CHAPTER 1

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CARDIOVASCULAR DISEASES

CORONARY HEART DISEASE (CHD)

Introduction

One million deaths per year are attributable to diseases of the cardiovascular system in the United States. Arteriosclerotic cardiovascular disease (ASCVD) is the leading cause of death in this country, accounting for greater than 50 percent of annual deaths; coronary heart disease (CHD) alone is responsible for 600,000 deaths per year. Cigarette smoking, hypercholesterolemia, and hypertension have been identified as major risk factors for the development of CHD.

Epidemiologic, autopsy, and experimental evidence presented in past editions of this report (1964, 1967, 1968, 1969, 1971, 1972, 1973) support a causal relationship between cigarette smoking and cardiovascular morbidity and mortality, as summarized below:

1. Both retrospective and prospective epidemiologic studies have demonstrated a strong relationship between cigarette smoking and increased CHD morbidity and mortality, with approximately a twofold higher risk of dying from CHD for all male cigarette smokers compared to nonsmokers.

2. A dose-response relationship has been demonstrated between cigarette smoking and CHD morbidity and mortality in men.

3. Cigarette smoking acts both independently of and synergistically with the other two major risk factors to produce these effects on CHD morbidity and mortality.

4. The above relationships between cigarette smoking and CHD morbidity and mortality have been demonstrated in Black and Asian, as well as Caucasian, populations.

5. The relative importance of cigarette smoking in the development of CHD in young men (less than 50 years old) is greater than that for any other risk factor.

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6. Most prospective and retrospective studies suggest that pipe and cigar smokers exhibit a slightly higher risk of development of CHD than nonsmokers (but a significantly lower risk than cigarette smokers), while some studies demonstrate no such relationship.

7. Prospective epidemiologic studies document that cessation of cigarette smoking results in reduced mortality from CHD.

8. Autopsy studies reveal greater frequency and severity of coronary and aortic atherosclerosis among cigarette smokers than nonsmokers; cigarette smokers have been reported to have greater myocardial arteriolar wall thickening at autopsy than nonsmokers.

9. Experimental evidence in humans suggests that cigarette smokers with preexistent angina have a greater impairment in cardiac work capacity than nonsmokers. The role of cigarette smoking in the etiology of angina is unclear.

10. Experimental studies on humans and animals have shown that the pathophysiologic changes commonly observed in patients with CHD may be aggravated by cigarette smoking; contributions from both nicotine and carbon monoxide have been demonstrated. In addition, some of the biochemical and anatomical abnormalities seen in CHD have been induced by cigarette smoke, carbon monoxide, and nicotine.

Most of the studies reviewed in the last year confirmed the knowledge of the relationship between cigarette smoking and CHD. A listing of these studies appears in a separate section of the Supplemental Bibliography. A number of studies extended the knowledge of the association between cigarette smoking and CHD, but several studies presented data which were either partially or wholly inconsistent with the known relationships; these two types of studies are reviewed below.

Epidemiologic and Autopsy Studies

I. Studies in Men Demonstrating a Relationship Between CHD and Smoking.

The Coronary Drug Project Research Group studied, by multivariate analysis, 2,035 survivors of myocardial infarction in a prospective investigation to determine the relationship of placebo-treated premature beats and other known risk factors to sudden coronary deaths and total mortality (CV 12). Nonsmokers with ventricular premature beats (VPB) had a significantly higher total mortality than nonsmokers without VPBs (P <.05), and smokers with VPBs had a higher incidence of sudden coronary

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deaths than smokers without VPBs (P <.01). Among patients without VPBs there was a significantly higher mortality rate in smokers compared to nonsmokers (P <.05). Even in the presence of VPBs, smokers had significantly higher total mortality (P <.05) than nonsmokers. A higher incidence of acute coronary deaths in smokers with VPBs compared to nonsmokers with VPBs was also found, but the difference was not statistically significant (P ~.08). Thus, in survivors of myocardial infarction, smoking was associated with a significantly increased mortality, and when complicated by the presence of ventricular premature beats, resulted in an incidence of sudden death greater than the sum of the mortality from sudden death attributed to either risk factor (cigarette smoking or VPB) alone (figure 1). In this study, "lethal interactions" of this nature were found only for smoking, digitalis therapy, cardiac enlargement, and heart failure. These results indicate that cigarette smoking is an
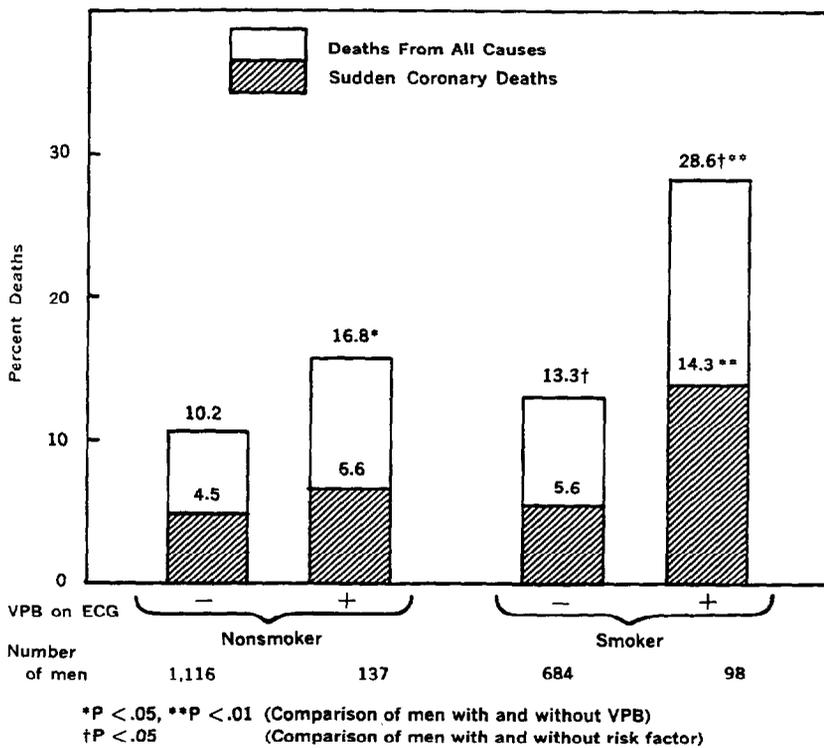

FIGURE 1.—Mortality for men with and without ventricular premature beats (VPB), according to presence or absence of smoking as a risk factor. Bars show percentages of men who died during 3-year period.

SOURCE : Coronary Drug Project Research Group (CV12).

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important risk factor in the occurrence of sudden death as well as death from all causes among patients with known CHD.

In a recent article, Mennotti and Puddu (*CV 26*) reported on the 10-year follow-up data of the 1,717 men between the ages of 40 and 59 who were part of the Seven Countries Study. Whereas at five years, no relation could be found between the incidence of CHD and cigarette smoking, the 10-year follow-up data revealed a correlation between cigarette smoking and CHD, with a relative risk of 1.30–1.62 for smokers of greater than 10 cigarettes per day; the relative risk varied with the stringency of criteria for diagnosis of CHD and the degree of smoking. In these two populations, the incidence of CHD was far below that found in the United States, yet the current data suggest that cigarette smoking is a significant risk factor in the development of CHD in Italy.

With regard to the relative risks of the various risk factors, analysis of the 12-year follow-up data from The Peoples Gas Company Study (*CV 31*) revealed that in the cohort of 903 men free of CHD at the initial examination, the risk factor which was associated with the highest 12-year mortality from all causes was cigarette smoking, whether alone or in combination with the other risk factors (table 1). For all "CVR" (cardiovascular-renal), sudden, and CHD deaths there was a trend toward increased mortality in the smokers, but the total number of cases in each category was small.

Carlson and Bottiger (*CV 10*), in the Stockholm Prospective Study, examined 3,168 men and found that, over a 9-year follow-up period, the development of fatal and nonfatal myocardial infarction and other coronary deaths was related to cigarette smoking, elevated serum cholesterol, and elevated serum triglyceride concentrations. The incidence of new events of ischemic heart disease was significantly higher for all smokers ($P <.01$) and for smokers less than 60 years old ($P <.001$) compared to nonsmokers. Smokers aged 35 to 60 had significantly higher serum cholesterol and triglyceride levels, and higher blood pressure readings than nonsmokers.

In terms of CHD morbidity and mortality, cigarette smoking exerts its most potent effect on men under 60. Blacket, et al. (*CV 7*), in a retrospective study of 70 men in New South Wales with CHD, diagnosed between the ages of 28 and 40, demonstrated that 27 percent of this "coronary group" smoked more than 30 cigarettes per day as compared with 11 percent of the controls ($P <.001$). A total of 23 percent of the coronary group smoked more than 40 cigarettes per day ($P <.01$).

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TABLE 1.—1958 serum cholesterol, diastolic blood pressure, cigarette smoking status, and 12-year mortality—cohort of 903 men, age 40 to 59 in 1958, free of evidence of organ system disease and ECG abnormalities and followed long-term without systematic intervention. Peoples Gas Company Study, 1958 to 1970.

Serum Choles-terol*	Diastolic Blood Pressure*	Cigarette Smoking*	No. of Men	12-Year Mortality				
				All causes	All CVR diseases	Sudden death	CHD	Stroke
NH	NH	NH	208	15,† 69.9‡	2, 8.1	0, 0.0	2, 8.1	0, 0.0
H	NH	NH	106	11, 80.4	5, 40.2	1, 7.8	3, 21.3	1, 6.6
NH	H	NH	40	3, 72.6	1, 23.8	1, 23.8	1, 23.8	0, 0.0
NH	NH	H	289	38, 135.3	17, 61.3	6, 21.1	13, 46.5	4, 14.7
H	H	NH	34	4, 83.9	1, 20.8	0, 0.0	1, 20.8	0, 0.0
H	NH	H	154	26, 172.2	15, 98.2	7, 44.8	10, 63.5	4, 26.6
NH	H	H	40	8, 170.7	2, 42.1	1, 22.4	1, 22.4	1, 19.7
H	H	H	32	10, 319.3	4, 118.0	1, 26.3	3, 76.4	1, 41.6
1 only high			435	52, 118.0	23, 53.2	8, 18.7	17, 39.4	5, 11.2
Any 2 only high			228	38, 162.8	18, 78.5	8, 36.9	12, 53.5	5, 20.4
Any 2 or all 3 high			260	48, 182.2	22, 84.1	9, 35.3	15, 57.6	6, 22.2
All			903	115, 124.1	47, 51.8	17, 19.3	34, 37.7	11, 11.7

*NH, not high; H, high for serum cholesterol, ≥250 mg/dl at entry (1958); for diastolic blood pressure, ≥90 mm Hg at entry (1958); and for cigarette smoking, ≥10 cigarettes/day at entry (1958).
†Number of deaths.
‡Age-adjusted death rate/1000.
SOURCE: Stamler, J., et al. (CV 51)

The Boston Collaborative Drug Surveillance Program conducted a retrospective study on the prevalence of coffee drinking and cigarette smoking in 276 patients with a diagnosis of acute myocardial infarction (*CV 8*) and another study on 440 patients with acute MIs (*CV 21*) comparing these patients with hospitalized controls. On the basis of their data, they suggested that the association between coffee drinking and acute myocardial infarction was stronger than that between cigarette smoking and acute MI. There was observed an almost twofold risk of developing acute MI in noncoffee drinking patients who currently smoked more than 1 pack per day as compared with noncoffee drinking nonsmokers.

Hrubec (*CV 20*) reviewed data from the veteran twin panel of The National Research Council on patients with angina pectoris diagnosed by questionnaire, and found no significant correlation between coffee consumption and angina, except in the group smoking more than 1½ packs of cigarettes per day (P <.03). There was a significant relationship (P <.05) between cigarette smoking of any magnitude and the presence of angina.

II. Studies Failing to Demonstrate a Definite Relationship Between Smoking and CHD.

Cotton, et al. (*CV 13*), in a retrospective study, examined 91 men with a past history of myocardial infarction (4 months to 10 years). Case material was obtained from the files of two referring physicians in England, and controls were chosen from a regional transfusion service. These workers found no increased prevalence of MI among current smokers, but did report a significantly increased prevalence of MI in men with a past history of smoking (P <.001). The authors concluded that the lack of significant difference between the patients and controls in their "current" smoking habits ". . . probably reflects the fact that some of the patients gave up smoking or reduced the amount smoked after their coronary attacks."

Durakovic and Saric (*CV 15*), in a retrospective study of 998 Yugoslavian industrial employees, found no statistically significant correlation between cigarette consumption and the prevalence of angina pectoris.

Malhotra (*CV 25*) found no difference between current smoking habits in 44 patients with myocardial infarction and 88 hospitalized age- and sex-matched controls in an Indian population. A significant difference was found between cases and nonhospitalized healthy controls (P =.02).

Bruschke, et al. (*CV 9*) reported follow-up from 5 to 9 years after coronary arteriography of 590 consecutive patients with

significant coronary artery obstructive disease, and found a higher mortality rate in smokers compared to nonsmokers, but the difference was not statistically significant.

In New Guinea, Sinnett and Whyte (CV 29) reported a very low prevalence of CHD in a rural tribal area. The incidence of other known coronary risk factors was low, but tobacco was smoked by 73 percent and 20 percent of males and females, respectively. However, the authors emphasized that the tobacco leaf is dried and rolled into a bamboo pipe at least 6 inches long "and the smoke is not inhaled."

De Soldati, et al. (CV 14) conducted a retrospective study on 66 patients with recurrent myocardial infarction in Buenos Aires, and found a statistically significant correlation between cigarette smoking and recurrent myocardial infarction, but also reported that the nonsmokers had a significantly shorter interval between infarctions than the moderate or heavy smokers.

III. Studies in Women Relating CHD and Smoking.

Most of the studies on the relation between the various risk factors and CHD morbidity and mortality have been done with male populations. Data from large-scale studies have shown a relationship between CHD mortality and smoking in women. In a recent retrospective series of 182 women who died suddenly and unexpectedly, Spain, et al. (CV 30) reported a significant correlation between cigarette smoking and sudden death attributed to CHD. In this study, there were 29 CHD-related deaths. There was a significantly greater number of nonsmokers dying of non-CHD causes than of CHD (P <.01) (table 2). In addition, 62 percent of the women dying suddenly from CHD smoked greater than 1 pack per day, as opposed to 28 percent of the control group composed of women dying suddenly of other causes (P <.01). In the CHD group, there was an inverse relationship between the degree of cigarette consumption and mean age at death, i.e., heavy smokers died of CHD at an earlier age than nonsmokers. The statistical significance of this observation was not recorded. The authors reported that the mean age at the time of sudden death for the entire group of 182 women was 19 years less for heavy smokers compared to nonsmokers. The authors also reported that in their autopsy populations the male:female mortality ratio for sudden death due to CHD was 11:1 for nonsmokers and ~3.8:1 for all smokers.

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TABLE 2.—*Cigarette smoking and sudden death from CHD in women*

| Smoking habits | Population* Number/percent | CHD sudden death | |
		Number/percent	Mean age/range
Nonsmoker	81/53	3/10	67/60–75
<20 cigarettes/day	29/19	8/28	55/52–61
≥20 cigarettes/day	43/28	18/62	48/32–58
Total	153/100	29/100	54/32–75

*All deaths exclusive of CHD.
SOURCE: Spain, D. M., et al. (CV 30).

Wink and Hager (*CV 35*), in a retrospective study of 10 pre-menopausal women with myocardial infarction, showed that there was a significantly higher incidence of cigarette smoking in this group of women than in postmenopausal women with acute myocardial infarction seen in the same clinic (P <.001).

CARBON MONOXIDE (CO)

Introduction

The importance of the effects of low levels of exposure to carbon monoxide on the pathophysiology of CHD is well recognized (1967, 1968, 1969, 1971, 1972, 1973).

It is known that the gas phase of cigarette smoke contains approximately 1 to 5 percent CO and that the concentration of CO increases as the cigarette burns down. Heavy cigarette smokers develop significantly higher COHb concentrations than non-smokers, reaching levels of 4 to 15 percent. Arterial hypoxemia may develop following CO exposure, and myocardial metabolism may be significantly altered under the conditions of CO exposure, thus limiting myocardial work capacity. A significant decrease in exercise performance in patients with angina has been induced by smoking non-nicotine cigarettes, with increases of carboxy-hemoglobin concentrations to approximately 8 percent. Some of the mechanisms responsible for these effects have been reviewed in previous editions of this report.

In experimental studies, CO increases coronary flow and heart rate in normal subjects, increases oxygen debt, and results in myocardial hypoxia. Carbon monoxide has also been implicated by some workers as an etiologic factor in the development of atherosclerotic lesions. Recent studies have contributed significantly to our understanding of the role of CO in the development and pathophysiology of CHD.

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Epidemiologic Studies

Wald, et al. (*CV 34*) found, in cross-sectional analysis of 950 Danish smokers, a correlation between the development of atherosclerotic diseases and carboxyhemoglobin levels. They concluded that COHb levels were better indicators than smoking history of a person's risk of developing ASCVD, including CHD. The heavy smokers had a higher prevalence of ASCVD than the nil and light smokers combined (P <.001). Only 8 of the 58 subjects had a past history of myocardial infarction.

Experimental Studies in Man

Aronow, et al. (*CV 3*) studied the effect of carbon monoxide exposure on myocardial work capacity and angina. Ten men with known CHD and angina, aged 40 to 56, who were exposed to heavy morning freeway traffic in Los Angeles for 90 minutes, performed cardiopulmonary tests in the pre-exposure, immediate post-exposure, and 2-hour post-exposure states. Each man served as his own control by breathing purified compressed air on a similar 90-minute excursion in heavy morning traffic. After breathing the freeway air, all 10 men developed marked increases in expired-air carbon monoxide levels (P <.001), and arterial carboxyhemoglobin levels (P <.001), both immediately and at 2 hours post-exposure. No differences were found in these parameters when the patients breathed compressed air. The mean exercise performance of the 10 men was significantly impaired in the immediate post-exposure period (P <.001) and also at 2 hours post-exposure (P <.05). The mean exercise performance was significantly increased from the immediate post-exposure period to the 2-hour post-exposure period (P <.05), corresponding to significant decreases in mean expired CO and percent COHb at 2-hours post-exposure. Significant decreases in heart rate (P <.001), systolic blood pressure (P <.01), and the product of the systolic blood pressure times the heart rate (P <.001) developed in relation to the onset of angina in the immediate post-exposure period, and significant decreases were noted at the time of onset of angina at the 2-hour post-exposure periods for heart rate (P <.001) and the BP x HR product (P <.001). No significant differences in any of these values were found when the patients breathed compressed air. Three of the 10 patients developed ischemic ST segment depression during the ride of carbon monoxide exposure; none of the 10 patients developed such changes during exposure to compressed air. As the BP x HR product is one measure of cardiac work capacity, these results strongly suggest that "less work can be done before the onset of

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exercise-induced angina in patients with elevated carboxyhemo-globin levels" (as manifested by diminution of both cardiac work measurements and actual exercise performances). Pollutants other than carbon monoxide may have contributed to the findings in this study.

Using a double-blind design, Aronow and Isbell (CV 4) studied the effects of the administration of purified CO and purified compressed air on 10 men with stable angina. All the subjects were nonsmokers. Administration of the compressed air for 2 hours resulted in a significant decrease of venous COHb (P <.001) from a mean of 1.07 percent to 0.77 percent and no significant changes in mean exercise time until onset of angina, systolic blood pressure (BP), heart rate (HR), or the BP x HR product. Administration of 50 p.p.m. CO for 2 hours resulted in a significant increase in venous COHb (P <.001) from a mean of 1.03 percent to 2.68 percent, and significant decreases in mean exercise time until onset of angina (P <.001) systolic blood pressure, heart rate, and the BP x HR product at the time of angina (P <.001). It is important to note that the levels of carboxyhemoglobin observed in the groups of patients from these two studies were below those frequently attained by cigarette smokers.

In a related study, Fortuin, et al. (CV 1, 2, 16) analyzed mid- and post-exercise ECG changes in "normal" subjects and patients with stable angina before and after exposure to purified CO. In the "normal" subjects, venous COHb concentrations of 5.7 to 7.1 percent were obtained, and exercise performance, as measured by time period of exercise before attaining a specified heart rate, was significantly impaired in both young (P <.005) and middle-aged subjects (P <.01). Seven of the 26 older "normal" subjects demonstrated some abnormality in their ECGs at some stage in the study, and all of these ECG changes (including ST segment abnormalities and arrhythmias) were exaggerated after CO exposure. In the 10 patients with stable angina, venous COHb levels were raised to 2.9 and 4.5 percent after exposure to 50 and 100 p.p.m. CO, respectively. The mean duration of exercise before the onset of anginal pain was significantly shortened following CO exposure at both dose levels (P <.005), ST segment depression was deeper in 5 of 10 patients, and, in general, had an earlier onset and longer duration after CO exposure. In addition, duration of pain was significantly lengthened with exposure levels of 100 p.p.m. (P <.01). These studies lend further support to the concept that CO exposure resulting in mild to moderate elevations in COHb concentrations may exacerbate exercise-

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induced myocardial ischemia in persons with preexisting clinical or subclinical coronary heart disease.

NICOTINE

Nicotine has been found to increase heart rate, blood pressure, cardiac output, stroke volume, and velocity of myocardial contraction. The cardiovascular effects of nicotine has been summarized in The Health Consequences of Smoking (1971). Experimental evidence suggests that these effects are mediated through release of catecholamines from sympathetic ganglia and myocardial chromaffin tissue, and that sympathetic ganglionic blockers inhibit these effects. There may also be neurogenic components to the cardiovascular effects of nicotine, as well as effects on regional coronary perfusion.

Experimental Studies

Bizzi, et al. (*CV 6*) studied the effects of nicotine on adipose tissue in the rat. Rats were administered nicotine intraperitoneally and subcutaneously, and the responses of plasma free fatty acids (FFA) and in vitro lipolysis were observed. Intraperitoneal nicotine tartrate (NT) caused a transient rise in FFA, and subcutaneous NT in 1 percent carboxymethylcellulose also resulted in a rise in plasma FFA in a dose-response relationship. Administration of the vehicle alone as a control was not performed. Inhibitors of lipolysis (including beta blockers) inhibited this stimulatory effect of nicotine on plasma FFA. Of particular note was that in adrenalectomized rats, NT failed to elevate plasma FFA, but did so when corticosterone was administered before sacrifice.

In vitro, NT added to a medium containing adipose tissue did not result in enhanced release of FFA into the medium, thereby implying an indirect effect of NT through enhanced catecholamine secretion as seen in the in vivo situation. Neither acute nor chronic doses of NT resulted in elevated tissue triglyceride concentrations.

These results confirm previous evidence of nicotine's ability, both acutely and chronically, to elevate plasma FFA, this action being mediated through enhanced catecholamine secretion. The new findings concerning the role of adrenocorticoids are of uncertain significance. The precise role of elevated FFAs in atherogenesis remains to be elucidated.

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A number of retrospective studies have implicated cigarette smoking as one of the major risk factors in the development and progression of peripheral atherosclerosis, arteriosclerosis obliterans (ASO) and thromboangiitis obliterans (TAO). The patency of peripheral bypass grafts may also be adversely affected by cigarette smoking.

The increased incidence of peripheral vascular disease associated with smoking may be in part due to elevated COHb levels. Experimental data suggest that cigarette smoking may chronically decrease peripheral flow capacity and acutely result in closure of precapillary sphincters, vasoconstriction, and decreased blood flow in human connective tissue in vivo.

Recent prospective and retrospective epidemiologic evidence, as well as experimental data add to our knowledge of the association between cigarette smoking and peripheral vascular disease.

Epidemiologic Studies

The 16-year follow-up data of the Framingham Study (CV 18) revealed strong relationships between cigarette smoking and the development of the three major manifestations of atherosclerosis: CHD, atherosclerotic brain infarction (ABI), and intermittent claudication (figure 2). The only exception to this was the absence of correlation between cigarette smoking and ABI in women, but for CHD deaths, MI, coronary insufficiency, and intermittent claudication, the correlations were as strong in women as in men. It appears that cigarette smoking is one of the major risk factors in the development of intermittent claudication (table 3) (CV 24). A higher total incidence over the 16 years of follow-up and a higher annual incidence of intermittent claudication occurred in smokers than in nonsmokers, the latter statistically significant for all age groups of both sexes. When the other risk factors were controlled for utilizing multivariate analysis, the effect of smoking became even more pronounced.

In a retrospective study of 100 patients with peripheral vascular disease evaluated by peripheral angiography and selective coronary angiography, Tomatis, et al. (CV 32) found that 98 percent of patients with aortoiliac disease, 91 percent of those with femoropopliteal disease, and 93 percent with abdominal aortic aneurysms had a history of smoking.

In a population of nondiabetic smokers with evidence of peripheral vascular disease, Linhart, in Astrup, et al. (CV 5), found
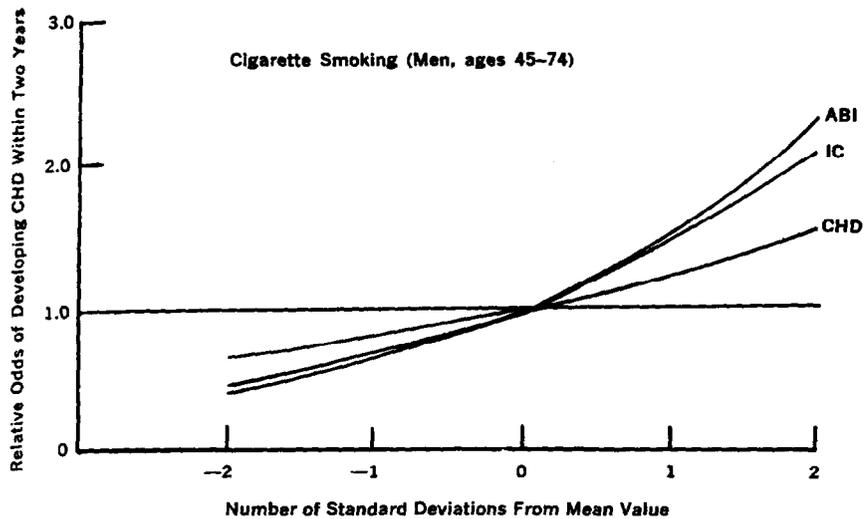
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FIGURE 2.—Relative odds of developing atherothrombotic brain infarction (ABI), coronary heart disease (CHD), or intermittent claudication (IC) according to levels of cigarette smoking.

SOURCE: Gordon, T., Kannel, W. B. (*CV 18*).

TABLE 3.—*Standardized multivariate regression coefficients of intermittent claudication for various characteristics*

Characteristic	Regression coefficient			
	Age 45-54	Age 55-64	Age 65-74	Mean (and standard error)
Men				
Cigarettes/day	0.362	0.618	0.016	0.451 (0.115)
Glucose intolerance	0.323	0.410	−0.115	0.351 (0.075)
Serum cholesterol	0.303	0.314	−0.103	0.259 (0.092)
Systolic blood pressure	0.105	0.318	−0.412	0.178 (0.107)
Left ventricular hypertrophy (ECG)	0.118	0.016	0.231	0.080 (0.087)
Women				
Cigarettes/day	0.731	0.270	0.462	0.405 (0.126)
Glucose intolerance	----	0.442	0.232	0.390 (0.101)
Serum cholesterol	0.404	0.286	0.113	0.334 (0.096)
Systolic blood pressure	0.540	0.247	0.420	0.356 (0.136)
Left ventricular hypertrophy (ECG)	0.242	0.223	0.304	0.247 (0.097)

Note: Incidence of intermittent claudication:

	45-54	55-64	65-74
Men	20	45	15
Women	5	21	12

SOURCE: Kannel, W. B., Shurtleff, D. (*CV 24*).

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a significant correlation between frequency of severe intermittent claudication and consumption of greater than 15 cigarettes per day (P <.01). There was no difference between these heavy smokers and the other smokers for development of gangrene, nor did development of claudication vary with number of years smoking or total number of lifetime cigarettes consumed. Of his 112 patients, 57 stopped smoking after initial diagnosis and treatment, and subsequent progress of their claudication was retarded with no fresh gangrene developing in any of these subjects. The 55 patients who continued smoking suffered from the same rate of complications as seen before treatment.

Experimental Studies

Goldman, et al. (*CV 17*) reported that the amount of heat loss from the hands of 10 normal subjects was found to be significantly less on exposure to cold after subjects smoked two cigarettes, when compared to the control state (P <.05). Smoking exerted no effect on heat loss from the feet of these subjects. These results corroborate previous reports of the vasoconstrictive effects of smoking on the peripheral vasculature. The differences in heat loss between upper and lower extremities were explained by differences in reactivity to vasomotor stimuli, differences in total blood flow, and greater vasoconstrictor tone in the lower extremity.

CEREBROVASCULAR DISEASE (CVD)

Retrospective studies have revealed a correlation between cigarette smoking and morbidity and mortality from CVD in men. No correlation has been found previously for women.

Acutely, cigarette smoking has been reported to increase cerebral flow and decrease cerebrovascular resistance. The exact role of cigarette smoking in the pathogenesis of CVD is unclear. Recent studies are summarized below:

Epidemiologic Studies

Data from a restrospective series of 598 nonpregnant women, ages 15 to 44, with a diagnosis of stroke (*CV 11*) revealed that 73 percent of the women with strokes were cigarette smokers as opposed to 43.4 percent of the nonhospitalized control group (P <.001) and 60 percent of the hospitalized control group (P <.001). The combined effect on thrombotic episodes in this study population of both smoking and oral contraceptives was greater

than that exerted by the use of oral contraceptives alone. It was concluded that cigarette smoking contributes significantly to the development of stroke in women, and enhances the effect of oral contraceptives on the development of thrombotic cerebrovascular events.

Analysis of the 16-year follow-up data of the Framingham study (CV 23) revealed an increased risk of ABI attributable to smoking in men, with a sixfold excess risk in male smokers aged 45 to 54. The numbers of cases are still too small to draw any firm conclusions from the data. No correlation between smoking and cerebrovascular events was found in women.

In a prospective study of 3,991 longshoremen followed for 18 years, Paffenbarger (CV 28) found no correlation between fatal stroke and cigarette consumption. Included in the study group were 59 cases (from a total of 132) of intracerebral hemorrhage.

CIGARETTE SMOKING AND ASSOCIATED CHD RISK FACTORS

There is conflicting evidence concerning the role of cigarette smoking in the chronic elevation of serum lipids. Results from studies of the acute effects of smoking on blood lipids, including FFA, cholesterol, and triglycerides, have also been contradictory.

A negative correlation between cigarette smoking and mean systolic and diastolic blood pressures has been shown in some studies and not others. This apparent correlation has been explained by the negative association between smoking and relative weight.

Recent contributions in this field are summarized below:

In a retrospective study of 42,804 military men in Belgium (CV 33), multiple regression analysis revealed that in all age groups smokers of greater than 20 cigarettes per day had a higher serum cholesterol than nonsmokers. This finding was of statistical significance in age groups 20 to 29 (P < .01), 30 to 39 (P < .001), and 40 to 49 (P < .01); i.e., the years of greatest risk of CHD for the combination of hypercholesterolemia and cigarette smoking (figure 3).

Mundy and Cutforth (CV 27) studied 85 patients with myocardial infarctions who had survived their infarctions for at least six months. They found no correlation between "lipid levels" and smoking. Only lipoprotein electrophoretic abnormalities were reported, although the authors stated that serum cholesterols and triglycerides were determined.
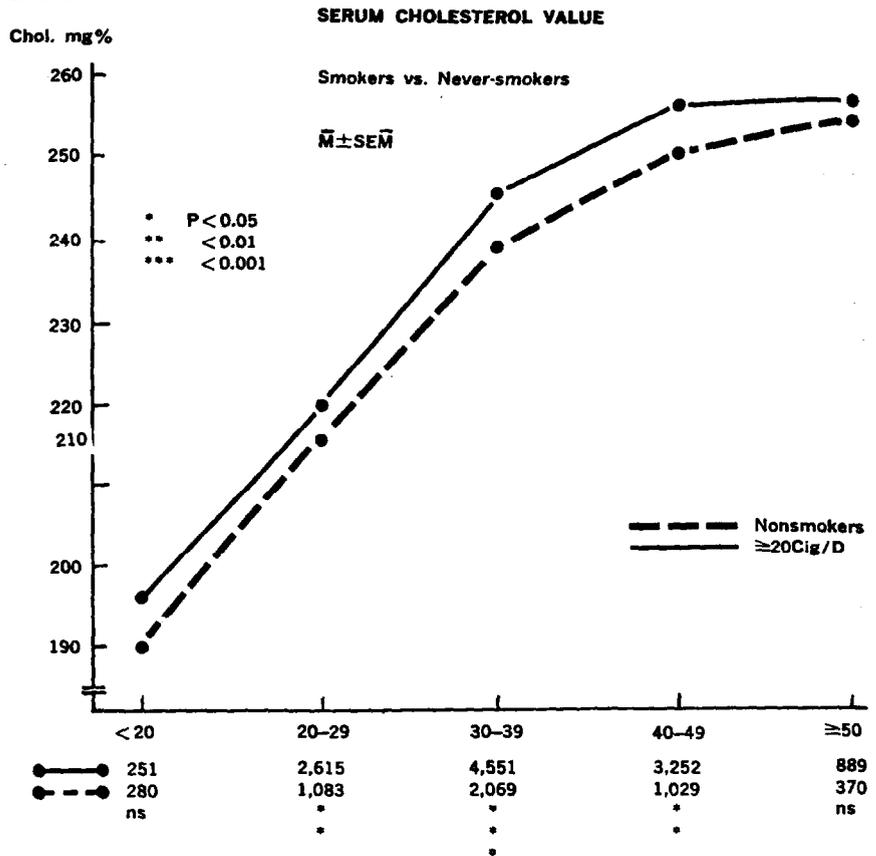
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FIGURE 3.—Serum cholesterol levels of cigarette smokers and nonsmokers in the Belgian military service.

In a prospective study of 10,000 male Israeli civil service workers, aged 40 and up, Kahn, et al. (CV 22) found a positive relationship between smoking habits at the start of the study and the incidence of hypertension over a 5-year follow-up period (P <.01).

THROMBOSIS

The role of cigarette smoking in promoting thrombosis has not been well defined. Hawkins (CV 19) conducted experiments on platelet functions of 30 healthy men and found that the biphasic electrophoretic mobility change of platelets was altered immediately after smoking and returned to normal at 15 minutes.

Whole blood coagulation (P <.05), rates of initial clot formation, maximum clot tensile strength (P <.05), and clot retraction were all altered in the smokers in the direction of favoring hypercoagulability as compared with nonsmokers, but were not altered further in the smokers either immediately or 15 minutes after smoking one cigarette.

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

1. Data from recent epidemiologic studies suggest that cigarette smoking acts independently of and in conjunction with certain cardiac arrhythmias to increase the risk of mortality from coronary heart disease in men. Smokers also have a greater probability of dying from CHD at an earlier age than nonsmokers.

2. New epidemiologic data suggest that women who smoke cigarettes have a greater risk of sudden death from CHD than do nonsmoking women.

3. The results of experimental studies demonstrate that the elevated levels of carboxyhemoglobin frequently seen in smokers may result in significantly decreased cardiac work performance and precipitation of ischemic electrocardiographic changes and arrhythmias in patients with clinical and subclinical CHD. Carboxyhemoglobin levels may be of value in determining a person's risk of developing arteriosclerotic cardiovascular disease.

4. Findings from experimental studies confirm that nicotine acts indirectly to cause elevations of plasma FFAs. The relative role of sympathetic versus adrenocortical stimulation of the rise in FFAs remains to be determined.

5. Epidemiologic data reveal strong associations between cigarette smoking and development of peripheral vascular disease.

6. Data from epidemiologic studies support a strong association between atherosclerotic brain infarction and cigarette smoking in premenopausal women and in men of all ages. No association between ABI and smoking has yet been demonstrated in menopausal women.

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