenced by congenital infections, hormonal deficiencies, and cervical incompetency. In addition to other factors, the frequency of stillbirth is influenced by premature separation of the placenta, uterine inertia, and dystocia. Along with other factors, the frequency of neonatal death is influenced by gestational maturity, birth injuries, and delivery room and nursery care. Separate analysis of the relationship of cigarette smoking to each different mortality outcome, with control of the unique set of factors which influences it, may facilitate understanding of the relationship.

Spontaneous Abortion

Previous epidemiological and experimental studies of the relationship between spontaneous abortion and cigarette smoking reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) form the basis of the following statements:

The results of several studies, both retrospective and prospective, have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (43, 65, 70, 99, 118). Data from some of these studies have documented a strong dose-response relationship between the number of cigarettes smoked and the incidence of spontaneous abortions (70, 99, 118). In general, variables other than cigarette smoking (e.g., maternal age, parity, health, desire for the pregnancy, and use of medication), which may influence the incidence of spontaneous abortions, have not been controlled. The results of the one study, in which adjustment for the woman's desire for the pregnancy was performed, indicated that after such adjustment cigarette smoking during the pregnancy retained an association with spontaneous abortion of borderline significance (43). The time period during which cigarette smoking might exert an influence on the incidence of spontaneous abortions has not been determined. Abor-

tions have been produced in animals only with large doses of nicotine (23, 96, 104); the relevance of these studies for humans is uncertain.

SPONTANEOUS ABORTION SUMMARY

Although several investigators have found a significantly higher, dose-related incidence of spontaneous abortion among cigarette smokers as compared to nonsmokers, the lack of control of significant variables other than cigarette smoking does not permit a firm conclusion to be drawn about the nature of the relationship.

Stillbirth

Epidemiological studies of the association between cigarette smoking and stillbirth previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) form the basis for the following statements:

In one group of retrospective and prospective studies, a higher stillbirth rate was found for the infants of smokers as compared to those of nonsmokers (14, 25, 43). In another group of retrospective and prospective studies, no significant difference was detected in the stillbirth rate among the infants of smokers and nonsmokers (16, 20, 85, 99, 100). Differences in study size, numbers of cigarettes smoked, or the presence or absence of control of variables, such as age and parity, which may influence stillbirth rates, were probably not sufficient to explain the differences in results obtained.

Several recent epidemiological studies have added to our understanding of the relationship between cigarette smoking and stillbirth. Niswander and Gordon (63) have reported data from 39,215 pregnancies followed prospectively and collected between 1959 and 1966 at 12 university hospitals in the United States. A random sample of women who presented to hospital prenatal clinics were enrolled in the study. The authors reported no increase in stillbirths among white smokers as compared with white nonsmokers. A higher incidence of stillbirths was found among black women who smoked than among nonsmoking black women, and a dose-response relationship with cigarettes smoked was suggested, although the findings did not attain statistical significance. The results were not adjusted for other variables. Rush and Kass (82) found, in a prospective study of 3,296 pregnancies at Boston City Hospital, a nonsignificant increase in

stillbirths among white women who smoked, but a statistically significant increase in stillbirths among black women who smoked ($P < 0.02$). These findings are consistent with those previously outlined by Frazier, et al. (25) and Underwood, et al. (99).

Rumeau-Roquette (81), in a prospective study of 4,824 pregnancies in Paris, demonstrated that the risk of stillbirth was significantly higher for cigarette smokers than for nonsmokers ($P < 0.001$). The authors also presented evidence that a woman with either a previous stillbirth or at least one prior infant weighing less than 2,500 grams at birth was significantly more likely to have a future stillborn infant than a woman without such an obstetrical history. After previous obstetrical history was controlled, smokers still retained a statistically significant increased risk of subsequent stillbirth as compared to nonsmokers ($P < 0.01$). Of further interest was the finding that among women who previously had delivered only living infants, weighing over 2,500 grams, cigarette smoking had no influence on the stillbirth rate.

Previous experimental studies were reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102). The authors demonstrated that exposure of pregnant rabbits to tobacco smoke and pregnant rats to large doses of injected nicotine resulted in a significant increase in stillbirths (7, 8, 23, 87).

STILLBIRTH SUMMARY

1. The results of recent studies suggest that cigarette smoking is most strongly associated with a higher stillbirth rate among women who possess less favorable socioeconomic surroundings or an unfavorable previous obstetrical history. In the United States, black women have higher stillbirth rates than white women. The finding that cigarette smoking is associated with an even greater difference between the stillbirth rates of the two groups merits special attention. These findings may provide at least a partial explanation for the lack of a significant difference in stillbirth rates between smokers and nonsmokers, which some investigators have found.
2. The results of experiments in animals demonstrate that exposure to tobacco smoke and some of its ingredients, such as nicotine, can result in a significant increase in stillbirth rate.

Late Fetal and Neonatal Deaths

Considerable variation has occurred in the definition of the study population among the studies in which the relationship of cigarette smoking to fetal mortality (other than abortion) and early infant mortality was examined. The most commonly identified study populations have been perinatal deaths, neonatal deaths, and late fetal plus neonatal deaths. Perinatal deaths are a combination of late fetal deaths (i.e., stillborn infants) and deaths occurring within the first week of life. Neonatal deaths include all deaths of liveborn infants within the first 28 days of life.

EPIDEMIOLOGICAL STUDIES

Most of the earlier epidemiological studies of the association between cigarette smoking and late fetal plus neonatal mortality were reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102). A review of previously unreported studies (67, 76), as well as reexamination of previously cited studies, forms the basis of the following statements:

The results of several prospective and retrospective studies indicate a statistically significant higher late fetal and/or neonatal mortality for the infants of smokers compared to those of nonsmokers (14, 17, 25, 43). The results of other prospective and retrospective studies identified no significant difference in the mortality rates between the infants of smokers and nonsmokers (20, 65, 72, 85, 100, 115).

If mortality rates were compared for those infants of smokers and nonsmokers weighing less than 2,500 grams, the infants of nonsmokers apparently had a considerably higher risk than did those of smokers.

The results of recent studies, coupled with a critical review of the design and analysis of previous studies, and a reexamination of existing data, may provide at least a partial explanation of discrepancies between the results of previous studies.

Comparisons of the Mortality Risks of Low-Birth-Weight Infants Born to Smokers and Nonsmokers

The perinatal mortality risk for infants weighing less than 2,500 grams appears to be lower for those infants born to women who smoke during pregnancy than for those born to nonsmokers (table

3). However, available evidence shows that cigarette smokers' infants tend to be small-for-gestational age rather than gestationally premature. Hence, within a given birth weight group, the infants of smokers are, on the average, gestationally more mature than those of nonsmokers. Data collected by the National Center for Health Statistics (103) demonstrate that within a given birth weight group, the more gestationally mature an infant, the lower is its mortality risk (fig. 6). Thus, the difference in perinatal mortality risks experienced by the infants of cigarette smokers and nonsmokers, within comparable birth weight classes, reflects the facts that the two sets of infants are not of the same average gestational age, and that gestational age is a major factor influencing late fetal and neonatal mortality. An accurate estimate of comparative mortality risks for the infants of cigarette smokers and nonsmokers requires adjustment for gestational age.

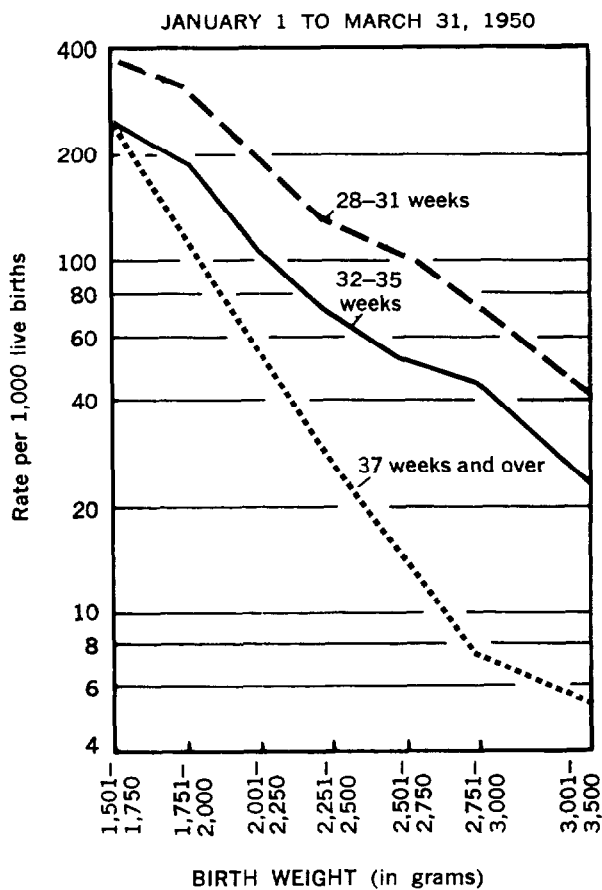
For infants of comparable gestational age, lower birth weight is associated with higher mortality (fig. 6). Since infants of cigarette smokers have, on the average, lower birth weights than the infants of nonsmokers, within groups of comparable gestational age, cigarette smokers' infants should experience higher mortality rates than nonsmokers' infants of similar gestational ages. In a recent review, Meyer and Comstock (51) provided a more extensive discussion of these points.

TABLE 3.—*Comparison of the perinatal mortality for infants weighing less than 2,500 grams, of smokers and nonsmokers*

Author, reference	Perinatal mortality rate (deaths per 1,000 live births)	
	Smokers	Nonsmokers
Underwood, et al. (100).....	187	269
Ontario Department of Health (67).....	232	300
Kullander and Källen (43).....	129	139
Rantakallio (76).....	288	344
Yerushalmy ¹ (112):		
Black women.....	114	202
White women.....	114	218
Butler and Alberman (14).....	269	284

¹ Reported neonatal mortality rates only.

Figure 6.—Neonatal mortality rates among single white births in hospitals (by detailed birth weight and specified gestation groups: United States).

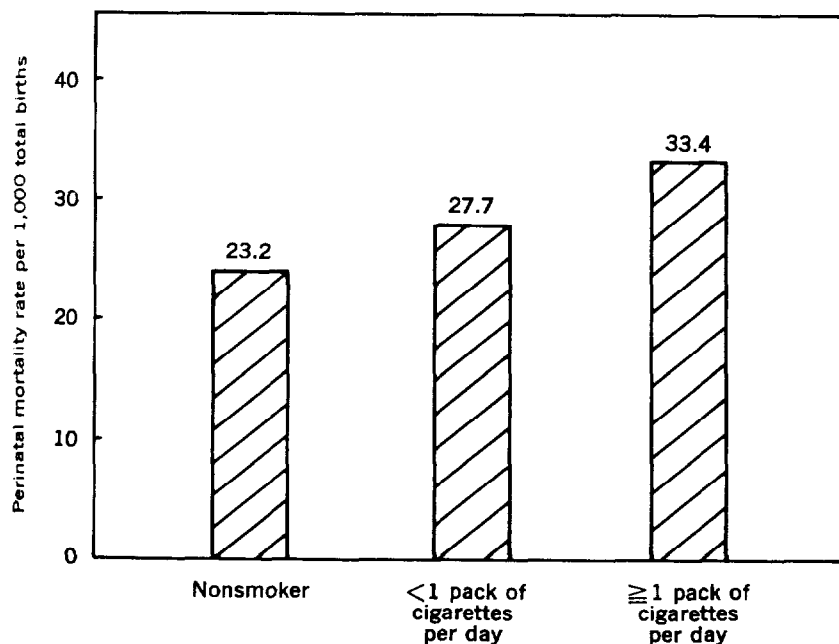


SOURCE: U.S. Public Health Service, National Center for Health Statistics (103).

Recent Studies

The Ontario Perinatal Mortality Study (66, 67) was conducted among 10 teaching hospitals during 1960 and 1961. In this retrospective study of 51,490 pregnancies, a statistically significant increase in the perinatal mortality rate was demonstrated for smokers' infants as compared with those of nonsmokers; the infants of smokers experienced an overall relative risk of 1.27 ($P < 0.001$). Moreover, the investigators found a statistically significant dose-response relationship between the amount of cigarettes smoked and the perinatal mortality rate ($P < 0.001$) (fig. 7).

Figure 7.—Perinatal mortality rate per 1,000 total births by cigarette smoking category.



Number of perinatal deaths:	659	425	220
Total births:	28,358	15,328	6,581

(P < 0.001)

SOURCE: Ontario Department of Health (66).

Recently Butler, et al. (15) further analyzed the British Perinatal Mortality Study. They found a highly significant association between maternal smoking after the fourth month of pregnancy and both late fetal and neonatal deaths. Infants of smokers had an increase in the late fetal mortality rate of 30 percent, and an increase in the neonatal mortality rate of 26 percent, compared to the infants of non-smokers. The overall mortality ratio of late fetal plus neonatal deaths was 1.28 (P < 0.001). Given the large number of women in the study, and the significant changes in smoking behavior which occurred, they found it possible to consider the effect of a change in smoking

behavior between the beginning of pregnancy and the fourth month on late fetal and neonatal mortality. A statistically significant and dose-related increase in mortality occurred among the infants of mothers who continued to smoke after the fourth month of pregnancy, as compared with the infants of nonsmokers and those of women who smoked prior to the pregnancy but gave up smoking by the fourth month of gestation.

Niswander and Gordon (63) reported data from the prospective Collaborative Perinatal Study of the National Institute of Neurological Disease and Stroke. The 39,215 pregnancies registered at 12 university hospitals in the United States were almost equally divided between black and white women. They found a nonsignificant increase in perinatal mortality among the infants of white smokers as compared to those of white nonsmokers; the overall mortality ratio was 1.13 ($P > 0.1$). The infants of black smokers, however, had a significantly higher mortality risk than did those of black nonsmokers; the mortality ratio was 1.18 ($P < 0.02$). Moreover, a definite dose-response relationship between cigarettes smoked by pregnant mothers and mortality risk was shown for black infants. Black women were noted to smoke significantly fewer cigarettes, on the average, than white women.

Rush and Kass (82) found, in a prospective study of 3,276 pregnancies followed at Boston City Hospital, a nonsignificant increase in late fetal plus neonatal mortality rate among the infants of white women who smoked as compared to those of white nonsmokers. However, the infants of black women who smoked had a statistically significant increase in mortality rate compared to the infants of black nonsmokers ($P < 0.01$). The overall mortality ratio for black women who smoked was 1.86. The difference in frequency of stillbirth among the infants of smokers and nonsmokers was the primary factor which contributed to the significance of the difference in mortality rates.

Analysis of Previously Reported Studies

Previously reported studies can be divided into two groups: A group in which the late fetal plus neonatal mortality rates for infants born to cigarette smokers were significantly higher than those for the infants born to nonsmokers, and a group in which no significant differences were detected in the mortality rates for the infants born to smokers and nonsmokers. The results of several studies (14, 17, 25, 42, 43, 55, 84, 92) yielded mortality ratios ranging from 1.38 to 1.78. The results of other studies (20, 65, 76, 85, 100, 115) yielded mortality ratios ranging from 1.01 to 1.06. Both groups contained retrospective and prospective studies of comparable size. The two groups did differ

significantly, however, with regard to control of variables other than cigarette smoking which influence perinatal mortality.

Factors Which Influence Perinatal Mortality Other Than Smoking

Butler and Alberman (13), on data from the British Perinatal Mortality Study, employed a logit transformation analysis of variance, and demonstrated that maternal height, age, parity, social class, and severe preeclampsia all had a significant independent effect on late fetal and neonatal mortality. Rumeau-Roquette (81) provided evidence that a previous stillbirth or low-birth-weight infant significantly increased the risk of a future stillbirth. Meyer and Comstock (51) provided examples of how the differential distribution of smoking and other factors which are related to perinatal mortality, in a population of women, can bias data (e.g., black women have higher perinatal mortality rates than do white women, but black women smoke less than white women do. Hence, nonsmokers will tend to include more black women, and smokers more white women. This will tend to reduce any differences between the groups in mortality rates.) Meyer and Comstock concluded, "Comparisons of mortality rates of smokers' and nonsmokers' babies should be made within subgroups according to parity, socioeconomic status, and other appropriate risk factors, and not separated by birth weight."

In three of the studies in which a significantly higher mortality risk was demonstrated for the infants of smokers, adjustment for other variables was performed. The results indicated that, after such adjustment, a significant independent association between cigarette smoking and infant mortality persisted (13 and 15, 17, 81). Of the studies which revealed no significant increase in mortality risks for smokers' infants, one (115) 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.

Another possible, at least partial, explanation of the discrepancy in results obtained by the two sets of studies is that cigarette smoke may be more harmful to the fetuses of certain women than others. Several developing lines of evidence suggest that this may be the case:

1. Cigarette smoking and socioeconomic background.

Butler, et al. (15) noted that when data from the British Perinatal Mortality Study are grouped by social class of the mother's husband, the late fetal plus neonatal mortality ratio for infants of smokers and nonsmokers in the upper social classes I and II is 1.10; the mortality ratio for the entire sample was 1.28. Rush and Kass (82) reviewed the British Perinatal Mortality Study, along with several other studies, and noted that all have shown the strongest association between excess infant mortality and cigarette smoking among the infants of those

mothers with lower socioeconomic status. Comstock and Lundin (16) found excess mortality among smokers' infants almost entirely confined to those whose fathers had a grammar school education or less. Several of the studies which revealed no significant difference in mortality among the infants of smokers and nonsmokers were conducted in predominately middle class populations (20, 100, 115).

2. Cigarette smoking and previous obstetrical experience.

Peterson, et al. (72) had rigid criteria for entry into his study population of 7,740 women. He included only those women who previously had healthy infants with a birth weight greater than 2,500 grams. He found a significant decrease in birth weight among smokers' infants, but no significant increase in mortality rates. Rumeau-Roquette (81) found that among women who previously had delivered only healthy infants weighing more than 2,500 grams, cigarette smoking was not associated with an increased risk of stillbirth; among those women with a previous stillbirth, smoking was significantly associated with increased risk of a future stillbirth.

3. Cigarette smoking and genetic differences.

The consistent finding that the mortality risk for the infants of black smokers is higher than the risk for the infants of white smokers, even when the socioeconomic background for both is ostensibly similar, suggests that genetic factors also may interact with smoking to produce enhanced risk (82, 99, 115).

Available evidence suggests that if those women, who are already likely to have small infants for reasons other than smoking, smoke during pregnancy, their infants will be most unfavorably affected. This means that the women in the United States whose infants will be most affected by cigarette smoking are those who have an unfavorable socioeconomic situation, have a history of previously unsuccessful pregnancies, and are black.

EXPERIMENTAL STUDIES

Studies in Animals

Studies previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) demonstrate that exposure of rabbits and rats to tobacco smoke and to injections of large doses of nicotine resulted in significantly increased late fetal and neonatal mortality. Astrup (2) has recently studied the effect of continuous exposure of pregnant rabbits to carbon monoxide on stillbirth rates. He found a significantly higher, dose-related incidence of stillbirths and deaths within the first 24 hours of life among the offspring of the experimental rabbits (table 4).

TABLE 4.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight and neonatal mortality*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits.....	17	14	17
Total number of babies.....	116	81	123
Stillborn and babies died within first 24 hours.....	¹ 1	² 8	³ 44
(P<0.001)			

¹ 1 percent.

² 10 percent.

³ 36 percent.

Source: Astrup, P. (2).

Studies in Humans

Some investigators have examined the causes of death among the infants of smokers as compared with those of nonsmokers. Comstock, et al. (17) found that infants of smokers died more frequently of asphyxia, atelectasis, and immaturity. Kullander and Källen (43) found abruptio placentae significantly increased as a cause of death among smokers' infants. Butler and Alberman (14) found little difference in the death rates for the infants of smokers and nonsmokers from isoimmunization and malformations, but higher rates were found for smokers' infants in the groups in which death occurred before or during labor, or in which death resulted from massive pulmonary hemorrhage, or pulmonary infection. As the authors noted, "The latter three are conditions known to be associated with small-for-dates babies." They pointed out that distribution of causes of death in the smoking group could be accounted for almost entirely by the excess of low-birth-weight babies. This supports the conclusion that the mechanism which affects birth weight also influences mortality.

SIGNIFICANCE OF THE ASSOCIATION

The following calculation is offered to give some idea of the order of magnitude of increased late fetal and neonatal mortality associated with cigarette smoking during pregnancy. If women who smoked dur-

ing pregnancy in the United States had an elevation in risk of 28 percent for late fetal and neonatal mortality, as demonstrated by Butler, et al. (15) for Britain, Scotland, and Wales, and if 20 percent of pregnant women smoked throughout the pregnancy,¹ the higher risk of stillbirth and neonatal death for the infants of mothers who smoke cigarettes during pregnancy would account for approximately 4,600 of the 87,263 stillbirth and neonatal deaths in the United States in 1968.

LATE FETAL AND NEONATAL DEATH SUMMARY

A strong, probably causal association between cigarette smoking and higher late fetal and infant mortality among smokers' infants is supported by the following evidence:

1. Twelve retrospective and prospective studies have revealed a statistically significant relationship between cigarette smoking and an elevated mortality risk among the infants of smokers. In three of these studies, of sufficient size to permit adjustment for other risk factors, a highly significant independent association between smoking and mortality was established. Part of the discrepancy in results between these studies and those in which a significant association between smoking and infant mortality was not demonstrated may be explained by a lack of adjustment for risk factors other than smoking.
2. Evidence is converging to suggest that cigarette smoking may be more harmful to the infants of some women than others; this may also, in part, explain the discrepancies between the results of the studies in which a significantly higher mortality risk was shown for the infants of smokers compared to those of nonsmokers and the results of those studies in which significant differences in mortality risk were not found.
3. Within groups of similar birth weight, the infants of nonsmokers appear to have a higher mortality risk than do the infants of cigarette smokers. This results from the fact that the infants of nonsmokers within such similar birth weight groups are on the average gestationally less mature than the infants of cigarette smokers. Available evidence indicates that within groups of similar gestational age, infants of lower birth weight experience a higher mortality risk. Since the infants of cigarette smokers are

¹Based on extrapolation of data on smoking behavior change during pregnancy from the British Perinatal Mortality Study, which probably yields a conservative estimate.

small-for-gestational age, one should expect that if the infants of cigarette smokers and nonsmokers are compared within similar gestational age classes, the infants of cigarette smokers would have the higher mortality rate.

4. The results of recent studies have documented a statistically significant dose-response relationship between the number or amount of cigarettes smoked and late fetal and neonatal mortality.
5. New data suggest that if a woman gives up smoking by the fourth month of pregnancy, she will have the same risk of incurring a fetal or neonatal loss as a nonsmoker.
6. Available evidence strongly supports cigarette smoking as one cause of fetal growth retardation. The causes of excess deaths among the infants of smokers are those associated with small-for-dates babies.
7. Data from experiments in animals have demonstrated that exposure to tobacco smoke or some of its ingredients, such as nicotine or carbon monoxide, results in a significant increase in late fetal and or neonatal deaths.
8. The results of studies in humans have shown that the fetus of a smoking mother may be directly exposed to agents such as carbon monoxide within tobacco smoke, at levels comparable to those which have been shown to produce stillbirth in experimental animals.

Sex Ratio

Although a number of small studies have found a slight, usually statistically nonsignificant, increase in the proportion of female infants born to smokers, the three largest studies of Underwood, et al. (48,505 pregnancies), Butler (15,791 pregnancies), and MacMahon (12,155 pregnancies) have found similar infant sex ratios among both smoking and nonsmoking mothers, with the expected slight excess of males among each (table 5).

Summary

Available evidence strongly indicates that maternal cigarette smoking does not influence the sex ratio of newborn infants.

TABLE 5.—Proportion of male infants delivered to smoking and non-smoking mothers

Author, reference	Pregnancies	Proportion of male infants		Statistical significance
		Smokers	Non-smokers	
Underwood, et al. (100)-----	48, 505	. 518	. 519	None.
Butler and Alberman (14)-----	15, 791	. 518	. 516	Do.
MacMahon, et al. (49)-----	12, 155	. 513	. 512	Do.
Kullander and Källén (43)-----	6, 363	. 515	. 501	Do.
Reinke and Henderson ¹ (78)-----	3, 156	. 498	. 517	Do.
Frazier, et al. ¹ (25)-----	2, 915	. 472	. 505	Do.
				(P>0.05)
Kizer (42)-----	2, 095	. 502	. 493	None.
Herriott, et al. (35)-----	2, 745	. 492	. 517	Do.
Ravenholt, et al (77)-----	2, 052	. 501	. 533	P<0.05
Lowe (46)-----	2, 042	. 532	. 529	None.
Russell, et al. (83)-----	2, 002	. 513	. 512	Do.

¹ Black women.

Congenital Malformations

Previous epidemiological studies which examined the relationship between cigarette smoking and congenital malformations were reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102). Recently, the authors of the Ontario Perinatal Mortality Study (66, 67), a retrospective study of 51,490 births, reported no difference in malformation rate for the infants of smokers and nonsmokers. The various studies of the association between cigarette smoking and congenital malformation have differed significantly with regard to study design, the type of population sampled, sample size and number of infants with malformations, the definition of malformation, and results (table 6).

Previous experimental work was reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102). The chick embryo has been employed in recent studies. The direct application of nicotine to the embryo results in cephalic hematomas (26), malformations of the cervical vertebrae (23), and anomalies of the heart (27), depending upon dose of nicotine and period of incubation in which exposure occurs. Anomalies of the limbs of chicken embryos can also be induced by exposure of the egg to high levels of carbon monoxide (4).

TABLE 6.—*Relative risk of congenital malformation for infants of cigarette smokers and nonsmokers, comparing available studies with regard to study design, study population, sample size, number of infants with malformations, and definition of malformation*

Author, reference	Study design	Study population	Sample size	Infants with malformations	Relative risk SM/NS	Definition of malformations
Lowe (46)	Retrospective	Stillborn plus 24-hour deaths.	2,042	23	1.36	Major.
Comstock, et al. (17)	do	Neonatal deaths	236	37	.31	Major, cause of death.
Yerushalmy (118)	Prospective	Infants less than 2,500 g.	695	59	.57	Major.
Ontario Department of Health (67)	Retrospective	Stillborn plus 1st-week deaths plus surviving infants.	51,490	1,744	.97	
Butler and Alberman (14)	do	Stillborn plus neonatal deaths.	7,123	1,382	1.19	Major, cause of death.
Kullander and Kallen (43)	Prospective	(a) Stillborn plus neonatal deaths plus remainder of deaths to age 1.	137	43	1.25	Major and minor malformations.
		(b) Surviving infants to age 1.	4,903	700	1.06	
Fedrick, et al. (24)	Retrospective	(a) ¹ Stillborn plus neonatal deaths ¹ and deaths to age 7, ¹ survivors ² to age 7.	17,418	86	1.55	(1).
		(b) Neonatal deaths ¹ (3-month study).	7,822	204	1.07	(2).

¹ Autopsy-proven congenital cardiac malformation.

² Clinically determined congenital heart disease.

Congenital Malformation Summary

Given the considerable variation in study design, study population, sample size, number of affected infants, definition of malformation, and results, no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformation at the present time.

Lactation

Introduction

The following section is a review of available evidence which bears upon any interaction between cigarette smoking and lactation. Emphasis is placed upon 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. (99), in a study of 2,000 women from various social and economic strata, observed a definite but statistically insignificant trend toward more frequent inadequacy of breast milk production among those smoking mothers who attempted to nurse compared to nonsmokers.

Mills (52), in a study of 520 women, found that among women who indicated either a desire to nurse or no desire to nurse yet continued to nurse beyond 10 days, and who had delivered their first live-born infant, the average period of nursing for mothers who smoked was significantly shorter 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.

Experimental Studies

STUDIES IN ANIMALS

Nicotine

Influence on the Lactation Process

Blake and Sawyer (11) 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.

Wilson (110) 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 dose was lower than that used in other studies.

Presence of Nicotine in the Milk

Hatcher and Crosby (32), using a frog bioassay, reported traces of nicotine in cow's milk 24 hours after the intramuscular injection of 5.0 mg./kg. and 5 hours after the injection of 0.5 mg./kg.

Evidence for an Effect Upon the Nursing Offspring

Hatcher and Crosby (32) found that 0.5 mg./kg. nicotine injected into nursing cats had no apparent harmful effect upon the kittens. Apparently 4.0 mg./kg. suppressed lactation. Kittens fed the milk from the cow which had been injected with 5.0 mg./kg. nicotine were also apparently unaffected.

Nitrosamines

Mohr (53) 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 these 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 (37, 79).

STUDIES IN HUMANS

Nicotine and/or Tobacco Smoke

Influence on the Lactation Process

Emanuel (22) noted no reduction in milk production among 10 wet nurses who were encouraged to smoke seven to 15 cigarettes daily;

some were observed to inhale the smoke. Hatcher and Crosby (32) noted that after a mother smoked seven cigarettes within 2 hours, it was difficult to obtain a specimen of breast milk. Perlman, et al. (71) found that of 55 women smokers with an adequate milk supply at the beginning of his study, 11 (20 percent) of the women 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.

Presence of Nicotine in the Milk

Hatcher and Crosby (32) found, using a frog bioassay, that the milk of a woman collected after she had smoked seven cigarettes in 2 hours contained approximately 0.6 mg./liter nicotine. Emanuel (22), 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 six 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. Bisdorn (10) demonstrated nicotine in the milk of a mother who smoked 20 cigarettes a day. Thompson (97) found approximately 0.1 mg./liter of nicotine in the milk of a mother who smoked nine cigarettes a day (plus three pipefuls). Perlman, et al. (71), using a *Daphnia* bioassay, demonstrated nicotine in the milk of all women who smoked in their study. Moreover, they found a direct dose-relationship between concentration of nicotine and the number of cigarettes smoked. No comment is 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 hind milk is different and perhaps the concentration of nicotine also differs.

Evidence for a Clinical Effect Upon the Offspring

Emanuel (22) noted that among the infants in his study, loose stools were observed only in the one whose wet nurse had smoked 20 cigarettes in the previous 4 hours. Bisdorn (10) 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 (30) also described a case of possible nicotine poisoning in a 3-week-old nursing

whose mother smoked 35 to 40 cigarettes a day. The symptoms included vomiting and loose stools. Following the curtailment of smoking, the symptoms gradually abated over a 3-day period. Perlman, et al. (71) 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 accorded with their clinical observations. The fact that they admitted to the study 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.

VITAMIN C

Venulet (105, 106, 107), in a series of studies, demonstrated 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.

Lactation Summary

1. The two pertinent epidemiological studies suggest a possible influence of smoking upon the adequacy of milk supply. However, with only limited numbers of women and without control of other potentially significant variables, no conclusions can be drawn.
2. Studies in rats have demonstrated that nicotine can interfere with suckling-induced rise in prolactin. The relevance for humans is uncertain.
3. Evidence exists that nicotine passes into breast milk. No clear evidence for an acute effect upon the nursing infant is available. Potential chronic effects have not been studied.
4. New evidence from experiments with mice suggests that nitrosamines, known carcinogens, pass through the milk to suckling young.

Preeclampsia

Previous epidemiological studies of the relationship between cigarette smoking and preeclampsia were reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) and form the basis of the following statements:

The results of several large prospective and retrospective studies indicate a statistically significant lower incidence of preeclampsia among smoking women (14, 43, 100). The results of one large retrospective study demonstrated a significant inverse relationship between the incidence of preeclampsia and the number of cigarettes smoked (100). When other risk factors, such as parity, social class, maternal weight before the pregnancy, and maternal weight gain during the pregnancy were controlled, smoking women retained a significantly decreased risk of preeclampsia (21). The lower risk of preeclampsia for cigarette smoking women has been demonstrated in Britain and Scotland (14, 21, 46, 83), The United States (100, 118), Venezuela (42), and Sweden (43). If a maternal smoker does develop preeclampsia, however, available data suggest that her infant has a higher mortality risk than does the infant of a nonsmoker with preeclampsia (21, 83).

Summary

1. Available evidence indicates that maternal cigarette smokers have a significantly lower risk of developing preeclampsia as compared to nonsmokers.
2. If a woman who smokes cigarettes during pregnancy does develop preeclampsia, her infant has a higher mortality risk than the infant of a nonsmoker with preeclampsia.

Pregnancy References

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CHAPTER 5

Peptic Ulcer Disease

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Introduction

Previous epidemiological and experimental studies of the relationship between cigarette smoking and peptic ulcer disease were reviewed in the 1971 and 1972 reports on the health consequences of smoking (17, 18) and form the basis of the following summary:

The results of epidemiological studies indicate that cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater mortality from peptic ulcer as compared to nonsmoking males. Among males, the association between cigarette smoking and peptic ulcer disease is stronger for gastric than for duodenal ulcer, but significant for both. For males, cigarette smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of peptic ulcer healing. The relationship between cigarette smoking and the prevalence of and mortality from peptic ulcer disease is less clear for females than for males.

Experimental studies of the effect of cigarette smoking in man, and of the effect of injection and infusion of nicotine in animals, on gastric secretion and motility have produced conflicting results. In dogs, an infusion of nicotine has been found to inhibit pancreatic and hepatic bicarbonate secretion, thus demonstrating a possible link between cigarette smoking and duodenal ulcer.

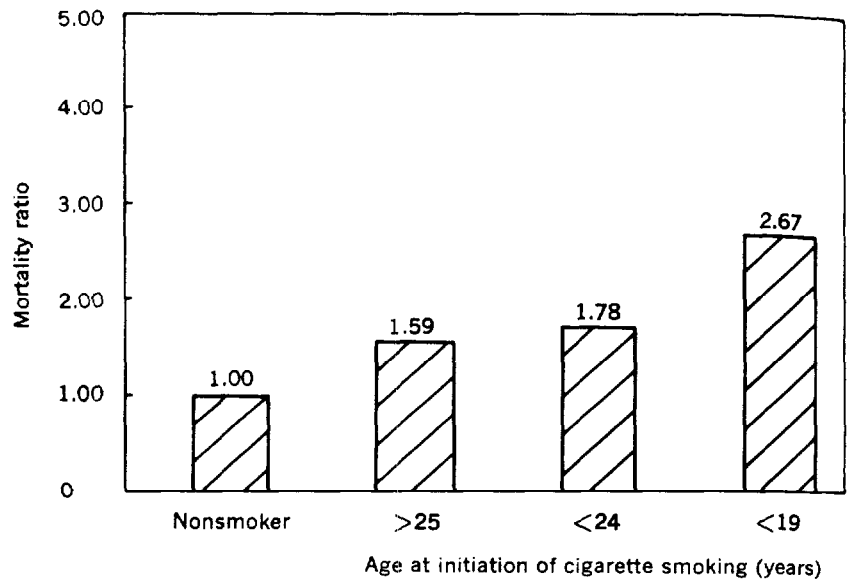
Recently, additional epidemiological, clinical, autopsy, and experimental studies have confirmed the association between cigarette smoking and gastric ulcer mortality and have clarified a mechanism through which cigarette smoking might be linked to duodenal ulcer.

Epidemiological and Clinical Studies

Previous studies of the relationship between peptic ulcer disease and cigarette smoking have been conducted in predominantly white, Western populations. A large prospective epidemiological study is currently being conducted in Japan. From this study, Hirayama (6) reported 5-year followup data on 265,118 men and women, aged 40 years and older, representing 91 to 99 percent of the total population in the area of the 29 health districts in which the study was conducted. Both male

and female cigarette smokers experienced higher death rates from gastric ulcer as compared with nonsmokers. The mortality ratio for cigarette smokers was 1.81 for males ($P < 0.001$) and 2.15 for females ($P < 0.05$). The mortality ratio for smokers (males and females combined) was dose-dependent as measured by age at initiation of smoking (fig. 1). The results of this study, in the context of the genetic and cultural differences between Japanese and Western populations, provide a significant confirmation of the association between cigarette smoking and gastric ulcer mortality.

Figure 1.—Gastric ulcer mortality ratios of Japanese (men and women combined) by age at initiation of cigarette smoking (1966–1970).



SOURCE: Hirayama, T. (6).

Alp, et al. (1) conducted a retrospective survey of 638 patients, admitted to two Australian teaching hospitals between 1954 and 1963, with chronic gastric ulcer confirmed by roentgenographic, endoscopic, or surgical examination. The findings in the patients were compared with information available about the South Australian population obtained at census in 1954 and 1961, and with a control group of 233 subjects matched for age and sex with the ulcer patients. Cigarette use, a family history of peptic ulcer, domestic stress, and aspirin and alcohol intake occurred significantly more frequently among ulcer patients. Alp, et al. (2) found that after surgical treatment, recurrence of the ulcer was significantly more likely to recur among those patients who continued to smoke, drink, and use aspirin ($P < 0.001$).

Fingerland, et al. (5) compared the autopsy findings from 765 males with their smoking history. The autopsies were performed without selection during 1965 and 1966 at the University of Hradec Králové, Czechoslovakia. Peptic ulcer was significantly more frequent among male ex-smokers and male lifelong smokers than among male non-smokers ($P < 0.02$). Among males, a dose-response relationship was found between estimated total cigarette consumption and the presence of peptic ulcer at autopsy.

Cooper and Tolins (4) reported results from a retrospective study of the relationship between cigarette smoking and postoperative complications among 2,988 males, admitted to 19 Veterans Administration hospitals, for the surgical treatment of duodenal ulcer. Smoking history was obtained for 1,441 of the men, and of these 273 were non-smokers, 1,018 smoked cigarettes only, and 93 smoked cigarettes plus a pipe and/or cigars. The authors found no evidence of an association between either the number of cigarettes smoked per day, or the number of years of cigarette smoking, and postoperative complications, operative mortality, or length of hospital stay. They emphasized that their results must be viewed with considerable caution and listed several potential sources of bias. In addition, they noted, “* * * that these results apply only to the immediate postoperative findings and do not apply to the long-range effects of smoking upon the patient after surgery for duodenal ulcer disease.”

Experimental Studies

Gastric Secretion

STUDIES IN HUMANS

Morales, et al. (10, 11) studied the effect of cigarette smoking on gastric secretion in a group of 312 patients. The patients included 138

with duodenal ulcer, 93 with gastric ulcer, and 81 with other gastrointestinal disorders, who served as controls. Cigarette smoking was significantly more frequent among the patients with peptic ulcer than among the controls.

The chronic effect of smoking on gastric secretion was quite variable. Male smokers among the controls and in the group with duodenal ulcers had a significantly increased baseline acid output as compared with nonsmokers in the same groups ($P < 0.05$). After a subcutaneous injection of histamine, only the group of male smokers with gastric ulcers had a significant increase in acid output over the values obtained for nonsmokers in the same group ($P < 0.05$). Among the smokers in the control group, the relationship between gastric acid output and the number of cigarettes smoked daily was dose dependent. No such relationship was obtained for either of the two groups with peptic ulcers.

In these experiments, the acute effect of smoking on gastric secretion was slight. In one set of experiments, a group of eight smokers served as its own control. The smoking of two cigarettes prior to collection of gastric juice had no significant effect on acid output as compared to baseline values. After smoking two cigarettes and also receiving a subcutaneous injection of histamine, the patients experienced no significant change in gastric acid output as compared to baseline values; 21 male patients, including members from the groups with ulcers and controls, smoked one cigarette 1 hour after an intravenous infusion of histamine. A transient depression of gastric acid output was noted as compared with the values obtained from nine patients who did not smoke.

STUDIES IN ANIMALS

Konturek, et al. (8) studied the effect of intravenous infusion of nicotine on the formation of acute, experimental duodenal ulcers in cats. The authors infused nicotine intravenously in doses comparable to the smoking of four, eight, and 16 cigarettes per hour into cats in whom near maximal gastric acid output had been stimulated with intravenous pentagastrin. The investigators found that nicotine in the two lower doses had no effect upon the gastric acid output stimulated by pentagastrin, but that the highest dose produced a significant decrease in response, due to a fall in both volume and acid concentration. Nicotine alone failed to alter a negligible basal gastric secretion. In control animals (pentagastrin alone), duodenal ulcers were found in eight of 10 animals. Nicotine at the two lower doses, in combination with pentagastrin, produced ulcers in all 26 animals. At the intermediate dose of nicotine, the mean ulcer area was twice that found in

the control group. At the highest dose of nicotine, peptic ulcers appeared in only two of six animals and the area of ulcer was reduced compared to controls.

Shaikh, et al. (14) studied the acute and chronic effects of subcutaneously injected nicotine on gastric secretion in rats. Under basal conditions, the volume of gastric secretion was initially depressed, then stimulated, and depressed again as the dose of nicotine was increased. Acid output was decreased over the entire range of nicotine dosage. Pepsin output reflected a similar triphasic response to increasing nicotine doses as did gastric secretory volume. In the absence of nicotine, pentagastrin stimulated gastric volume, acid, and pepsin output. The injection of nicotine, in increasing doses, administered simultaneously with pentagastrin, resulted in a gradual decrease in response for all parameters. Volume of gastric juice, acid output, and pepsin output were all increased significantly by chronic exposure to nicotine alone. Based on an average smoking dose of nicotine, the dose of nicotine employed in the chronic experiments corresponded to the smoking of three to five cigarettes per day.

Thompson, et al. (16) extended the study of rats described above by studying the effects of chronic nicotine injections in vagotomized rats and rats with discrete lesions in the hypothalamus. In sham-operated animals, chronic nicotine injections significantly increased baseline volume of gastric juice, acid output, and pepsin output. Following vagotomy, the nicotine response was completely suppressed. Caudal hypothalamic lesions did not influence the response to nicotine in the presence of intact vagus nerves. Anterior hypothalamic lesions, ranging from the anterior hypothalamic area to the ventromedial hypothalamus, blocked the nicotine-induced gastric secretory stimulation in the presence of intact vagi. The authors concluded that chronic nicotine-induced gastric secretory stimulation is mediated via anterior hypothalamic activation and intact vagus nerves. The importance of local effects remained uncertain.

Pancreatic Secretion

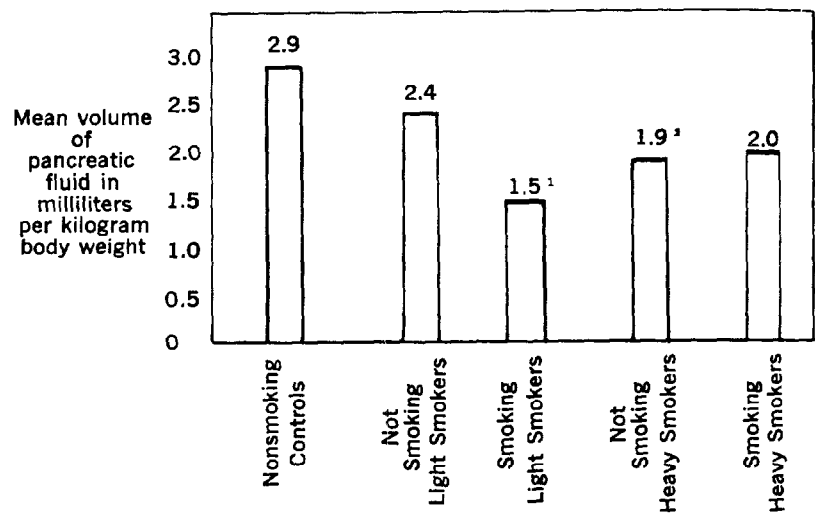
STUDIES IN HUMANS

Bynum, et al. (3) studied the effect of cigarette smoking upon pancreatic secretion in 23 healthy young males and females. Five control male nonsmokers were compared with seven male and two female light smokers (less than one pack of cigarettes per day for less than 3 years) and eight male and one female heavy smokers (more than one pack of

cigarettes per day for more than 3 years). Pancreatic secretion was measured by the double secretin test, using Boots secretin. The experiment was divided into two parts for the smokers: A basal collection period and an experimental period during which the subjects smoked seven nonfiltered cigarettes at the rate of four per hour. Light smokers had basal values for pancreatic secretory volume and bicarbonate output in response to secretin which were not significantly different from controls. After the subjects had smoked, significant depression of both pancreatic volume and bicarbonate output was noted ($P < .001$). Heavy smokers had basal values that were significantly less than in the control subjects ($P < 0.01$). Smoking, however, did not further depress the response to secretin (figs. 2 and 3).

Solomon and Jacobsen (15) reviewed some possible mechanisms whereby the increased prevalence and mortality from duodenal ulcer among cigarette smokers might be produced. They concluded that evidence from studies in animals, coupled with the findings of Bynum, et al. (3), supported the hypothesis that the mechanism active in humans involves impaired neutralization of acid secondary to the inhibition of pancreatic bicarbonate secretion.

Figure 2.—Effect of cigarette smoking on volume of secretin-stimulated pancreatic secretion in humans.

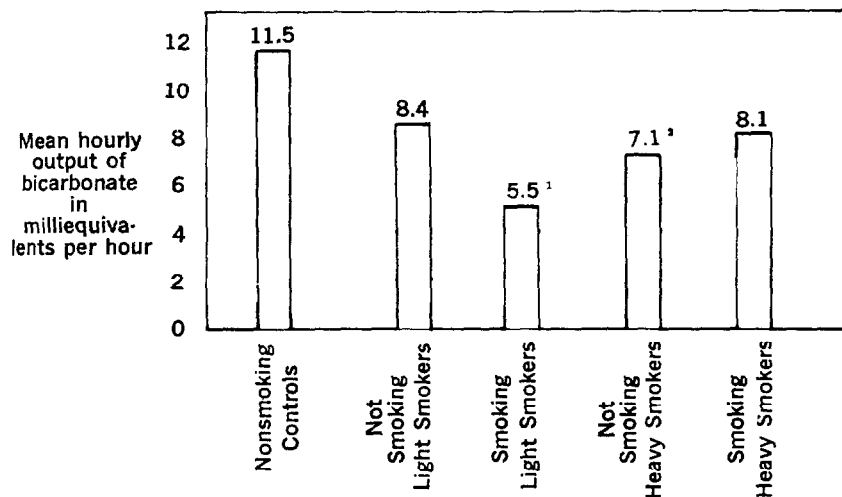


¹ Significantly different from nonsmoking test within group of light smokers ($P < 0.001$).

² Significantly different from nonsmoking controls ($P < 0.01$).

SOURCE: Bynum, et al. (3).

Figure 3.—Effect of cigarette smoking on secretin-stimulated pancreatic bicarbonate output in humans.



¹ Significantly different from nonsmoking test within group of light smokers ($P < 0.001$).

² Significantly different from nonsmoking controls ($P < 0.01$).

SOURCE: Bynum, et al. (3).

STUDIES IN ANIMALS

Konturek, et al. (7) extended his research on the mechanism of nicotine-induced inhibition of pancreatic secretion in the dog, using the design previously employed (9). Infused secretin alone led to a sustained increase in pancreatic bicarbonate output. Intravenous nicotine, at all four doses of infused secretin, produced a significant inhibition of pancreatic volume and bicarbonate output ($P < 0.05$). Infused nicotine appeared to inhibit competitively the effect of secretin on pancreatic secretion of fluid and bicarbonate. Topical (intraduodenal) nicotine failed to affect significantly the response to infused secretin. Stimulation of endogenous secretin by an acid infusion into the duodenum produced the expected pancreatic secretory response. Nicotine either applied to the duodenal mucosa or injected intravenously significantly inhibited the pancreatic secretory response to endogenous secretin. Nicotine had no significant effect on total pancreatic protein output. Nicotine did not alter the cholecystokinin-induced stimulation of pancreatic secretion. The authors concluded that nicotine may inhibit pancreatic secretion of fluid and bicarbonate both

by a direct effect on pancreatic secretory mechanisms, acting as a competitive inhibitor of secretin, and by a secondary effect on the duodenal mucosa, depressing the endogenous release of secretin by acid.

Robert (12) studied the potentiation of active duodenal ulcers by nicotine administration in the rat. Subcutaneous infusion of pentagastrin and carbachol resulted in the dose-dependent formation of duodenal ulcers within 24 hours. Nicotine alone produced no ulcers. Increasing doses of subcutaneously infused nicotine, in combination with the other two agents, resulted in a steadily increasing dose-related incidence and severity of the duodenal ulcers. Robert noted that Kouturek, et al. (9) found that nicotine inhibited pancreatic and biliary bicarbonate secretion in dogs, and that Thompson, et al. (16) found that acute doses of nicotine in rats either depressed or did not alter gastric secretion. He concluded that the most probable mechanism by which nicotine potentiated acute duodenal ulcer formation in the rat was via a suppression of pancreatic secretion.

Robert, et al. (13) further tested this hypothesis by infusing acid via the esophagus of rats in doses found to cause duodenal ulcers in one-third of the experimental animals. One group of rats also received a subcutaneous infusion of nicotine. Another received nicotine, but only water was infused via the esophagus; 31 percent of the animals receiving acid but no nicotine had duodenal ulcers; 93 percent of the nicotine-acid group had duodenal ulcers, while none of the nicotine-water group had ulcers. The ulcers in the nicotine-acid group were more numerous, extensive, and deeper than those in the animals which received acid alone.

Summary of Recent Peptic Ulcer Disease Findings

In addition to the findings relating cigarette smoking to peptic ulcer disease, summarized in previous reports on the health consequences of smoking (17, 18) and cited in the introduction to this chapter, recent studies have contributed further to our understanding of the association:

1. The finding of a significant dose-related excess mortality from gastric ulcers among both male and female Japanese cigarette smokers, in a large prospective study, and in the context of the genetic and cultural differences between the Japanese and previously investigated Western populations, confirms and extends the association between cigarette smoking and gastric ulcer mortality.

2. Data from experiments in several different animal species suggest that nicotine potentiates acute duodenal ulcer formation by means of inhibition of pancreatic bicarbonate output.
3. Cigarette smoking has been demonstrated to inhibit pancreatic bicarbonate secretion in healthy young men and women.

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CHAPTER 6

Pipes and Cigars

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Introduction

This chapter is a review of the epidemiological, pathological, and experimental data on the health consequences of smoking cigars and pipes, alone, together, and in various combinations with cigarettes. Previous reviews on the health consequences of smoking have dealt primarily with cigarette smoking. Although some of the material on pipes and cigars presented in this chapter has been presented in previous reports of the Surgeon General, this is the first attempt to summarize what is known about the health effects of pipe and cigar smoking. Since the use of pipes and cigars is limited almost exclusively to men in the United States, only data on men are included in this review.

The influence of pipe and cigar smoking on health is determined by examining the overall and specific mortality and morbidity experienced by users of these forms of tobacco compared to nonsmokers. Epidemiological evidence suggests that individuals who limit their smoking to only pipes or cigars have overall mortality rates that are slightly higher than nonsmokers. For certain specific causes of death, however, pipe and cigar smokers experience mortality rates that are as great as or exceed those experienced by cigarette smokers. This analysis becomes more complex when combinations of smoking forms are examined. The 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 might seem to suggest that smoking pipes or cigars in combination with cigarettes diminishes the harmful effects of cigarette smoking. However, an 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 smoked, 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 cigarettes at the level of a pack a day, assuming that both groups smoke their 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 their cigars and pipes and also

resist inhaling their cigarettes. Unfortunately, little of the published material on mixed cigarette, pipe, and cigar smoking contains these types of analyses or controls.

A paradox seems to exist between the mortality rates of ex-smokers of pipes and cigars and ex-smokers of cigarettes. 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 the elevated mortality rates experienced by current cigarette smokers. In contrast to this finding, several prospective epidemiological investigations, Hammond and Horn (40), Best (9), Kahn (50), and Hammond (38), 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 (39). 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 some people who are ill from smoking-related diseases, and death rates are high among persons in ill health.

As a result, ex-cigarette smokers initially have higher overall and specific mortality rates than continuing cigarette smokers, but because of the relative decrease in mortality that occurs in those who quit smoking for reasons other than ill health, and because of the dwindling number of ill ex-smokers, a relative decrease in mortality is observed (within a few years) following cessation of cigarette smoking. The beneficial effects of cessation would be obvious sooner were it not for the high mortality rates of those who quit smoking for reasons of illness. A similar principle operates for ex-pipe and ex-cigar smokers, but because of the lower initial risk of smoking these forms and therefore 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 the above reasons a bias is introduced into the mortality rates of current smokers and ex-smokers of pipes and cigars, so that a more accurate picture of mortality might be obtained by combining the ex-smokers with the current smokers and looking at the resultant mortality experience.

Because of a lack of data that would allow a precise analysis of mortality among ex-pipe and ex-cigar smokers, a detailed analysis of these groups could not be undertaken in this review.

For each specific cause of death, tables have been prepared which summarize the mortality and relative risk ratios reported in the major

prospective and retrospective studies which contained information about pipe and cigar smokers. The smoking categories used include: cigar only, pipe only, total pipe and cigar, cigarette only, and mixed. The total pipe and cigar category includes: those who smoke pipes only, cigars only, and pipes and cigars. The mixed category includes: those who smoke cigarettes and cigars; cigarettes and pipes; and cigarettes, pipes, and cigars. Mortality and relative risk ratios were calculated relative to nonsmokers.

The Prevalence of Pipe, Cigar, and Cigarette Usage

The 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, and 1970 (98, 99, 100). In each survey, about 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 is summarized in tables 1 and 2. The prevalence of pipe, cigar, and cigarette smoking in Great Britain for the years 1965, 1968, and 1971 is presented in table 3.

TABLE 1.—Percent distribution of U.S. male smokers aged 21 and older by type of tobacco used for the years 1964, 1966, and 1970

Forms used	1964 (percent)	1966 (percent)	1970 (percent)
1. Cigar only.....	6.8	5.5	5.6
2. Pipe only.....	1.7	3.0	3.6
3. Pipe and cigar.....	3.9	4.9	4.4
4. Cigarette only.....	28.6	31.2	25.9
5. Cigarette and cigar.....	11.3	9.9	6.6
6. Cigarette and pipe.....	5.3	4.9	5.3
7. Cigarette, pipe, and cigar.....	7.7	6.3	4.6
8. Nonsmoker.....	34.7	34.3	44.0
Total.....	100.0	100.0	100.0
Number of persons in sample.....	2,389	2,679	2,861
Total pipe users (2+3+6+7).....	18.7	19.2	17.9
Total cigar users (1+3+5+7).....	29.9	26.7	21.2
Total cigarette users (4+5+6+7).....	52.9	52.4	42.3

Source: U.S. Department of Health, Education, and Welfare (98, 99, 100).

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: U.S. Department of Health, Education, and Welfare (100).

TABLE 3.—*Percent distribution of British male smokers aged 25 and older by type of tobacco used for the years 1965, 1968, and 1971*

Forms used	1965	1968	1971
1. Cigars only.....	1.9	2.8	3.3
2. Pipe only.....	5.1	5.6	5.9
3. Cigarettes only.....	46.8	45.7	40.8
4. Cigarettes and pipe.....	8.0	7.0	6.1
5. Mixed smokers.....	7.5	9.1	8.4
6. Nonsmokers.....	30.7	29.9	35.4
Total.....	100.0	100.0	100.0
Number of persons in sample.....	3,576	3,566	3,594
Total pipe users.....	13.9	14.3	13.3
Total cigar.....	9.0	11.7	11.3
Total cigarette.....	67.6	67.6	61.6

Source: Todd, G. F. (9).

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 (96).

American brands of cigarettes contain blends of different grades of Virginia, Burley, Maryland, and oriental tobaccos. Several varieties of cigarette tobaccos are flue-cured. In this process, tobacco leaves are cured in closed barns where the temperature is progressively raised over a period of several days. This results in "color setting," fixing, and drying of the leaf. The most conspicuous change is the conversion of starch into simpler sugars and suppression of oxidative reactions. Flue-cured tobaccos produce an acidic smoke of light aroma (35, 112).

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)" (112). 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" (102). 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" (102).

Cigars are also classified by size. "Small cigars" weigh not more than 3 pounds per thousand and "large cigars" weigh more than 3 pounds per thousand. "Large cigars" are further divided into seven classes for tax purposes based on the retail price intended by the manufacturer for such cigars (96).

Cigars are made of filler, binder, and wrapper tobaccos. Most cigar tobaccos are air-cured and then fermented. More recently, reconstituted cigar tobaccos have been used as wrapper, binder, or both. Cigars are either hand-rolled or machine made. Some brands of small cigars are manufactured on regular cigarette making machines. The aging and fermentation processes used in cigar tobacco production produce chemical catalytic, enzymatic, or bacterial transformations as evidenced by increased temperature, oxygen utilization, and carbon dioxide generation within fermenting cigar tobaccos. In this complex process, up to 20 percent of the dry weight of the leaf is lost through decreases in the concentration of the most readily fermentable materials such as carbohydrates, proteins, and alkaloids. The flavor and aroma of cigar tobaccos are in large measure the results of precisely controlled treatment during the fermentation process (35, 36, 112).

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 (112).

Conclusion

Because of the unique curing and processing methods used in the production of cigar and pipe tobaccos, significant physical and chemical differences exist 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 has 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. (43) 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" (table 4). Kuhn (58) 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

TABLE 4.—Amounts of several components of 1 g. of particulate material from mainstream smoke of tobacco products

Compound	Tobacco product ¹					
	U.S. cigar A (b)	Havana cigar B (b)	Standard pipe tobacco in pipe (b)	Cigarette tobacco in pipe	85 mm. plain U.S. cigarette (a)	85 mm. plain U.S. cigarette (b)
Nicotine (mg.)-----	46.2	63.6	56.1	61.0	65.9	77.4
Benzo(a)pyrene (μg.)----	3.9	3.6	6.0	3.6	1.2	1.3
Phenol (mg.)-----	8.2	6.7	15.0	7.3	2.9	4.1
o-Cresol (mg.)-----	1.6	1.7	1.9	1.4	.6	.8
m+p-Cresol (mg.)-----	4.8	3.8	5.6	3.4	1.4	1.9
m+p-Ethylphenol (mg.)--	1.4	1.5	1.1	1.3	.7	.7

¹ Smoking conditions:

(a) 1 puff per minute, duration 2 sec., puff volume 35 ml.

(b) 2 puffs per minute, duration 2 sec., puff volume 35 ml.

Source: Hoffmann, et al. (43).

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 2½ times higher in the cigar condensate.

Campbell and Lindsey (17) measured the polycyclic hydrocarbon levels in the smoke of a small popular-type cigar 8.8 cm. long, weighing 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 5 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. (69) 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 (68) 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.

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

TABLE 5.—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 This is a light pipe tobacco.

Source: Campbell, J. M., Lindsey, A. J. (17).

in cigarette smoke. Most of these compounds are found in concentrations which equal or exceed levels found in cigarette "tar." A more complete picture of the carcinogenic potential of cigar "tars" is obtained from experimental data in animals.

Mortality

Overall Mortality

Several large prospective studies have examined the health consequences of various forms of smoking. The results of these investigations have been reviewed in previous reports of the Surgeon General in which the major emphasis has been 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. (31), Buell, et al. (16), Hirayama (42), and Weir and Dunn (105) 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 who were followed for 44 months were reported by Hammond and Horn (41). 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.

In a study of 41,000 British physicians, Doll and Hill (26, 27) reported the overall mortality of pipe and cigar smokers as being only 1 percent greater than that among nonsmokers. Best (9), in a study of 78,000 Canadian veterans, reported overall mortality rates of pipe and cigar smokers slightly above those of nonsmokers. Kahn (50) examined the death rates and smoking habits of more than 293,000 U.S. veterans and Hammond (38) examined the smoking habits of and mortality rates experienced by 440,559 men. In these studies, 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 6 summarizes the results of these five 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 cigarettes in addition to pipes and cigars appear to experience an intermediate level of mortality that approaches the mortality experience of cigarette smokers.

TABLE 6.—*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 (40) . . .	1. 00	1. 22	1. 12	1. 10	1. 36	1. 50	1. 43	1. 68
Doll and Hill (26)	1. 00	-----	-----	1. 01	-----	-----	1. 11	1. 28
Best (9)	1. 00	1. 06	1. 05	. 98	1. 22	1. 26	1. 13	1. 54
Kahn (50)	1. 00	1. 10	1. 07	1. 08	-----	-----	1. 51	1. 84
Hammond ² (38)	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.

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 (40) 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 10 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 7). 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 (9) 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 8). Kahn (50) reported a consistent increase in overall mortality with an increase in the amount smoked for both pipe and cigar smokers (table 9). Hammond (38) found no consistent relationship between overall mortality and the number of cigars or pipefuls smoked (table 10).

TABLE 7.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Hammond and Horn*

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. (40).

TABLE 8.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Best*

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. (9).

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 examines 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.

TABLE 9.—*Mortality ratios for total deaths of cigar and pipe smokers by age and amount smoked—Kahn*

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. 18

Source: Kahn, H. A. (50).

TABLE 10.—*Mortality ratios for total deaths of cigar and pipe smokers by amount smoked—Hammond*

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. (58).

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 only reaches the oral cavity and the upper digestive and respiratory tracts and does not reach the lungs where further direct effects and systemic absorption of various chemical compounds can occur.

Although the smoker has some voluntary control over the inhalation of smoke, the physical and chemical properties of tobacco smoke to a degree determine its acceptability and "inhalability."

The condensate of pipe and cigar smoke is generally found to be alkaline when the pH is measured by suspending a Cambridge filter in CO₂-free water. Cigarette condensate is slightly acidic as measured by this method. Since alkaline smoke is more irritating to the respiratory 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 (15) 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. Available epidemiological evidence indicates that most cigar smokers do not inhale the smoke and 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 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 (3, 15, 79). This suggests that cigar smokers may be able to absorb some nicotine through the oral cavity without having to inhale, particularly during the time that the smoke from the cigar is alkaline.

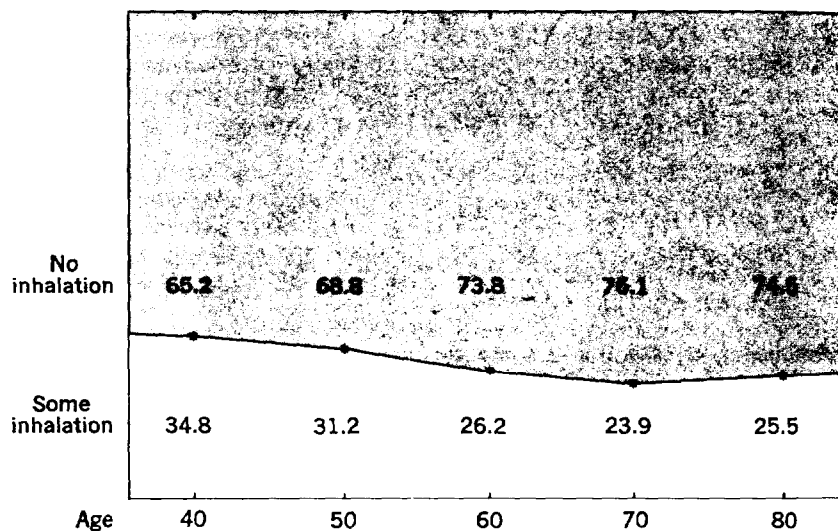
With the development of sensitive measures of serum nicotine levels (48) the extent to which nicotine is absorbed through the membranes of the mouth in pipe and cigar smokers can be more accurately determined.

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 (26) and Hammond (38) presented information on inhalation patterns of pipe, cigar, and cigarette smokers (figs. 1, 2, 3, and table 12). Some 80 to 90 percent of cigarette smokers reported inhaling, with the majority of individuals inhaling moderately or deeply, whereas most pipe and cigar smokers denied inhaling at all. Pipe smokers reported slightly more inhalation than cigar smokers. 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.

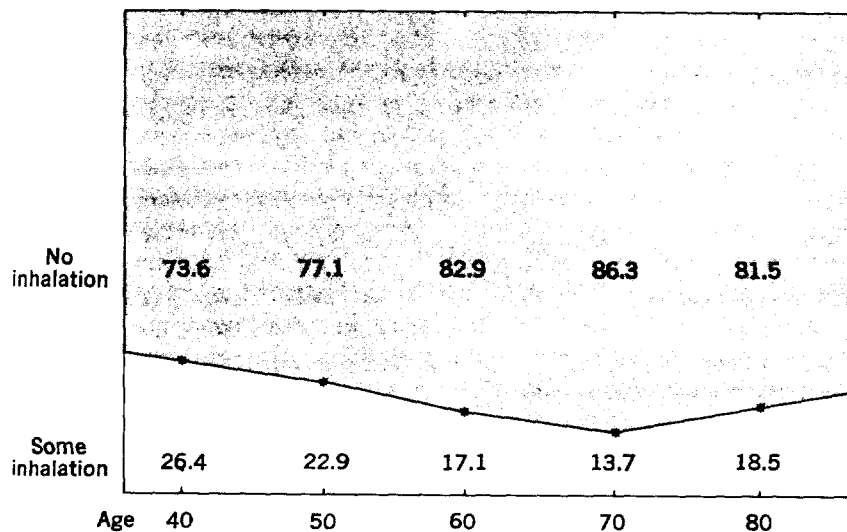
The Tobacco Research Council of the United Kingdom has, since 1957, periodically reported the use of tobacco products by the British.

Figure 1.—Inhalation among pipe smokers by age.



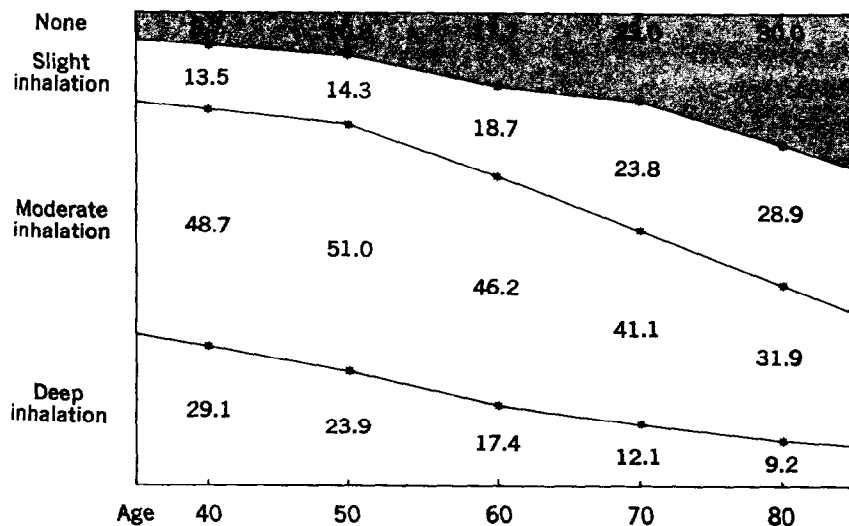
SOURCE: Hammond, E. C. (38).

Figure 2.—Inhalation among cigar smokers by age—Hammond.



SOURCE: Hammond, E. C. (38).

Figure 3.—Depth of inhalation among cigarette smokers by age.—Hammond.



SOURCE: Hammond, E. C. (38).

Recent reports edited by Todd have contained data on the inhalation pattern of cigar, pipe, and cigarette smokers (92, 93, 94). Table 11 shows that most cigarette smokers inhale a "lot" of "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.

Best (9) reported inhalation data among male cigarette smokers by smoking intensity and age group, but did not report the inhalation

patterns of pipe and cigar smokers. The overall mortality rates of current pipe smokers who inhaled at least slightly were reported by Hammond (38) 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 (table 13).

Available evidence indicates that cigarette smokers inhale smoke to a greater degree than smokers of cigars or pipes. Once a smoker has learned to inhale cigarettes, however, there appears to be a tendency to also 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 (tables 14, 15, 16).

Bross and Tidings (14) examined the inhalation patterns of smokers of large cigars, cigarettes, and those who switched from one tobacco product to another (table 15). Nearly 75 percent of those who were 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 re-

TABLE 11.—*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. (93, 94).

TABLE 12.—*Inhalation among cigar, pipe, and cigarette smokers by age—Doll and Hill*

Smoking type	Percentage of inhalers, age					
	25 to 34	35 to 44	45 to 54	55 to 64	65 to 74	>74
Cigar and pipe.....	12.00	10.00	7.00	5.00	4.00	4.00
Mixed (cigarette and other).....	74.00	60.00	47.00	36.00	30.00	26.00
Cigarette only.....	90.00	85.00	75.00	66.00	58.00	41.00

Source: Doll, R., Hill, A. B. (86).

ported inhaling almost every puff and 89 percent said 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 (93) reported similar data for a sample of smokers in the United Kingdom (table 16). 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 main-

TABLE 13.—*Mortality ratios for total deaths of cigar and pipe smokers by age and inhalation—Hammond*

Inhalation	Mortality ratio, age	
	45 to 64	65 to 84
Nonsmoker.....	1. 00	1. 00
Cigar only:		
Total.....	1. 09	. 98
No inhalation.....	1. 02	. 91
Some inhalation.....	1. 28	1. 37
Pipe only:		
Total.....	1. 04	. 95
No inhalation.....	. 98	. 87
Some inhalation.....	1. 21	1. 11

Source: Hammond, E. C. (98).

TABLE 14.—*Percentage of British male cigar smokers who reported inhaling a lot or a fair amount by type of product smoked*

Type of product	1968		1971	
	Number of individuals	Percent	Number of individuals	Percent
Cigars only.....	706	23. 0	111	27. 0
Cigars and cigarettes.....	1, 193	42. 0	277	44. 0
Cigars and pipes.....	596	35. 0	109	32. 0
Cigars, cigarettes, and pipes.....	26	52. 0	15	32. 0

Source: Todd, G. F. (93, 94).

tained somewhat higher levels of cigar smoke inhalation than those cigar smokers who had never smoked cigarettes (30 percent).

Todd (93) 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 (table 17).

TABLE 15.—Percentage of individuals reporting inhalation of "almost every puff" of tobacco smoke by current and previous tobacco usage and type of tobacco used

Type of tobacco smoked		Number of patients	Type inhaled	Percentage inhaled	Confidence limits	
Current usage	Previous usage				Lower	Upper
Cigarettes only	Cigarettes only	2,359	Cigarette	74.8	73.1	76.6
Cigars only	Cigars only	649	Cigars	4.5	3.0	6.0
Cigarettes and cigars	Cigarettes and cigars	520	do	20.4	10.5	28.0
Cigars	Cigarettes and cigars	93	do	18.3	9.0	30.0
None	Cigarettes and cigars	186	do	21.5	17.8	24.2
Cigars	Cigarettes only	64	do	17.2	16.0	28.0

Source: Bross, I. D. J., Tidings, J. (14).

TABLE 16.—Percentage of British males who reported inhaling a lot or fair amount of cigar smoke by current and previous tobacco usage and type of tobacco previously smoked (1968)

Type of tobacco smoked		Number of individuals	Type inhaled	Percentage inhaled
Current usage	Previous usage			
Cigarettes only	Cigarettes only	2,586	Cigarette	77.7
Cigars only	Nonsmoker	306	Cigars	18.0
Cigars only	Cigarettes only	321	do	30.0

Source: Todd, G. F. (94).

TABLE 17.—Extent of reported inhalation of cigar smoke by British male cigar smokers who were ex-cigarette smokers in 1968, analyzed by extent of reported inhalation of cigarette smoke when previously smoking cigarettes

Extent of inhaling cigars	Extent of inhaling cigarettes	
	Inhale a lot or fair amount	Inhale a little or not at all
	<i>Percent</i>	<i>Percent</i>
Inhale a lot or fair amount.....	44. 0	5. 0
Inhale a little or not at all.....	56. 0	95. 0
Total	100. 0	100. 0
Sample size.....	244	56

Source: Todd, G. F. (93).

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 18).

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 detailed in the following sections.

TABLE 18.—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 (40).....	1. 00	1. 34	1. 44	-----	1. 97
Best (9).....	1. 00	1. 13	1. 38	-----	2. 06
Hammond (38).....	1. 00	-----	-----	1. 21	1. 76
Kahn (50).....	1. 00	1. 22	1. 25	1. 25	2. 21

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 (13) 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 (32) 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. (60) reviewed a series of 143 cases of cancer of the lip, and Sadowsky, et al. (77) reviewed 571 cases of cancer of the lip. In both studies, a strong association was found between pipe smoking and cancer of the lip. No significant association was found between the use of tobacco in other forms and cancer at this site.

In a study of environmental factors in cancer of the upper alimentary tract, Wynder, et al. (113) found an association between pipe smoking, cigarette smoking, and cancer of the lip. There were only 15 cases of cancer of the lip in this study.

Staszewski (87) examined the smoking habits of 394 men with carcinoma or precancerous lesions of the lips. An association was found between the smoking of pipes and cigars and cancer of the lip, but this was only of doubtful significance. A significant association was found between the use of cigarettes and cancer of the lip.

Keller (51) conducted a study of lip cancers in which he considered a number of factors including histologic types, survival, race, occupations, habits, and associated diseases. A total of 304 patients with primary basal cell or squamous cell carcinoma of the lip and 304 controls from the same hospital matched for age and race were considered in this series. A significant association was found between smoking in all forms and combinations and carcinoma of the lip. It was also found that increasing age and outdoor occupations with exposure to the sun were equally significant factors in the etiology of lip cancer.

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 19 summarizes the results of these retrospective studies.

Oral Cancer

The lips, oral cavity, and pharynx are the first tissues exposed to tobacco smoke drawn in through the mouth. Variations in inhalation during the smoking of various tobacco products result in different patterns of distribution of smoke throughout the respiratory tree. However, the oral cavity and adjacent tissues are the sites most consistently exposed to tobacco smoke. For this reason, differences in inhalation should result in less variation in exposure to tobacco smoke for these sites than for the lower trachea and the lung. The inherent carcinogenicity of pipe, cigar, and cigarette smoke is most reliably compared at those tissue sites where dosage and exposure to tobacco smoke are most nearly equal. 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 (40) 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. All the deaths from cancer of the lip, oral cavity, and pharynx reported by Doll and Hill (26) occurred in smokers. The death rates from cancer at these sites were 0.04 per 1,000 for pipe and cigar smokers, 0.10 per 1,000 for mixed smokers, and 0.05 per 1,000 for cigarette smokers. A fairly detailed analysis of oral cancer was presented by Kahn (50) 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 4.20 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 and 7.76 for smokers of pipes and cigars. Hammond (38) combined cancers of 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.

TABLE 19.—*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					
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Broders (13):		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 (32):		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, et al. (60):		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, et al. (77):		Relative risk.....	1.0	1.1	4.3	2.6	0.4
Cases.....	571	Percent cases.....	8	2	18	6	22
Controls.....	615	Percent controls.....	13	3	7	4	19
Wynder, ¹ et al. (118):		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 (87):		Relative risk.....	1.0			2.1	2.4
Cases.....	394	Percent cases.....	7			12	73
Controls.....	912	Percent controls.....	13			11	61
Keller (51):		Relative risk.....	1.0	1.4	4.0	2.6	
Cases.....	301	Percent cases.....	7	2	6	1	60
Controls.....	265	Percent controls.....	17	4	3	0	53

¹ Percentage based on less than 20 patients. Ratios: relative to cigarette smokers.

These studies are summarized in table 20. 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.

A number of retrospective studies have examined the relationship between smoking in various forms and cancer of the oral cavity. The results of these studies are presented in table 21. Some of the variations in relative risk of developing oral cancer observed in the retrospective studies is probably due to the lack of a uniform definition of oral cancer by anatomical site and the various means used in selecting and defining cases and controls. It appears, however, that a significant risk of developing oral cancer exists for smokers compared to nonsmokers and this risk is similar for smokers of pipes, cigars, and cigarettes.

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 (52, 62, 63, 109) 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.

TABLE 20.—*Mortality ratios for oral cancer in cigar and pipe smokers. A summary of prospective epidemiological studies*

Author, reference	Smoking type					Mixed
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	
Hammond and Horn ¹ (40)	1. 00	5. 00	3. 50	-----	5. 06	-----
Doll and Hill ² (26, 27)	0. 00	-----	-----	0. 80	1. 00	2. 00
Hammond (38)	1. 00	-----	-----	4. 94	³ 9. 90	-----
Kahn (50):						
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 Ratios: relative to cigarette smokers.

³ Mortality ratios for ages 45 to 64 only are presented.

⁴ Excludes pharynx.

Cancer of the Larynx

The larynx is situated at the upper end of the trachea. Because of its proximity to the oral cavity, the larynx probably has a similar exposure to smoke drawn through the mouth as 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. These

TABLE 21.—*Relative risk of oral 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						
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed	
Mills and Porter (65):		Relative risk.....	1.0			7.0	4.1	
Cases.....	124	Percent cases.....	10			55	36	
Controls.....	185	Percent controls.....	38			30	32	
Sadowsky, et al. (77):		Relative risk.....	1.0	2.0	4.4		1.4	2.1
Cases.....	1,136	Percent cases.....	8	4	18		42	28
Controls.....	615	Percent controls.....	13	3	7		53	23
Schwartz, et al. (83):		Relative risk.....	1.0		1.6		1.5	
Cases.....	332	Percent cases.....	16		3		63	
Controls.....	608	Percent controls.....	23	77	3		58	
Wynder, et al. (109):		Relative risk.....	1.0	3.6	6.1		3.0	3.3
Cases.....	543	Percent cases.....	3	20	11		57	8
Controls.....	207	Percent controls.....	10	13	6		63	8
Wynder, et al. (113):		Relative risk.....	1.0	1.7	.9		1.2	1.4
Cases.....	115	Percent cases.....	23	13	12		37	16
Controls.....	115	Percent controls.....	26	9	16		36	13

Wynder, et al. (116):		Relative risk.....	1.0	6.0	-----	4.0	-----
Cases.....	178	Percent cases.....	4	33	-----	45	-----
Controls.....	220	Percent controls.....	16	22	-----	45	-----
Pernu (73):		Relative risk.....	1.0	-----	3.6	-----	2.2 2.9
Cases.....	1,400	Percent cases.....	21	-----	10	-----	59 11
Controls.....	713	Percent controls.....	39	-----	5	-----	50 7
Staszewski (87):		Relative risk.....	1.0	-----	-----	3.5	3.6
Cases.....	383	Percent cases.....	6	-----	-----	13	72
Controls.....	912	Percent controls.....	17	-----	-----	11	61
Keller (52):		Relative risk.....	1.0	3.1	3.8	2.2	3.4
Cases.....	408	Percent cases.....	5	7	4	10	69
Controls.....	408	Percent controls.....	14	6	3	13	56
Martinez (62):		Relative risk.....	1.0	1.7	1.3	-----	1.5 2.3
Cases.....	170	Percent cases.....	8	10	1	-----	39 34
Controls.....	510	Percent controls.....	14	10	2	-----	44 25
Martinez ¹ (63):		Relative risk.....	1.0	2.0	2.8	-----	1.7 2.5
Cases.....	346	Percent cases.....	12	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.

rates are several times the rates 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 (40) 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 (26); however, 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 (50) reported mortality ratios for cancer of the larynx of 10.33 for cigar smokers, 9.44 for pipe and cigar smokers, 7.28 for all pipe and cigar categories combined, and 9.95 for cigarette smokers. No deaths from cancer of the larynx occurred in pipe smokers. Hammond (38) 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. These studies are summarized in table 22.

Several retrospective studies have examined the smoking habits of patients with cancer of the larynx and appropriately matched controls. The small number of pipe and cigar smokers in each study results in relative risk ratios that are quite unstable; however, it appears that pipe and cigar smokers experience a risk of developing cancer of the larynx that is similar to the risk observed among cigarette smokers (table 18).

TABLE 22.—Mortality ratios for cancer of the larynx 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 (40).....	1.00	5.00	3.50	-----	5.06	-----
Doll and Hill ² (26, 27)....	0.00	-----	-----	2.00	1.00	0.60
Hammond (38).....	1.00	-----	-----	3.37	³ 6.09	-----
Kahn (50).....	1.00	10.33	-----	7.28	9.95	-----

¹ Combines data for oral, larynx, and esophagus.

² Ratios relative to cigarette smokers.

³ Only mortality ratios for ages 45 to 64 are presented.

Wynder, et al. (108, 113) distinguished between intrinsic and extrinsic larynx cancers. For smokers the relative risk of developing cancer of the intrinsic larynx was similar to the relative risk of lung cancer whereas the relative risk of developing extrinsic larynx cancer was more like the relative risk of cancer of the upper digestive tract.

Histologic changes of the larynx in relation to smoking in various forms were described by Auerbach, et al. (5). 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 similar percentage of cells with atypical nuclei as cigarette smokers who smoked one to two packs per day. With respect to the proliferation of cell rows in the basal layer of the true vocal cord, the least proportion of cases with eight or more cell rows was found in men who never smoked, and the greatest proportion was found in heavy cigarette smokers. Pipe and cigar smokers had a distribution of cell rows that was comparable to that of cigarette smokers who consumed about a pack a day.

Several retrospective studies have reported an association between the combined use of tobacco and alcohol and cancer of the larynx. A study by Wynder, et al. (108) included some information on pipe and cigar smoking in relation to drinking habits and the development of cancer of the larynx, but because of the limited number of pipe and cigar smoking subjects this relationship could not be adequately determined.

Cancer of the Esophagus

The esophagus is not directly exposed to tobacco smoke drawn into the mouth; however, the esophagus does have contact with that portion of 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 that is 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 suggestion 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 23.—*Relative risk of cancer of the larynx 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					
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Schrek, et al. (81):		Relative risk.....	1.0	0	1.1	2.3	
Cases.....	73	Percent cases.....	14	0	7	80	
Controls.....	522	Percent controls.....	24	10	11	59	
Sadowsky, et al. (77):		Relative risk.....	1.0	2.2	2.3	3.7	4.1
Cases.....	273	Percent cases.....	4	2	5	60	29
Controls.....	615	Percent controls.....	13	3	7	53	23
Wynder, et al. (108):		Relative risk.....	1.0	15.5	27.7	11.1	24.6
Cases.....	209	Percent cases.....	.5	8	5	1	86
Controls.....	209	Percent controls.....	11	10	4	2	74
Wynder, et al. (113):		Relative risk.....	1.0	9.7	4.5	6.3	6.3
Cases.....	60	Percent cases.....	5	17	15	47	17
Controls.....	271	Percent controls.....	24	9	16	36	13
Wynder, et al. (116):		Relative risk.....	1.0	14.5	16.0	22.0	16.0
Cases.....	142	Percent cases.....	1	20	1	62	16
Controls.....	220	Percent controls.....	16	22	1	45	16

Pernu (73):		Relative risk.....	1.0	4.5	8.7	3.2
Cases.....	546	Percent cases.....	7	4	78	4
Controls.....	713	Percent controls.....	39	5	50	7
Staszewski (87):		Relative risk.....	1.0	5.9	50.2	
Cases.....	207	Percent cases.....	5	2	88	
Controls.....	912	Percent controls.....	17	11	61	
Svoboda (90):		Relative risk.....	1.0	2.6	10.0	
Cases.....	205	Percent cases.....	3	3	95	
Controls.....	320	Percent controls.....	22	7	71	
Stell (88):		Relative risk.....	1.0	1.3	2.4	
Cases.....	190	Percent cases.....	11	8	79	
Controls.....	190	Percent controls.....	17	10	50	

In the prospective epidemiological studies, cigar, pipe, and cigarette smokers all had similar mortality ratios from cancer of the esophagus. Hammond and Horn (40) 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. Doll and Hill (26) reported an esophageal cancer mortality ratio of 2.0 for pipe and cigar smokers, 4.8 for mixed smokers, and 1.5 for cigarette smokers. Kahn (50) reported the following mortality ratios for smoking in various forms compared to nonsmokers: cigar only, 5.33; pipe only, 1.99; pipe and cigar, 4.17; all pipes and cigars combined, 4.05; and cigarettes only, 6.17. The results of these prospective studies are summarized in table 24.

Several retrospective investigations have also examined the association between smoking in various forms and cancer of the esophagus. These studies have been summarized in table 25. The evidence suggests 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. (7), who looked for atypical nuclei, disintegrating nuclei, hyperplasia, and hyperactive esophageal glands. A total of 12,598 sections were made from tissues obtained from 1,268 subjects. For each of the parameters investigated, pipe and cigar smokers demonstrated significantly more abnormal histologic changes than nonsmokers; however, these changes were not as severe or as frequent as those seen in cigarette smokers.

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 (12, 62, 63, 107). It appears that smoking in any form in combination with heavy drinking results in especially high rates of cancer of the esophagus.

TABLE 24.—*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 (40)	1.00	5.00	3.50	-----	5.06	-----
Doll and Hill (26, 27)	1.00	-----	-----	2.00	1.50	4.80
Hammond (38)	1.00	-----	-----	3.97	² 4.17	-----
Kahn (50)	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.

TABLE 25.—*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						
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed	
Sadowsky, et al. (77):		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, et al. (113):		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 (73):		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, et al. (84):		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 (107):		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

TABLE 25—Relative risk of cancer of the esophagus 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						
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed	
Bradshaw and Schonland (12):		Relative risk.....	1.0		4.8		2.3	
Cases.....	117	Percent cases.....	15		41		63	
Controls.....	366	Percent controls.....	32		18		58	
Martinez (62):		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 (63):		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.

Lung Cancer

Abundant evidence has accumulated from epidemiological, experimental, and autopsy studies establishing that cigarette smoking is the major cause of 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 26 presents a summary of these prospective studies. 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 (26) reported increased death rates from lung cancer for pipe and cigar smokers with increasing tobacco consumption (table 27). Kahn (50) also demonstrated a dose-response relationship for lung cancer by the amount smoked (table 28).

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, 61, 74, 77). 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 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 Stümpfen, 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.

Several pathologists have reported histologic changes in the bronchial epithelium in relation to smoking in various forms. Knudtson (57) examined the bronchial mucosa of 150 lungs removed at autopsy and correlated the histologic changes noted with the history of smoking, age, occupation, and residence. Specimens obtained from the six cigar and pipe smokers demonstrated basal cell hyperplasia; however, there was no squamous or atypical proliferative metaplasia as is frequently seen in the heavy cigarette smokers.

Sanderud (78) 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 54 percent of the nonsmokers had this abnormality.

Auerbach, et al. (6) examined 36,340 histologic sections obtained from 1,522 white adults for various epithelial lesions including: 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 are compared to those found in nonsmokers and cigarette smokers (table 25). 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.

TABLE 26.—*Mortality ratios for lung cancer deaths in male cigar and pipe smokers. A summary of prospective studies*

Author, reference	Type of smoking					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (40)	1. 00	3. 35	8. 50	-----	23. 12	19. 71
Doll and Hill (26, 27)	1. 00	-----	-----	6. 14	13. 29	7. 43
Best (9)	1. 00	2. 94	4. 35	-----	14. 91	-----
Hammond (38)	1. 00	1. 85	2. 24	1. 97	9. 20	7. 39
Kahn (50)	1. 00	1. 59	1. 84	1. 67	12. 14	-----

TABLE 27.—*Lung cancer death rates for cigar and pipe smokers by amount smoked—Doll and Hill*

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., Hill, A. B. (26).

TABLE 28.—*Lung cancer mortality ratios for cigar and pipe smokers by amount smoked—Kahn*

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. (60).

TABLE 29.—*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					
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Levin, et al. (60):		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, et al. (81):		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 (111):		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 (25):		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 (56):		Relative risk.....	1.0		9.6	29.3	
Cases.....	812	Percent cases.....	.6		2	77	
Controls.....	300	Percent controls.....	18		6	76	
Sadowsky, et al. (77):		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 (110):		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 (74):		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 (65):		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 (66):		Relative risk.....	1.0		2.8	4.5	
Cases.....	484	Percent cases.....	8		13	78	
Controls.....	1,588	Percent controls.....	28		16	57	
Schwartz and Denoix (82):		Relative risk.....	1.0		4.7	13.5	
Cases.....	430	Percent cases.....	1		6	96	
Controls.....	430	Percent controls.....	11		14	78	
Stocks (89):		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 (61):		Relative risk.....	1.0		1.7	8.1	
Cases.....	500	Percent cases.....	2		4	95	
Controls.....	1,839	Percent controls.....	10		15	75	
Pernu (73):		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

TABLE 29.—*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						
		Nonsmoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed	
Wicken (106):		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	30.7	21.8	39.9	31.0	24.7
Cases.....	118	Percent cases.....	2	28	7	58	25	24
Controls.....	524	Percent controls.....	35	19	6	31	17	10
Wynder, et al. (115):		Relative risk.....	1.0			2.0	12.4	
Cases.....	210	Percent cases.....	3			5	92	
Controls.....	420	Percent controls.....	21			15	47	

TABLE 30.—*Changes in bronchial epithelium of male cigar, pipe, and cigarette smokers as compared to nonsmokers*

Group	Number of subjects	Sections with epithelium	Percent sections with epithelial lesions	Percent 3 plus cell rows with cilia	Percent atypical cells present	Total sections	Percent hyperplasia and goblet cells in glands
1st set (none vs. pipe vs. cigarette—matched on 1:1 basis):							
Nonsmoker.....	20	985	21.7	11.2	2.6	1,031	10.3
Pipe only.....	20	924	65.5	38.1	37.0	979	35.9
Cigarette only.....	20	914	96.8	88.6	95.2	982	72.1
2d set (none vs. pipe vs. cigarette—matched on frequency basis):							
Nonsmoker.....	25	1,246	22.9	13.4	.7	1,277	11.5
Pipe only.....	25	1,164	68.7	38.7	38.2	1,247	37.9
Cigarette only.....	25	1,126	96.3	88.7	89.5	1,237	75.5
3d set (none vs. cigar vs. cigarette):							
Nonsmoker.....	35	1,706	27.4	12.7	.8	1,748	15.3
Cigar only.....	35	1,733	90.8	40.0	73.6	1,828	52.5
Cigarette only.....	35	1,526	99.0	92.7	97.8	1,693	80.2

Source: Auerbach et al. (6).

Tumorigenic Activity

The tumorigenic activity of tobacco smoke can be modified in both a quantitative and qualitative sense. Physical or chemical changes in tobacco that result in a reduction of total particulate matter upon combustion of a given quantity of tobacco may result in a reduction of carcinogenic potential. Such factors as tobacco selection, treatment, blending, cut, and additives may quantitatively alter tar production. Wrapper porosity and filtration may also affect tar production.

Quantitative changes in the tumorigenic activity of tobacco tar on a gram-for-gram basis can be produced by the selection and treatment of tobacco, the use of additives or tobacco sheets, or adjustments in the cut and packing density.

Combustion temperature can also produce quantitative changes in the particulate matter of tobacco smoke. Although high-temperature burning produces less particulate matter in the smoke, it appears that tumorigenic components occur in higher concentration when tobacco is pyrolyzed at temperatures higher than 700° centigrade (34).

Cigars, pipes, and cigarettes are similar in that they are smoked orally and have a common site of introduction to the body. The tissues of the mouth, larynx, pharynx, and esophagus appear to receive approximately equal exposure to the smoke of these products. Inhalation causes smoke to be drawn deeply into the lungs and also allows for systemic absorption of certain constituents of tobacco smoke which then can be carried further to other organs.

Pipe tobacco and cigars vary from cigarettes in a number of characteristics that can produce both quantitative and qualitative changes in the total particulate matter produced by their combustion. Experimental evidence suggests that although there is some difference in the amount and quality of tar produced by cigars, this cannot account for the reduced mortality observed in cigar smokers compared to cigarette smokers.

Experimental Studies

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 (117) 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 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° centigrade 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 CAF₁ 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 CAF₁ and the Swiss mice, and the latent period was about 2 months shorter.

Extending these data, Croninger, et al. (20) 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 CAF₁ 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. 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 (53) 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 of the cigarette smoke condensate. Similarly, there was no difference between cigar and cigarette smoke condensates when carcinoma incidences were compared.

Homburger, et al. (45) 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 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 CAF₁ mice three times a week for the lifespan 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 (22) prepared tars from small cigars especially manufactured from a composite blend of cigar tobacco representing small cigar brands smoked in the United Kingdom, cigarettes especially manufactured from the same tobacco used for the cigars described above, and plain cigarettes especially manufactured from a composite blend of flue-cured tobacco representing the major plain cigarette brands smoked in the United Kingdom. The whole tar was diluted to four concentration levels and applied to the shaved backs of female albino mice for their lifespan using four dosing regimens. A statistically significant increase in mouse skin carcinogenicity was shown with the cigar smoke condensate compared with the tars obtained from either flue-cured or cigar tobacco cigarettes. These results are consistent with those of the previously reported investigations.

The effect of curing on carcinogenicity was examined by Roe, et al. (76). Bright tobacco grown in Mexico was either flue-cured or air-cured and bulk fermented. Both flue-cured and air-cured tobaccos were made into cigarettes standardized for draw resistance and were smoked under similar conditions. Condensates from these cigarettes were applied to mouse skin three times each week in an acetone solution. The development of skin tumors was higher in mice treated with the flue-cured condensate than in mice treated with the air-cured condensate ($P < 0.01$). The difference may have been due to the use of equal weights of condensate rather than the use of extracts from an equal number of cigarettes. The air-cured cigarettes produced a greater weight of condensate than did the flue-cured cigarettes. A chemical analysis of the two tobaccos and two condensates revealed only small differences in composition. Evidently air curing of Bright tobacco in the method used is not associated with a loss of reducing sugars.

A more detailed analysis of these experimental studies is presented in table 31.

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.

TABLE 31.—*Tumorigenic activity of cigar, pipe, and cigarette smoke condensates in skin painting experiments on animals*

[Key: A=Method. B=Frequency. C=Duration. D=Material.]

Author, reference	Animal	Activity	Treatment	Number	Percent	
					Papillomas	Carcinomas
Wynder and Wright (117).	CAF ₁ and Swiss mice.	A. Painting shaved skin.	CAF ₁ :			
		B. 3 times a week.	Pipe (cigarette tobacco)-----	30	60	20
		C. Lifespan (24 months).	Cigarette-----	30	30	3
		D. Neutral fraction tar from cigarettes and cigarette tobacco smoked in pipes.	Swiss: Pipe (cigarette tobacco)----- Cigarette-----	30 30	63 63	50 33
Croninger, et al. (20).	Female Swiss mice.	A. Painting shaved skin.	Cigar, nicotine free (1:1)-----	46	65	41
		B. 3 times a week.	Pipe, nicotine free (1:1)-----	45	71	44
		C. Lifespan.	Cigar (1:2)-----	78	33	18
		D. Whole tar diluted in acetone.	Pipe, nicotine free (1:2)-----	89	30	16
			Cigarette (1:1)-----	86	47	37
Acetone controls-----	23	0	0			
Kensler (53)	Swiss mice-----	A. Painting shaved skin.	Cigar tar (J) 100 mg. per week--	100	42	41
		B. 3 times a week.	Cigarette tar (G) 100 mg. per week.	100	40	28
		C. Lifespan.				
		D. Whole tar diluted in acetone.	Cigarette tar (E) 100 mg. per week.	100	34	34

TABLE 31.—*Tumorigenic activity of cigar, pipe, and cigarette smoke condensates in skin painting experiments on animals—Continued*

[Key: A=Method. B=Frequency. C=Duration. D=Material.]

Author, reference	Animal	Activity	Treatment	Number	Percent	
					Papillomas	Carcinomas
Homburger, et al. (45).	CAF ₁ mice.....	A. Painting shaved skin.	Cigar tobacco cigarettes ¹ 65 mg. per week.	100	37.5	19
		B. 2 to 3 times a week.	Pipe tobacco cigarettes ¹ 64 mg. per week.	100	23	20
		C. Lifespan (2 years).	Cigarettes ¹ 62 mg. per week.....	100	15	23
		D. Whole tar diluted 50 per cent in acetone.	Acetone controls.....	100	0	0
Davies and Day (22).	Female albino mice.	A. Painting shaved skin.	Cigars, small 83 mm. long 150 per week.	144	44	27
		B. Varied.	Cigar tobacco cigarettes 150 per week.	72	32	14
		C. 116 weeks.	Cigarettes 150 per week.....	144	28	13
		D. Whole tar in 150 mg. acetone.				
Roe, et al. (76).	Female Swiss mice.	A. Painting shaved skin.	Flue-cured Bright tobacco 180 mg. per week.	400	52	30
		B. 3 times a week.	Air-cured Bright tobacco 180 mg. per week.	400	68	23
		C. Lifespan.	Acetone controls 0.75 cc. per week.	400	1.3	0.5
		D. Whole tar diluted in acetone.				

¹ Cigar, pipe, and cigarette tobacco smoked as cigarettes at similar combustion temperatures.

CARDIOVASCULAR DISEASES

The majority of deaths in the United States each year are due to cardiovascular diseases. Cigarette smoking has been identified as a major risk factor for the development of coronary heart disease (CHD). However, 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 32 summarizes the major prospective epidemiological investigations that examined the association of smoking in various forms and total cardiovascular diseases, coronary heart disease, and cerebrovascular disease. Doll and Hill. (28), Best (9), and Kahn (50) 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. (49) in the Western Collaborative Group Study of coronary heart disease, 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 disease was seen among the pipe and cigar smokers in the younger age groups. Shapiro, et al. (85), in a study of the health insurance plan (HIP) population, reported incidence rates for myocardial infarction, 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 (47) 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. (30) 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 (64), Villiger and Heyden-Stucky (104), Schimmler, et al. (80), and Hood, et al. (46) 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 (86) reported lower rates of coronary heart disease in all smoking categories than were found in nonsmokers.

Van Buchem (103) and Dawber, et al. (23) 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 (91) and Dawber, et al. (23) 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.

In an experimental study using anesthetized dogs, Kershbaum and Bellet (54, 55) examined the effects of inhaled and noninhaled cigarette, cigar, and pipe smoke on serum free fatty acid levels and urinary catecholamine and nicotine excretion. In this study, inhalation of tobacco smoke from all these sources resulted in similar increases in serum free fatty acids and in catecholamine and nicotine excretion.

TABLE 32.—*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 (40).	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 (26, 27).	Cardiovascular total.	1.00	-----	-----	0.99	1.26	1.13
	Coronary-----	1.00	-----	-----	.94	1.23	1.18
	Cerebrovascular-----	1.00	-----	-----	.95	1.13	.97
Best (9)-----	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 (38).	Cardiovascular total.	1.00	-----	-----	1.06	1.90	-----
	Coronary-----	1.00	1.35	1.19	-----	1.84	1.58
	Cerebrovascular-----	1.00	-----	-----	1.09	1.41	1.40
Kahn (50)-----	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.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic bronchitis and pulmonary emphysema account for most of the morbidity and mortality from chronic respiratory disease in the United States. Cigarette smokers have higher death rates from these

diseases and have more pulmonary symptoms and impaired pulmonary function than nonsmokers. Cigarette smokers also have more frequent and more severe respiratory infections than nonsmokers. The relationship between smoking pipes and cigars and these diseases is summarized in this chapter. The major prospective epidemiological studies are summarized in table 33.

In a retrospective study of 1,189 males and matched controls in Northern Ireland, Wicken (106) 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 34.

Only a few studies have examined pulmonary function in pipe and cigar smokers. There appears to be little difference in pulmonary function values for pipe and cigar smokers as compared to nonsmokers (table 35).

Naeye (67) 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. (8). 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.

Tobacco smoke has been shown experimentally to have a ciliostatic 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 (21) 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 smoke is not necessarily correlated to the level of one or several of the substances found in the smoke.

Passey, et al. (70, 71, 72) studied the effect of smoke from flue-cured cigarette tobacco cigarettes and air-cured cigar tobacco cigarettes on the respiratory system of rats. In two separate but similar experiments, a total of 48 animals were exposed to English cigarette tobacco smoke, 48 were exposed to air-cured cigar tobacco smoke, and 12 were exposed to an air-cured Burley tobacco smoke. The rats in groups were exposed to the specific smoke in a smoke-filled cabinet. Animals exposed to the smoke from air-cured tobaccos remained healthy throughout the experiments, even at high levels of smoke exposure. The three deaths that occurred within this group were from nonrespiratory causes. In both experiments, the rats exposed to cigarette tobacco smoke began to die within 1 or 2 months, and in each experiment most of the animals died within a week or two of the first deaths. At autopsy the rats exposed to flue-cured tobacco smoke on gross examination were found to have greatly enlarged lungs, the trachea was often full of mucus, and there was evidence of pneumonia. On microscopic examination it was found that the trachea and bronchi contained purulent cellular exudates, evidence of metaplastic changes, an absence of cilia, and goblet cell hyperplasia. Typically, the cause of death was a lobar or bronchopneumonia. The author concluded that, "the smokes of flue-cured tobaccos are more dangerous to man and to animals than those of air-cured tobaccos."

Unfortunately, few details were published concerning the method used to expose the animals to the different types of smoke. The frequency and duration of exposure were not specified, and the extent of actual inhalation of smoke by the different groups of rats was either not determined or not reported. It is also difficult to determine the effect of smoke exposure on the frequency and severity of respiratory infections when animals are exposed to smoke in groups where common exposure occurs. The rat strain used was not identified, but it was noted that animals appeared to suffer from an endemic rat bronchiectasis. It is not known to what extent epidemics of respiratory infections occurred among these animals. Because of these difficulties, no firm conclusion can be drawn concerning the effect of smoking flue-cured or air-cured tobaccos on the incidence of respiratory infections in rats.

TABLE 33.—*Mortality ratios for chronic obstructive pulmonary 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	Ciga-rette only Mixed
Hammond and Horn (40).	COPD total	1.00	1.29	1.77	2.85	
	Emphysema					
	Bronchitis					
Doll and Hill (26, 27).	COPD total					
	Emphysema					
	Bronchitis	1.00			4.00	7.00 6.67
Best (9)	COPD total					
	Emphysema	1.00	3.33	.75	5.85	
	Bronchitis	1.00	3.57	2.11	11.42	
Hammond (38)	COPD total					
	Emphysema	1.00			1.37	6.55
	Bronchitis					
Kahn (50)	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.

TABLE 34.—*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 (10)---	Parents of 59 families.	Cough.....	32	32	48	-----
		Sputum production.	24	15	20	-----
		Chest illness.....	5	4	5	-----
Edwards, et al. (33).	1,737 male outpatients.	Chronic bronchitis.	17	19	31	14
Ashford, et al. (4).	4,014 male workers in 3 Scottish collieries.	Bronchitis.....	10	35	21	37
		Pneumoconiosis....	11	34	14	2
Bower (11)---	95 male bank employees.	Cough.....	0	0	29	-----
		Sputum production.	8	15	33	-----
		Wheeze.....	8	31	33	-----
		Chest illness.....	15	54	40	-----
Wynder, et al. (114).	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, et al. (24).	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, et al. (18).	4,379 twin pairs, all U.S. veterans.	Cough.....	4	7	17	-----
		Prolonged cough...	2	4	11	-----
		Bronchitis.....	2	3	10	-----
Rimington (75).	41,729 male volunteers.	Chronic bronchitis.	5	9	17	-----

TABLE 34.—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, et al. (19).	670 male telephone employees.	Persistent cough	10	16	41	-----
		Persistent sputum.	13	20	42	-----
		Dyspnea	33	39	44	-----
		Chest illness in past 3 years.	14	18	20	-----
Lefcoe and Wonnacott (59).	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	-----

¹ Figures for pipe only.

TABLE 35.—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, et al. (4).	4,014 male workers in 3 Scottish collieries.	FEV _{1.0}	3.39	¹ 2.59	3.14	2.62
Goldsmith, et al. (37).	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, et al. (19).	670 male telephone employees.	FEV _{1.0}	3.12	3.26	2.82	-----
Lefcoe and Wonnacott (59).	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.

GASTROINTESTINAL DISORDERS

Cigarette smokers have an increased prevalence of peptic ulcer disease and a greater peptic ulcer mortality ratio than is found in nonsmokers. These relationships are stronger for gastric ulcer than for duodenal ulcer. Cigarette smoking appears to reduce the effectiveness of standard peptic ulcer treatment regimens and slows the rate of ulcer healing. 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. Table 31 presents the mortality ratios for ulcer disease in cigar and pipe smokers as reported in the prospective epidemiological studies.

Retrospective or cross-sectional studies by Trowell (95), Allibone and Flint (2), Doll, et al. (29), and Edwards, et al. (33) contain data on ulcer disease in pipe smokers as well as cigarette smokers. No association was found between pipe smoking and ulcer disease in these investigations.

TABLE 36.—Mortality ratios for peptic ulcer disease in male cigar and pipe smokers. Summary of prospective studies

Author, reference	Illness	Type of smoking					
		Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
Hammond and Horn (40).	Duodenal ulcer.....	1.00	0.25	1.67	2.16		
Doll and Hill (26, 27).	Gastric ulcer.....	1.00			4.00	7.00	5.30
Hammond (38)	Gastric ulcer.....	1.00			2.04	2.95	
	Duodenal ulcer.....	1.00			.92	2.86	
Kahn (50)	Gastric ulcer.....	1.00	2.90	2.84	2.48	4.13	
	Duodenal ulcer.....	1.00	1.58	1.59	1.39	2.98	

Little Cigars

In the past year, several new brands of little cigars (weighing 3 pounds or less per 1,000) have appeared on the national market. These cigarette-sized products are manufactured, packaged, advertised, and sold in a manner similar to cigarettes. Little cigars enjoy several legal advantages over cigarettes: They have access to television advertising; they are taxed by the Federal Government and by most States, at much lower rates than cigarettes, resulting in a significant price advantage;

and they do not carry the warning label required on cigarette packages and in cigarette advertising. A market appears to be developing for these products, as there has recently been a sharp increase in the shipment of little cigars destined for domestic consumption (table 37).

It is important to estimate the potential public health impact of these little cigars. An adequate epidemiological evaluation of the effect of little cigar smoking on health could take 10 or 15 years and is probably an impractical consideration; however, a review of the epidemiological, autopsy, and experimental data concerning the health consequences of cigarette, pipe, and cigar smoking summarized in this and previous reports is helpful in considering the potential impact on health of smoking little cigars. An analysis of the chemical constituents suggests that both cigarettes and cigars contain similar compounds in similar concentrations. Two exceptions are reducing sugars, which are not found in quantity in the fermented tobaccos commonly used in cigars, and the pH of the inhaled smoke. The pH of the smoke from U.S. commercial cigarettes is below 6.2 from the first to the last puff, whereas the smoke from the last half of a cigar may reach as high as pH 8 to 9. With increasing pH, nicotine is increasingly present in the smoke as the free base. Skin painting experiments in mice indicate that tumor yields with cigar or pipe "tars" are nearly identical with those obtained with cigarettes "tars". In addition, the epidemiological data suggest that depth of inhalation probably accounts for the fact that cigarettes are so much more harmful than cigars and pipes in contributing to the development of lung cancer, coronary heart disease, and nonneoplastic respiratory disease. For such diseases as cancer of the oral cavity, larynx, and esophagus, where smoke from cigars, pipes, and cigarettes is available to the target organ at comparable levels, the mortality ratios are very similar for all three forms of tobacco use. Several factors, including "tar," nicotine, and the pH of the smoke, probably operate to influence inhalation patterns of smokers. The relative contribution of individual factors to the inhalability of a tobacco product has not been determined.

Smoking those brands of little cigars which can be inhaled by a significant portion of the population in a manner similar to the present use of cigarettes would probably result in an increased risk of developing those pulmonary and cardiovascular diseases which have been associated with cigarette smoking. On the other hand, smoking those little cigars which are used like most large cigars whereby the smoke is rarely inhaled would probably result in lower rates of those pulmonary and cardiovascular diseases than would be found among cigarette smokers.

Only a limited analysis is available comparing the chemical compounds found in little cigars, cigarettes, and large cigars. The FTC analyzed the tar and nicotine content of all the little cigars (34) and cigarettes (97) currently available on the market. Little cigars have

generally a higher "tar" and nicotine level than cigarettes, although considerable overlap results in some little cigar brands having "tar" and nicotine levels comparable to those of some brands of cigarettes (figs. 4 and 5). Hoffmann and Wynder (44) recently compared three brands of little cigars with an unfiltered cigarette, a filtered cigarette, and a large cigar. They measured a number of smoke constituents, including: "tar," nicotine, carbon monoxide, carbon dioxide, reducing sugars, hydrogen cyanide, acetaldehyde, acrolein, pyridines, phenols, benz(a)anthracene, and benzo(a)pyrene (table 32). Cigarette A was the Kentucky reference cigarette, cigarette B was a popular brand of filter cigarette. Cigar A was an 85 mm. little cigar, cigar B was an 85 mm. little cigar, cigar C was a 95 mm. small cigar, and cigar D was a 112 mm. popular brand of medium sized cigar.

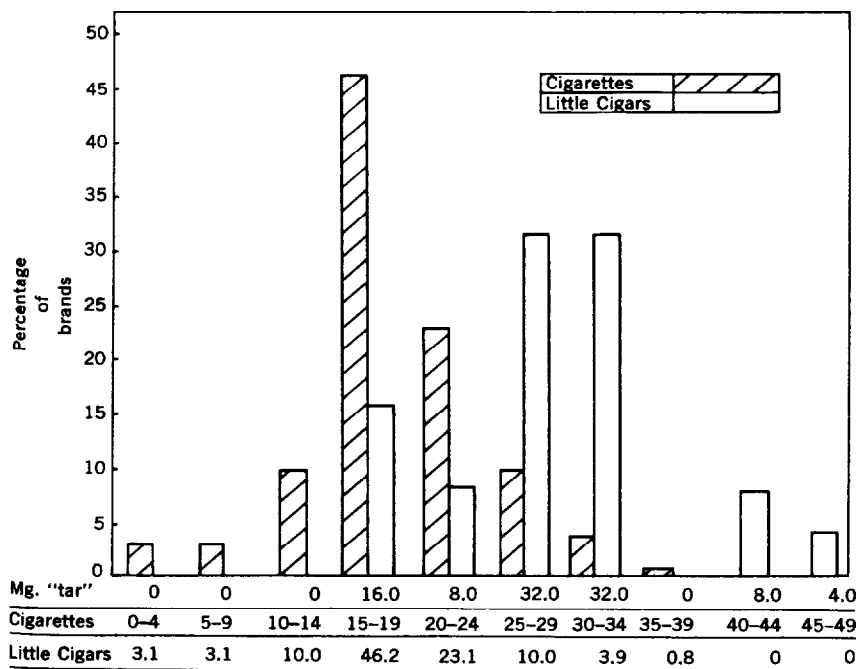
The smoke pH was analyzed puff by puff (table 39). Cigarette smoke was found to be acidic (pH less than 7) for the entire cigarette. The smoke from little cigars became alkaline only in the last puff or two, whereas about the last 40 percent of the puffs from the larger cigar were alkaline. Although the pH of the total condensate obtained from cigarettes is usually acidic and the total condensate obtained from cigars is usually alkaline, the above data indicate that smoke pH of tobacco products changes during the combustion process. Smoke from large cigars may be acidic during the first portion of the smoke and not become alkaline until the last half of the cigar is smoked.

Brunnemann and Hoffmann (15), using the same techniques described above, examined the effect of 60 leaf constituents on smoke pH. For several varieties of cigarette tobacco, they found a high correlation between the total alkaloid and nitrogen content and smoke pH. Stalk position also affected smoke pH. Tobacco leaves near the top of the plant, which contain high levels of tar and nicotine, yielded a smoke with a much higher pH than leaves lower on the plant. At present it is not known to what extent these factors influence the pH of the smoke of tobaccos commonly used in cigars or how these kinds of pH changes influence the inhalability of tobacco smoke.

The inhalation of smoke, however, appears to be the most important factor determining the impact a cigar will have on overall health. Those physical and chemical characteristics of a tobacco product which most influence inhalation of tobacco smoke have not been accurately determined. Nevertheless, it appears likely that the smoke of some brands of cigars may be compatible with inhalation by a significant portion of the smoking population, since: (a) Little cigars have tar and nicotine levels which, in some brands, are similar to the levels found in cigarettes, and (b) the pH of the smoke of some little cigar brands is acidic for the major portion of the little cigar and becomes alkaline only in the last puff or two.

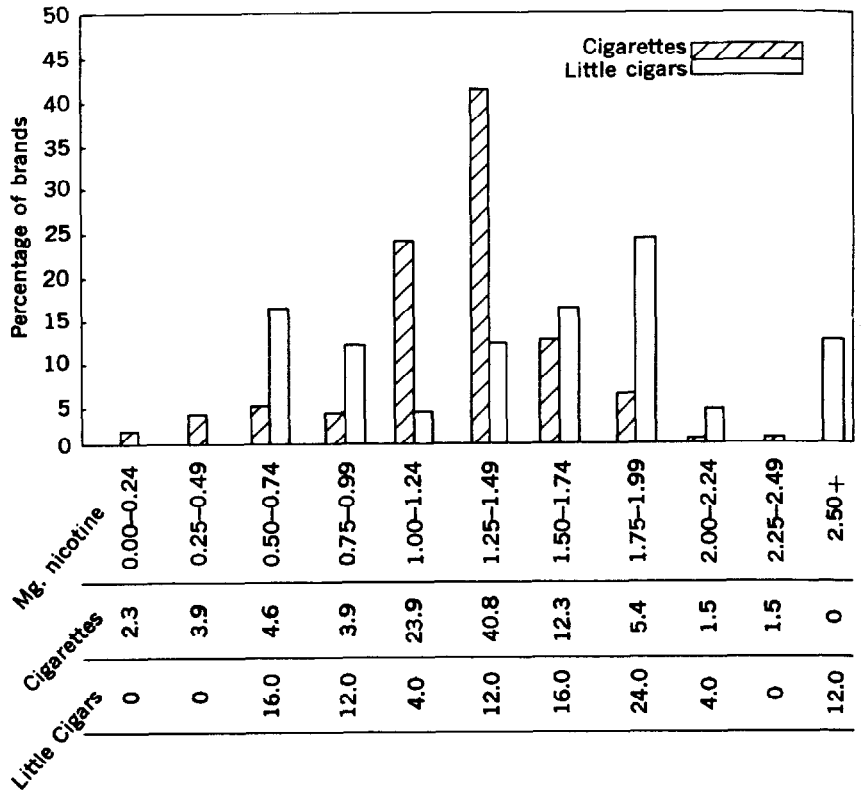
It is reasonable to conclude that smoking little cigars may result in health effects similar to those associated with smoking cigarettes if little cigars are smoked in amounts and with patterns of inhalation similar to those used by cigarette smokers, for the reasons cited above, and these additional reasons: (a) In those little cigars for which preliminary data are available, the concentrations of carbon monoxide, hydrogen cyanide, acetaldehyde, acrolein, pyridine, phenol, and polycyclic hydrocarbon levels are comparable to those found in cigarettes; (b) cigarette smokers who switch to cigars appear to be more likely to inhale cigar smoke than cigar smokers who have always smoked cigars (14); and (c) cigarette smokers who switch to little cigars may be inclined to use them as they did cigarettes because of the physical similarities between the little cigars and cigarettes, including their size and shape, the number in a package, the burning rate, and the time it takes to smoke them.

Figure 4.—Percent distribution of 130 brands of cigarettes and 25 brands of little cigars by "tar" content.



SOURCE: U.S. Department of Health, Education, and Welfare (97) and Federal Trade Commission (34).

Figure 5.—Percent distribution of 130 brands of cigarettes and 25 brands of little cigars by nicotine content.



SOURCE: U.S. Department of Health, Education, and Welfare (97) and Federal Trade Commission (34).

TABLE 37.—*Shipment of small and large cigars destined for domestic consumption (1970, 1971, 1972)*

Year	1970	1971	1972
Small cigars			
January.....	58,328,520	85,753,780	123,477,550
February.....	63,431,580	72,092,205	179,817,839
March.....	85,881,860	46,542,800	198,165,593
April.....	101,613,500	59,059,920	125,335,740
May.....	81,093,180	93,237,473	159,334,565
June.....	82,471,120	94,560,140	180,582,243
Subtotal.....	472,819,760	451,246,318	966,713,530
July.....	62,143,140	70,332,500	127,713,320
August.....	68,220,365	127,709,310	670,936,869
September.....	79,101,045	95,027,340	422,534,705
October.....	90,752,880	109,567,900	708,116,830
November.....	64,290,600	106,666,107	551,326,888
December.....	63,806,010	123,809,553	485,587,014
Subtotal.....	428,314,040	633,112,710	2,966,215,626
Yearly total.....	901,133,800	1,084,359,028	3,932,929,156
Large cigars			
January.....	581,742,001	573,039,120	534,565,488
February.....	595,249,522	586,810,844	562,414,577
March.....	629,977,375	665,998,099	654,827,796
April.....	652,800,200	655,850,213	554,242,048
May.....	748,040,796	670,064,933	719,489,529
June.....	644,539,031	692,436,529	578,501,068
Subtotal.....	3,852,348,925	3,844,199,738	3,604,040,506
July.....	647,397,547	619,838,386	520,873,339
August.....	673,082,971	662,970,148	682,331,630
September.....	721,561,449	680,476,418	594,843,957
October.....	797,601,253	679,420,968	693,150,668
November.....	696,526,464	742,948,802	650,746,540
December.....	596,244,159	516,879,415	437,429,996
Subtotal.....	4,132,413,843	3,902,534,137	3,579,356,130
Yearly total.....	8,084,762,768	7,746,733,875	7,183,396,636

Source: U.S. Department of the Treasury (101).

TABLE 38.—Selected compounds in mainstream smoke

Smoke compound	Cigarette A (nonfilter)	Cigarette B (filter)	Little cigar A	Little cigar B	Small cigar C
"Tar", milligram per cigarette...	36.1	20.3	17.4	31.8	40.6
Nicotine, milligram per cigarette...	2.7	1.4	.6	1.8	3.1
Carbon monoxide, volume percent.....	4.6	4.5	5.3	11.1	7.7
Carbon dioxide, volume percent...	9.4	9.6	8.5	13.2	12.7
Reducing sugars, percent of tobacco weight.....	9.3	7.9	1.5	2.9	2.7
Hydrogen cyanide, microgram per cigarette.....	536.0	361.0	381.0	697.0	1,029.0
Acetaldehyde, microgram per cigarette.....	770.0	774.0	630.0	1,238.0	1,150.0
Acrolein, microgram per cigarette.....	105.0	71.0	41.0	54.0	66.0
Total pyridines, micrograms per cigarette.....	82.8	27.3	58.0	85.3	80.3
Phenol, microgram per cigarette...	124.2	33.0	35.1	63.4	94.1
Benz(a)anthracene, nanogram per cigarette.....	74.0	31.0	34.0	25.0	39.0
Benzo(a)pyrene, nanogram per cigarette.....	47.0	20.0	18.0	22.0	30.0

Source: Hoffmann, D., Wynder, E. L. (44).

TABLE 39.—The pH of the mainstream smoke of selected tobacco products

[Numbers in parentheses indicate number of last puff.]

Average pH	Cigarette A (nonfilter)	Cigarette B (filter)	Little cigar A	Little cigar B	Small cigar C	Cigar D
3d puff.....	6.19	6.15	6.44	6.55	6.53	6.47
5th puff.....	6.14	6.12	6.34	6.46	6.49	-----
7th puff.....	6.09	6.01	7.03	6.51	6.56	-----
9th puff.....	6.02	5.83	-----	6.98	6.59	6.27
13th puff....	-----	-----	-----	-----	-----	6.39
18th puff....	-----	-----	-----	-----	-----	6.41
23d puff....	-----	-----	-----	-----	-----	6.81
28th puff....	-----	-----	-----	-----	-----	7.22
33d puff....	-----	-----	-----	-----	-----	7.53
38th puff....	-----	-----	-----	-----	-----	7.78
Last puff....	5.96(11)	5.76(10)	7.73 (8)	7.25(10)	7.11(11)	7.96(43)

Source: Hoffmann, D., Wynder, E. L. (44).

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 these rates are 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 five cigars a day and the typical pipe smoker smokes less than 20 pipefuls a day. Most pipe and cigar smokers report that they do not inhale the smoke. Those who do inhale, inhale infrequently and only slightly. As a result, the harmful effects of cigar and pipe smoking appear to be largely limited to increased death rates from cancer at 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. Although these are serious forms of cancer, they account for only about 5 percent of the cancer mortality among men.

Coronary heart disease, lung cancer, emphysema, chronic bronchitis, cancer of the pancreas, and cancer of the urinary bladder are diseases which are clearly 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 issue 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.

Available data on the chemical constituents of cigar, pipe, and cigarette smoke suggest that there are marked similarities in the composition of these products. 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 that little difference exists 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.

One must conclude 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. Nevertheless, changes in patterns of usage that would bring about increased exposure either through increased individual use of cigars and pipes or increased inhalation of pipe and cigar smoke have the potential of producing risks not unlike those now incurred by cigarette smokers. Mechanical or chemical modifications of pipe tobacco and cigars that would result in a smoke more compatible with inhalation could have this effect.

Pipe and Cigar References

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CHAPTER 7

Exercise Performance

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Introduction

Although it has long been held by athletes and coaches that cigarette smoking is associated with "shortness of wind" and impaired performance, until recently there has been little scientific evidence to support this view. In the past few years, a variety of studies have appeared dealing with the effect of cigarette smoking on the response of man to exercise. The following is a review of these studies.

Age, sex, training, health, weight, and other factors are known to influence exercise performance. Because most of the investigations were carried out in healthy, young male volunteers, the groups were quite comparable with regard to age, sex, and health; however, weight, training, and other factors were often inadequately controlled. Furthermore, problems in study design and statistical analysis limit the value of several of these studies.

Many forms of exercise were performed in these experiments, including: pedaling a bicycle ergometer, running on a treadmill, running on a track, swimming, step climbing, gripping a hand dynamometer, and doing several different exercise activities as part of a battery of tests. Small to maximum amounts of work were carried out in the various studies reviewed.

Studies of Smokers

Most of the studies of habitual cigarette smokers followed a similar format with respect to smoking: (*a*) The subjects refrained from smoking for a few hours prior to testing, and (*b*) two test runs were performed, one without smoking and one in which smoking immediately preceded the exercise or was incorporated with the exercise protocol.

Several investigators (*1, 15, 28*) studied the effect of smoking on maximum grip strength. Willgoose (*28*) reported a greater mean percent recovery of grip strength after the nonsmoking trial than after the smoking trial. Kay and Karpovich (*15*) and Anderson and Brown (*1*) all followed a protocol similar to that of Willgoose except that they randomized the smoking and nonsmoking trials, and substituted

a "placebo" cigarette for the nonsmoking trial. In neither of these studies were statistically significant differences observed between the grip scores for the smoking and nonsmoking trials.

Reeves and Morehouse (24) administered a battery of tests to 15 college students. The tests were: A tapping test, a strength test, a jumping test, and the short form of the Harvard step test. No statistically significant differences in performance were noted under conditions of smoking or nonsmoking.

A total of 32 college students from intermediate swimming classes abstained from smoking for 15 minutes, 2 hours, and 12 hours in a study conducted by Pleasants, et al. (23). Following the abstinence, they swam distances of 100 and 200 yards. Although actual swimming times were not published, the authors reported no statistically significant differences between the mean swimming times after the different periods of abstinence for either distance.

In 1946, Juurup and Muido (13) carried out several experiments in which three young cigarette smokers exercised on a Krogh's bicycle ergometer. Smoking was found to increase the pulse rate at rest as well as during exercise. Although the effect was less consistent than on the heart rate, smoking was also associated with elevated blood pressure. Smoking had no effect on oxygen consumption. Henry and Fitzhenry (12), in 1949, using the bicycle ergometer, also found that smoking exerted no effect on oxygen consumption. In the same year, Karpovich and Hale (14) studied bicycle ergometer performance in eight young men. In all subjects, the average riding time was better in nonsmoking tests than in smoking tests; however, the results were statistically significant for only three of the eight subjects.

Kerrigan, et al. (16) more recently measured direct arterial blood pressure, heart rate, and cardiac output in 25 habitual smokers at rest and after exercise. Smoking two cigarettes produced statistically significant ($P < 0.01$) increases in cardiac index, heart rate, and arterial mean pressure compared to the immediately preceding control period. Exercise after smoking resulted in an increase in cardiac index over either the resting period or the exercise period which followed abstinence; the resultant cardiac index appeared to be approximately the sum of the exercise and smoking effects. Exercise tests preceded by smoking were also associated with significantly higher ($P < 0.01$) and more prolonged elevations of blood pressure than those not preceded by smoking.

In the study by Goldbarg, et al. (11) of nine habitual smokers performing submaximal exercise on a bicycle ergometer, cardiovascular responses were measured via pulmonary and subclavian artery catheters. At rest, after smoking, the mean cardiac index and mean heart rate increased. During successively increasing levels of exercise, the heart rate was greater and stroke index lower than values for

comparable work before smoking. The net effect of smoking was to decrease the efficiency of the heart during exercise in the upright position by causing a smaller stroke volume and a higher heart rate.

Rode and Shephard (26) investigated near maximal treadmill exercise performance in six habitual smokers. A 1-day abstinence from cigarette smoking was associated with a 13- to 79-percent decrease in the oxygen cost of breathing. Abstinence was also followed by a slowing of the heart rate and a decrease in expiratory minute volume after exercise.

The study of Krumholz, et al. (18) is different from those cited previously in that bicycle ergometer exercise performance was measured in habitual smokers both before and after 3 to 6 weeks of abstinence. Among the 10 subjects who abstained from smoking for 3 weeks, there was a statistically significant ($P < 0.05$) decrease in heart rate, oxygen debt, and ratio of oxygen debt to total increase in oxygen uptake produced by the 5 minutes of exercise.

Using a "double 9-inch progressive step test" Rode and Shephard (25) studied several hundred participants of a smoking withdrawal clinic at the time of entry and at a 1-year followup. Among those who returned for the followup and who gave up smoking, absolute aerobic power increased insignificantly; however, the relative aerobic power diminished in both sexes among those who quit smoking because of the weight gain experienced.

Studies Comparing Smokers to Nonsmokers

Athletic Performance

In 1968 Cooper, et al. (6) evaluated 419 airmen during their initial 6 weeks on active duty in the USAF. A 12-minute maximum running test was performed at least 1 hour after cigarette smoking. The mean distance covered in 12 minutes by the nonsmokers was significantly greater ($P < 0.05$) than that covered by the smokers at the beginning, the middle, and the end of training. All categories of smokers and nonsmokers improved their performance at the end of training; however, the maximum change in performance of those smoking 10 to 30 cigarettes per day was significantly ($P < 0.001$) less than that of nonsmokers.

David (7) administered a battery of tests to 88 military personnel, aged 19 to 39 years. A 1-mile run was included in the testing, and cigarette smoking was associated with a significant decrease in performance in this event.

Some 45 special forces soldiers were investigated at sea level and 13,000 feet above sea level by Fine (8). The subjects were randomly assigned to a placebo group or an acetazolamide treated group. Cigarette smoking was positively correlated to decrements in 600-yard running performance from sea level to altitude in both groups.

Pleasants (22) studied 106 students from intermediate university swimming classes. Swimming times were measured for 100- and 200-yard distances before and after training and for 800-yard distances after training. The mean swimming times of nonsmokers were less than those of smokers in six of seven listed categories, but these differences were not statistically significant.

Bicycle Ergometer Performance

Chevalier, et al. (5) investigated cardiovascular parameters in 32 young physicians after a standard 5-minute ergometer test. Oxygen debt accumulation among smokers was significantly ($P < 0.01$) greater than among nonsmokers. The heart rate at rest and 3 minutes after exercise was significantly ($P < 0.02$) faster in smokers than in nonsmokers.

Using a 5-minute ergometer test, 18 housestaff physicians, half of whom smoked, were investigated by Krumholz, et al. (17). They noted the following: Oxygen debt accumulation after exercise was significantly ($P < 0.02$) greater in smokers than non-smokers, the ratio of the oxygen debt to total increased oxygen uptake during exercise was significantly ($P < 0.001$) greater in smokers than in nonsmokers, and the diffusing capacity at rest and with exercise was significantly ($P < 0.05$) decreased in smokers compared to nonsmokers.

Kerrigan, et al. (16) studied cardiovascular parameters in smokers and nonsmokers at rest, during, and after a 5-minute bicycle ergometer ride. Cardiac index and blood pressure values obtained during exercise performed immediately after smoking were greater than those found in nonsmokers performing the same exercise. Similarly, heart rate and blood pressure remained elevated for longer periods in those who exercised immediately after smoking than in nonsmokers performing the same task.

Aerobic capacity scores were examined in 60 university student volunteers by Peterson and Kelley (20). Subjects worked at submaximal levels on a bicycle ergometer before, during, and after a training program. At all of these intervals, nonsmokers had significantly ($P < 0.05$) higher mean aerobic capacity scores than smokers. Both groups increased their aerobic capacity during training but nonsmokers consistently performed better throughout training.

Treadmill Performance

In 1960 Blackburn, et al. (4) carried out several measurements of cardiovascular function after different amounts of treadmill exercise were performed by 233 professional men, 159 university students, and 414 railroad workers. The differences between the smokers and nonsmokers were of small magnitude. Basal oxygen consumption was slightly higher in smokers than in nonsmokers. Also, resting pulse rates were higher in smokers of most groups.

Cooper, et al. (6) studied 47 out of 419 airmen with treadmill testing. Cardiopulmonary indices measured on the treadmill, including maximum indices, were comparable in smokers and nonsmokers except for a significant ($P < 0.01$) reduction in the maximum minute volume among the smokers.

A total of 277 prospective Canadian firemen performed the Balke-Ware test of work capacity in treadmill studies carried out by Glassford and Howell (10). The mean performance scores of nonsmokers were significantly ($P < 0.01$) greater than those of smokers.

The effect of vitamin C supplementation on treadmill exercise performance was investigated in 40 male volunteers by Bailey, et al. (3). Significant differences in oxygen utilization and ventilatory function between smokers and nonsmokers were noted in only two of the 24 separate analyses of variance performed.

Maximal oxygen intake during treadmill exercise was examined by McDonough, et al. (19) in 86 healthy, middle-aged male volunteers. Cigarette smoking was one of six variables which together provided a multiple correlation coefficient of 0.73.

Performance in Other Tests of Fitness

When physical fitness tests were administered to 88 military personnel by David (7), cigarette smoking was found to be associated with a significant ($P < 0.001$) decrease in performance in the dodge and jump test, and a significant ($P < 0.02$) decrease in performance in the crawling test.

Using a step test, a breath holding test, and an ergometer test, Franks (9) examined 58 middle-aged men. Nonsmokers were able to hold their breath longer and had greater vital capacity residual after the step test than the smokers.

In 1971, Wysokinski (29) studied 200 young Polish soldiers using Letunov's test which included 20 knee-bending exercises, a fast run for 20 seconds, and a run for 3 minutes. Cigarette smoking was associated with a significant ($P < 0.01$) reduction in the vital capacity and a

marked rise in the pulse rate at rest and after exercise. Intense exercise also caused a greater rise in the systolic blood pressure in smokers than in nonsmokers.

Discussion

Most of the studies in habitual cigarette smokers compared exercise performance in "smoking" and "nonsmoking" runs after only a few hours of abstinence. In some studies, smoking adversely affected performance (11, 13, 14, 16, 18, 26, 28), while in others it did not (1, 12, 15, 23, 24). Some of these apparently discrepant results are due to differences in methodology and in amounts and types of work performed. In all of the more recent studies of habitual smokers in which moderate to near maximal amounts of work were performed and sophisticated measurements of oxygen transport and cardiopulmonary function were made, impairment of function during smoking trials was found (11, 16, 18, 26).

The data of Krumholz, et al. (18) also raise the question of whether residual effects of cigarette smoking influence "nonsmoking" trials performed after a few hours of abstinence; they found statistically significant decreases in heart rate and oxygen debt produced by exercise after 3 weeks of cessation.

The work of Rode and Shephard (25) suggests that physical fitness improves with cessation, but this improvement may be negated if the subject gains a substantial amount of weight after giving up smoking.

Several investigators compared exercise performance or postexercise cardiopulmonary function of smokers to nonsmokers. Although only minor differences between smokers and nonsmokers were found in a few of these studies (3, 4, 22), in most of them (5, 6, 7, 8, 10, 16, 17, 20, 29) the performance or function of the nonsmokers was better than that of the smokers. Both nonsmokers and smokers improved their performance with training, but nonsmokers maintained their advantage throughout training (6, 20).

Biomechanisms

The cited studies indicate that cigarette smoking exerts its adverse effect on exercise performance through several mechanisms. Cigarette smoking appears to impair cardiac performance during exercise by increasing the heart rate and exerting a variable effect on cardiac

output (5, 11, 13, 16, 18, 26, 29). Cigarette smoking is associated with an increased oxygen debt after exercise (5, 18). Also, one study indicated that the oxygen cost of hyperventilation was greater among smokers than among nonsmokers (26).

Some of these adverse effects of smoking on oxidative metabolism are mediated by the elevated carboxyhemoglobin levels found in smokers. CO exerts these effects through one or more of the following mechanisms: (a) Reduction of the amount of hemoglobin available for oxygen transport, (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level, (c) induction of arterial hypoxemia, and (d) possible interference with the homeostatic mechanism by which 2,3,DPG controls the affinity of hemoglobin for oxygen (27). Because carboxyhemoglobin has a half life in the body of at least 3 to 4 hours, its influence may still be measurable several hours after abstinence from smoking (27).

A recent investigation of maximal muscular exercise during CO intoxication in five male volunteers demonstrated reduced maximal O₂ consumption in spite of a much higher heart rate and a relative hyperventilation (21).

Astrand and Rodahl (2) commented recently on the adverse effect of cigarette smoking on oxygen transport: "All other factors being equal, a reduction in the oxygen-transporting capacity is associated with a corresponding reduction in physical performance capacity during heavy or maximal work * * *. Because a regular physical training program only increases the maximal oxygen uptake by some 10 to 20 percent, a 5- to 10-percent reduction in maximal aerobic power due to smoking may play a significant role in many types of athletic events and in very heavy work."

Other studies cited in this review document the adverse effect of smoking on pulmonary diffusing capacity (18) and on pulmonary function with exercise (6, 29).

Summary

Clinical studies in healthy, young men have shown that cigarette smoking impairs exercise performance, especially for many types of athletic events and activities involving maximal work capacity. Some of these effects are mediated by reduced oxygen transport and reduced cardiac and pulmonary function.

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