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.

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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.

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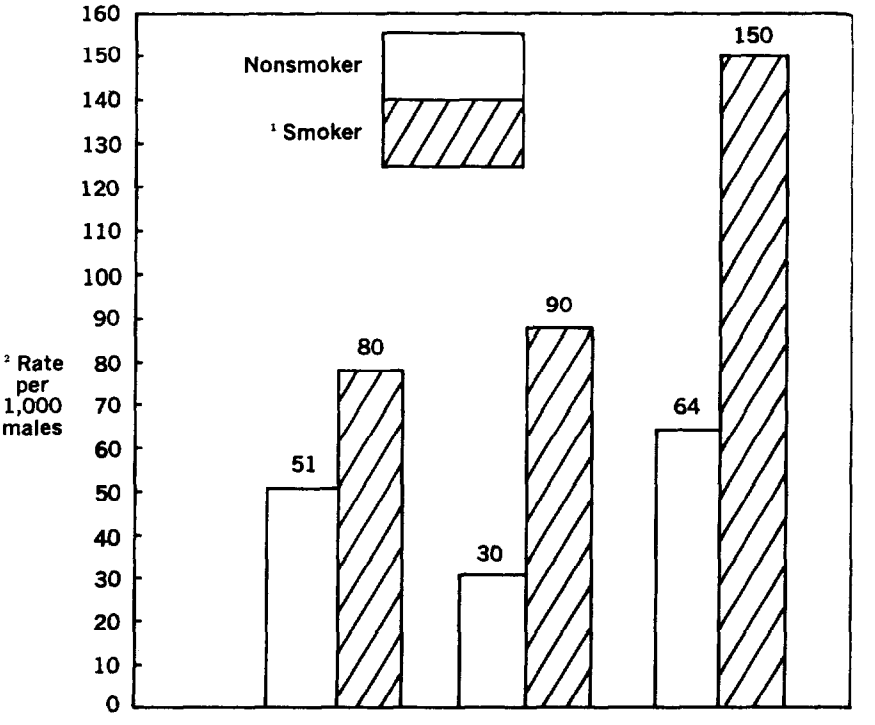
[1] Quetelet index $= \frac{\text{weight}}{\text{height}^2} \times 100$.

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

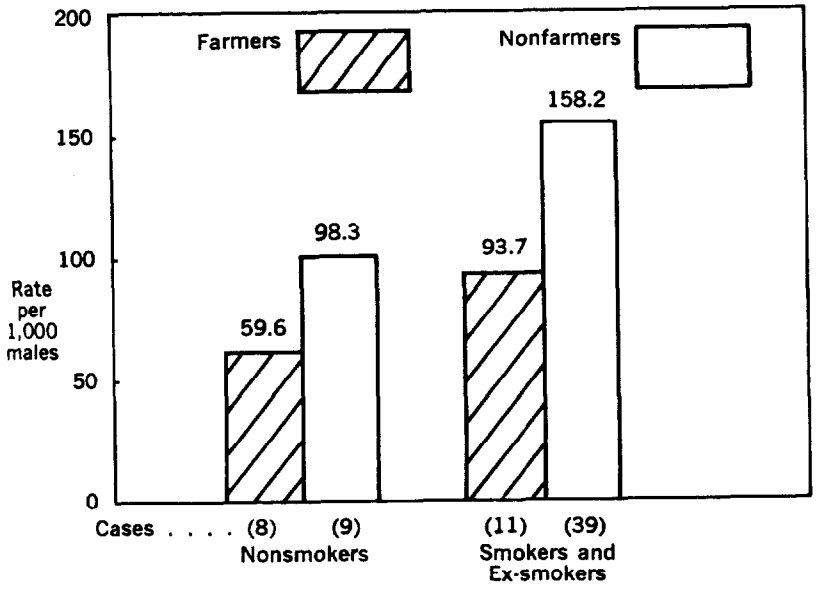


[3] Distribution by weight	Lower third (lean)		Middle third		Upper third (obese)	
Number	90	183	99	161	127	119
Cases	5	15	3	14	16	9

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

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

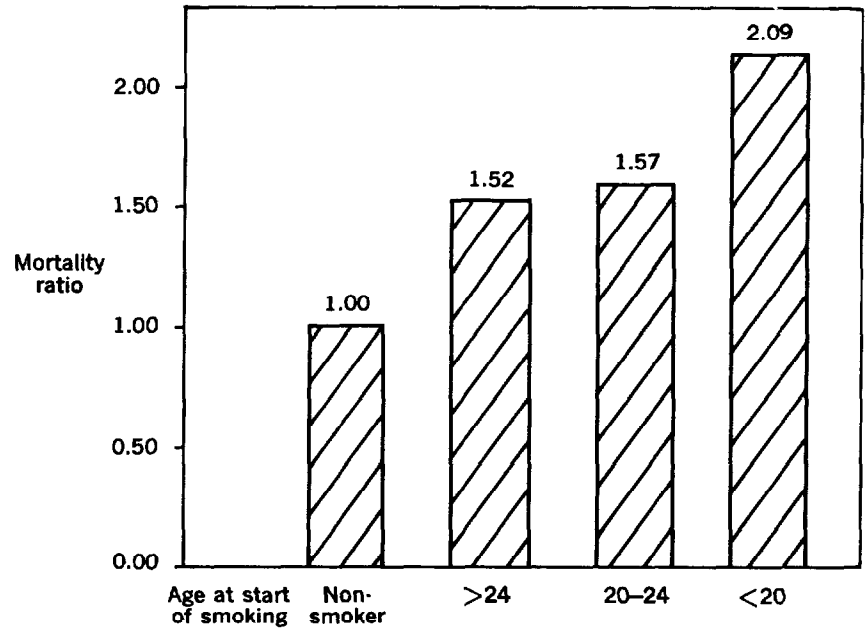
Figure 2.—Age-adjusted incidence rates of CHD comparing farmers who smoke cigarettes with nonsmoking farmers.



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

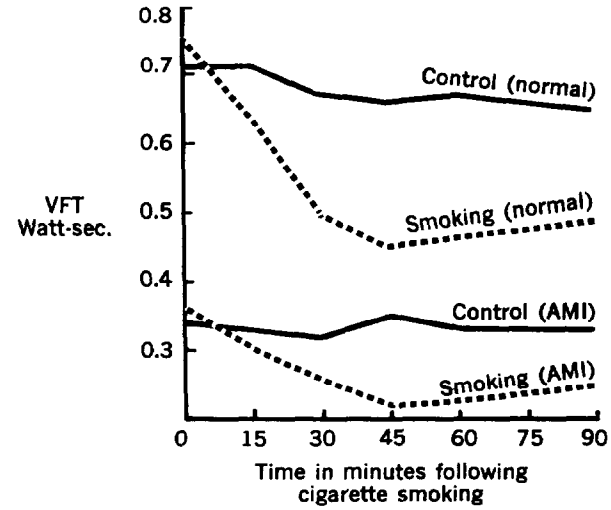
Studies in Man

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).



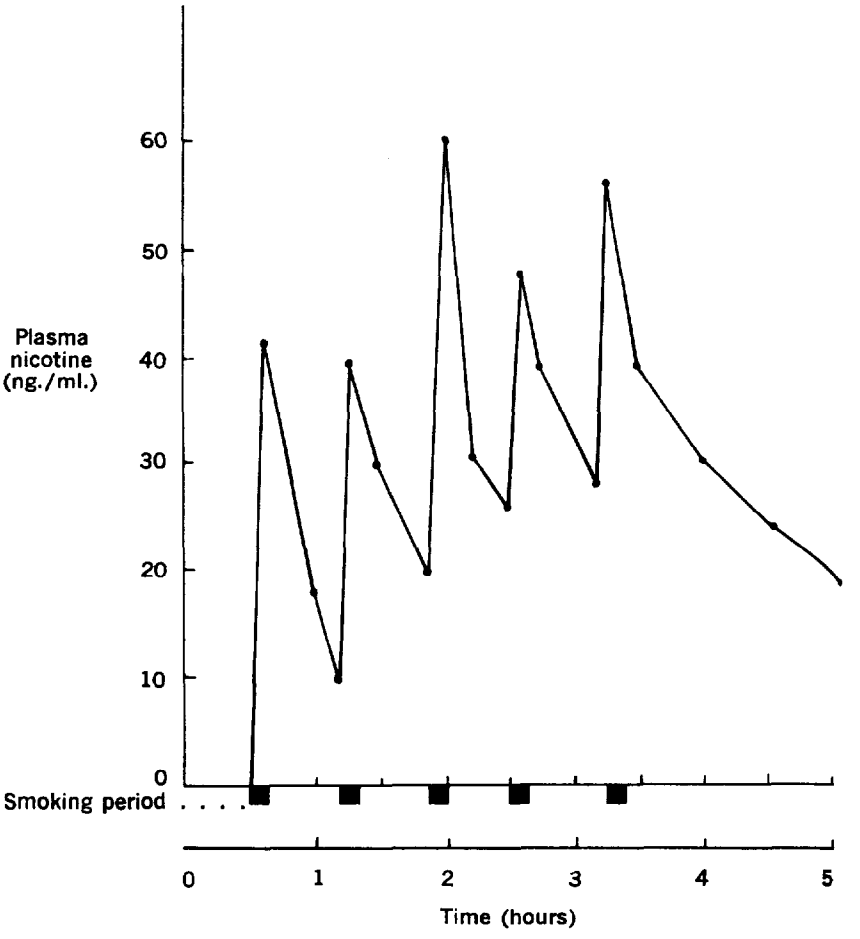
SOURCE: Bellet, S., et al. (6).

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 cadiac enlargement, ST segment depression, and an increase in post-exercise serum lactate concentrations.

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 (*49*, *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 14α-methyl group of lanosterol.

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 nonfatal 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;

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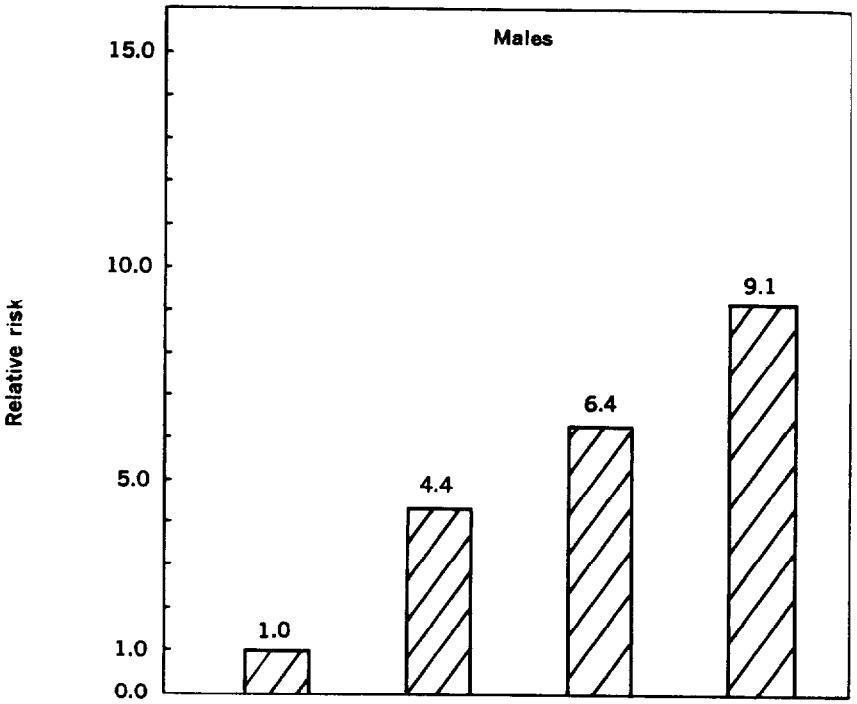
and, for males, whether they smoked cigars or a pipe, A total of 214 male cases, 206 male controls, 390 female cases, and 913 female controls were studied. The control group was composed of patients with peripheral vascular problems other than ASO but who had dorsalis pedis pulses present on initial 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.

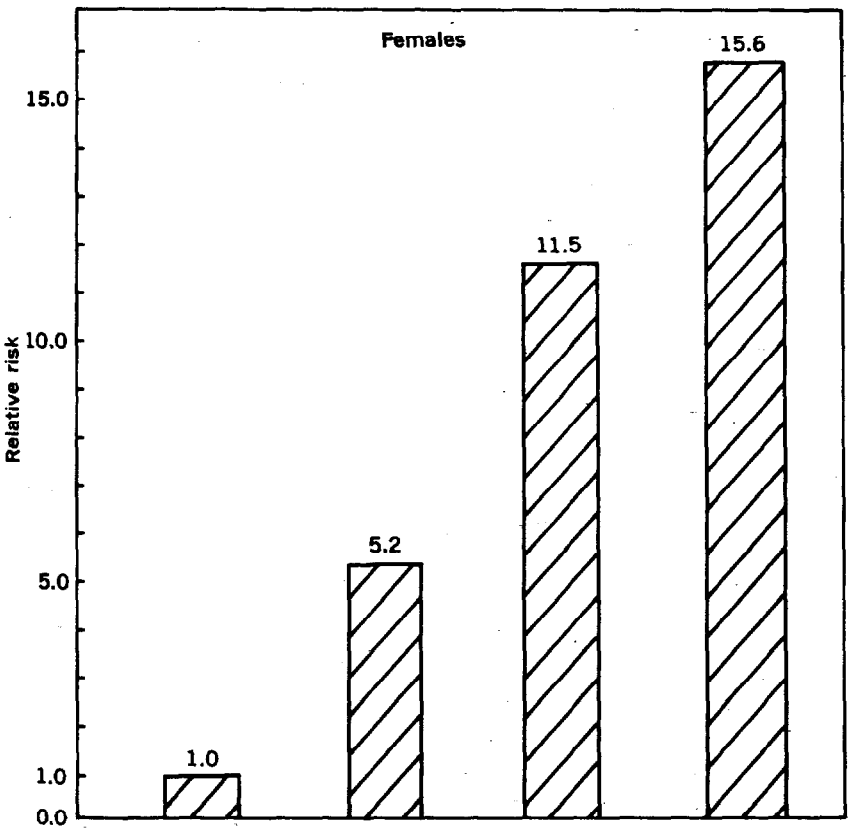
Figure 6.—Relative risk of developing arteriosclerosis obliterans (ASO) for males by amount of cigarettes smoked.



Cases	18	21	33	69
Controls	53	15	26	37
Amount smoked	Non-smoker	<1 pack day	1 pack day	>1 pack day

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

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



Amount smoked	Non-smoker	<1 pack day	1 pack day	>1 pack day
Cases	79	50	60	41
Controls	429	83	69	33

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 vasconstrictor 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.

Cardiovascular References

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