TABLE A27.—*Smoking and thrombosis*

Author, year, country, reference	Number and type of population	Experimental conditions [1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Blackburn et al., 1959, U.S.A. (25).	16 adult schizophrenic patients, 8 university students, all smokers.	12 individuals smoked 2 high-nicotine standard brand cigarettes.									*Plasma styptven time* (−)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35–72 years of age.	Compared after periods of abstinence or continuation of smoking.	(−)	(−)	(−)		(−)	(−)	(+) decrease	(+) increase	*Platelet clumping time* (±)	
Ambrus and Mink, 1964, U.S.A. (4).	20 healthy male nonsmoking medical students <30 years of age.	Deep inhalation of one nonfiltered cigarette.	(−)		(−)	(−)	(±) increase	(−)			*Thromboplastin generation time* (−)	2 students became ill. Results reflect data on 18.
Ashby et al., 1965, Ireland (8).	27 male medical students and hospital staff members.	13 controls measured at 2 separate times 14 subjects measured before and after smoking 2 cigarettes in 20 minutes.					(+) increase					Increase of subjects greater than that of controls at $p < 0.01$.

TABLE A27.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Sognal and Joshi, 1955, India (*174*).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(–)	(–)		(–)	(+) increase				*Fibrinolysis* (+) decrease	Biri—tobacco wrapped in tobacco leaf.
Engelberg, 1965, U.S.A. (*58*).	40 male and 20 female hospital patients, all smokers 17–68 years of age.	2 cigarettes in 20 minutes.									*Chandler (in vitro) thrombosis time* + decrease	
Kedra and Koroliko, 1965, Poland (*100*).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 18–25 years of age.	5 cigarettes in 1 hour.	(±) decrease	(–)		(+) decrease					*Thrombin time* (±) decrease	
Murchison and Fyfe, 1966, Scotland (*139*).	8 males and 4 female patients with various diseases, all heavy smokers 37–67 years of age.	2 cigarettes in 15 minutes. lit or unlit cigarettes.					(†)	(+) increase				† Smoking both lit and unlit cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma non-esterified fatty acids.

TABLE A27.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions [1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Glynn et al., 1966, Canada (*71*).	20 male and 17 female smokers and 9 male and 21 female nonsmokers 17–76 years of age.	3 cigarettes in 30 minutes.					(–)				*Platelet serotinin* (–) *Platelet adenosine nucleotide* (–)	Smokers found to have a greater tendency for platelet aggregation than nonsmokers.
Engelberg and Futterman, 1967, U.S.A. (*59*).	94 male and 53 female patients and medical house staff.	1 cigarette in 5 minutes.									*Thrombus formation time* (+) decrease	No relation found with increase in free fatty acids.
Murphy, 1968, U.S.A. (*140*).	Literature review with summary of data and conclusions.						(±) increase	(±) increase	(+) decrease		*Platelet adherence to vascular endothelium* (+) increase *Fibrinolysis* (±) decrease *Thrombus formation time* (+) decrease	

Symbols:
– = No effect.
± = Questionable effect.
+ = Definite effect.

[1] Results, unless otherwise stated, concern specific coagulation test as measured before and after smoking procedure noted.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system*

Author, year country, reference	
Moyer and Maddock, 1940, U.S.A. (*154*).	20 subjects (including heavy smokers) were studied for the effects of the following procedures on skin temperature: the inhalation of a lit cigarette, inhalation through an empty paper tube, or the administration of 1 mg. nicotine intravenously. All subjects responded with decreased cutaneous temperature following the smoking and nicotine procedures. No changes were noted following sham smoking.
Mulinos and Shulman, 1940, U.S.A. (*158*).	A number of experimental groups, each consisting of 6–17 persons, were studied for the effects of deep breathing and cigarette smoking on skin temperature and digit or limb plethysmography. The authors concluded that deep breathing alone could account for the changes in temperature and blood flow noted upon smoking and noted that denicotinized cigarettes evoked the same or greater vasoconstriction as that noted following the smoking of a standard cigarette.
Shepherd, 1951, Ireland (*173*).	50 young male smokers were studied with plethysmography before and after the normal and rapid inhalation of a standard cigarette. The author noted that rapid inhalation was associated with a prolonged decrease in extremity blood flow while a more natural rate of inhalation was followed by a momentary decrease in flow. The author considered the former reaction to represent the pharmacologic effect of the smoke and the latter to represent the physiologic response to deep breathing, as the natural inhalation of an unlit cigarette produced the same transient decrease in flow as did the natural inhalation of the lit cigarette.
Friedell, 1953, U.S.A. (*79*).	52 male and 48 female young smokers and nonsmokers were studied for the effects of smoking on hand blood volume as measured by the use of radioactive iodinated albumin. The inhalation of unfiltered cigarettes was associated with an average decrease in hand blood volume of 19 percent in men and 33 percent in women; while filtered cigarettes showed respective decreases of 11 percent and 21 percent.
Stromblad, 1959, Sweden (*131*).	11 male and female subjects (smokers and nonsmokers) were studied for the effect of the intra-arterial administration of nicotine (brachial artery) on blood flow to the hand as measured by venous occlusion plethysmography. Increasing doses of nicotine were associated with increasing numbers of individuals manifesting vasoconstriction. The vasoconstrictive effects of nicotine were abolished by the prior administration of either hexamethonium or pentolinium.
Barnett and Boake 1960 Australia (*18*).	9 male patients with intermittent claudication (7 were heavy smokers) were studied for the effect of smoking on blood flow to the leg as measured by venous occlusion plethysmography. Smoking an unfiltered cigarette was found not to produce any consistent changes in blood flow to the calf or foot of the affected leg.
Freund and Ward, 1960, U.S.A. (*68*).	15 male prison inmates (less than 35 years of age) and 14 male patients with peripheral vascular disease (approximately 65 years of age) were studied for the effect of smoking on digital circulation as measured by skin temperature, plethysmography, and radiosodium clearance from the skin. Smoking was found to adversely affect the first and third measures in a significant manner (while plethysmographic values were variable) only in the healthy prisoners and not at all in the patient group.
Roth and Schick, 1960, U.S.A. (*151*).	100 normal individuals underwent 425 experimental procedures concerning the effect of smoking on the peripheral circulation. Smoking was found to be associated with a decrease in extremity skin temperature.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system (cont.)*

Author, year, country, reference	
Rottenstein et al., 1960, U.S.A. (*162*).	8 males (18-31 years of age) were studied for the effect of intravenous nicotine on extremity temperature and blood flow. Intravenous nicotine was found to evoke a decrease in skin temperature while increasing muscle blood flow. The former effect began sooner and lasted longer than the latter.
Allison and Roth, 1969, U.S.A. (*3*).	30 healthy individuals (19-59 years of age) were studied for the effect of smoking two cigarettes on extremity pulse volumes and skin temperature. Smoking was found to be associated with a 2-6 percent decrease in skin temperature and a 45-50 percent decrease in blood pulse volumes to segments of the finger, calf, and toe.

Chapter 2

Cardiovascular Diseases

Part II

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CORONARY HEART DISEASE (CHD)

Introduction

Coronary Heart Disease (CHD) is the most frequent cause of death in the United States and is the most important single cause of excess mortality among cigarette smokers. The evidence relating smoking to CHD has been reviewed in previous reports on the health consequences of smoking (*61, 62, 63, 64, 65, 66, 67, 68*). The following is a brief summary of the relationships between smoking and CHD presented in these reports.

Cigarette smoking, hypertension, and elevated serum cholesterol are the major alterable risk factors for myocardial infarction and death from CHD. Cigarette smoking acts both independently as a risk factor and synergistically with the other CHD risk factors. The magnitude of the risk increases directly with the amount smoked. The excess risk of CHD among smokers has been demonstrated in some Asian, Black, and Caucasian populations and is proportionately greater for younger men, especially those below age 50. Cessation of cigarette smoking results in a reduced mortality rate from CHD compared with the mortality rate for those who continue to smoke.

Pipe and cigar smokers have a slightly higher risk of death from CHD than nonsmokers, but they incur a much lower risk than cigarette smokers. This has been attributed to the lower levels of inhalation that characterize most pipe and cigar smoking.

Data from autopsy studies have shown coronary atherosclerosis to be more frequent and more extensive in cigarette smokers than in nonsmokers, and experimental work in humans and animals has suggested several mechanisms by which smoking may influence the development of atherosclerosis and CHD. The formation of carboxyhemoglobin, release of catecholamines, creation of an imbalance between myocardial oxygen supply and demand, and increased platelet adhesiveness leading to thrombus formation have all been demonstrated in smokers and proposed as explanations for the excess CHD mortality and morbidity among smokers.

Cigarette Smoking as a Major Risk Factor for Coronary Heart Disease

The evidence establishing smoking as a major risk factor in CHD has been reviewed in previous reports (*61, 62, 63, 64, 65, 66, 67, 68*). During the last year new epidemiologic data have been published on the relationship between coronary artery disease and smoking.

Bengtsson (*9, 10*) studied the smoking habits of women with myocardial infarction (MI) in Goteborg, Sweden. He found that smoking was significantly more common in a group of 46 women (80 percent smokers), ages 50-54, who had a myocardial infarction than in a control group of 578 healthy nonhospitalized women (37.2 percent smokers).

Other investigators examined the effect of cigarette smoking on survival of people with acute myocardial infarction. In a study of 400 patients with documented myocardial infarction who survived to be admitted to a coronary care unit, Helmers (*26, 27, 28*) found no significant difference between the percentages of smokers and nonsmokers among survivors studied after the first 24 hours, from 2 days until discharge, and from discharge to 3 years. Reynertson and Tzagournis (*52*), in a 5-year prospective study of 137 patients with documented CHD at age 50 or less, were also unable to find any relationship between CHD mortality rates and smoking habits. Smoking habits after entrance into the study were also considered and again no difference in mortality rates was found.

The Coronary Drug Project (*17*) found an effect of cigarette smoking on mortality after myocardial infarction. This group studied 2,789 men ages 30-64 years for 3 years after myocardial infarction and found a statistically significant correlation between cigarette smoking determined 3 months after a myocardial infarction and mortality (t-value of 2.94). None of these studies (*17, 26, 27, 28, 52*) were able to examine the smoking habits of the group of people who die suddenly as a first manifestation of CHD, and therefore may have excluded that group in which there is the highest excess mortality due to cigarette smoking (*31*).

Additional data from the Swedish twin study of Friberg, et al. (*23*) have been reported. They found an excess CHD mortality among smokers in dizygotic twins with different degrees of smoking, but no similar excess in monozygotic twins. Although the numbers were too small to be significant, the authors suggest that this tends to support the theory that both smoking and CHD are constitutionally

determined. These data must be viewed with caution, however, since the difference was demonstrable only in the older age group (born 1901 - 1910). When the younger age group (born 1911 - 1925) was considered, no excess CHD mortality was seen in the dizygotic group but a small excess was noted in the monozygotic group (three CHD deaths in the high smoking group and one in the low smoking group). Also the difference in cigarette consumption between the high and low smoking groups was relatively small (seven cigarettes per day). Consequently, data from this study are not sufficient to warrant the conclusion that both smoking and excess CHD mortality are constitutionally determined rather than smoking being a cause of the excess CHD mortality.

Cigarette Smoking in Relation to Other Risk Factors for Coronary Heart Disease

Cigarette smoking, elevated serum cholesterol, and elevated blood pressure are generally accepted as the three major modifiable risk factors for CHD. However, there is less agreement concerning other CHD risk factors – obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, psychologic type A behavior, etc. The following studies present recent evidence on the relationships between smoking and hypertension, coffee drinking, and ventricular premature beats.

Hypertension

Results from several studies have shown that smokers on the average have slightly lower blood pressure than nonsmokers. Some investigators have attributed this finding to the fact that smokers on the average weigh slightly less than nonsmokers. Three current studies (*24, 36, 55*) discuss this relationship. Gyntelberg and Meyer (*24*), based on their evaluation of 5,249 men ages 40-59, were of the opinion that lower blood pressure in smokers could not be accounted for by differences in weight, age, or physical fitness. Kesteloot and Van Houte (*36*), in a study of 42,804 men, performed a multiple regression analysis on age, weight, and height and found that cigarette smokers had lower blood pressure than nonsmokers; however, when they included serum cholesterol values in the analysis, the difference in blood pressure was reduced to approximately 1 mm Hg. Although this difference was statistically significant based on the large population, the actual difference in blood pressure was too small to be of clinical importance.

Seltzer (*55*) studied 794 men selected for their initial good health and normal blood pressure (below 140 systolic and 90 diastolic) and followed them for changes in cigarette smoking habits, weight, and blood pressure. During the 5-year period of the study 104 men gave up smoking. For every age group except those over 55, there was a significantly greater weight gain (8 lb) among the "quitters" than among the continuing smokers (3.5 lb). Blood pressure increased 4 mm Hg systolic and 2.5 mm Hg diastolic in the quitters with no change in systolic and a slight reduction in diastolic (-1.1 mm Hg) in persons who continued to smoke. In order to examine blood pressure changes in relation to weight change, both continuing smokers and quitters were grouped according to their weight changes during the period of study (Table 1). The most significant finding was an increase in the systolic blood pressure (+1.77 mm Hg) among the quitters even in that group with significant weight loss. In contrast, the continuing smokers with significant weight loss had a decline in systolic blood pressure (-3.28 mm Hg). Diastolic blood pressure in quitters showed an increase with weight gain and no change with weight loss, while continuing smokers showed a decrease in diastolic pressure with weight loss and no change with weight gain. The data on subjects whose blood pressure had increased to hypertensive levels (systolic > 150 and diastolic > 95) were evaluated, and it was found that quitters had a much higher frequency of becoming hypertensive than continuing smokers (Table 2).

Seltzer, in interpreting these data, suggested that cigarette smoking tends to inhibit blood pressure increases, with only minimal pressure rises occurring even in instances of substantial weight gain. When this inhibiting effect of cigarette smoking is removed as in the case of the quitters, sharp rises in blood pressure become evident. He cautioned, however, that the development of hypertension in some quitters may have been responsible for decisions to lose weight and that his data do not allow an evaluation of the degree of blood pressure changes according to how recently cigarettes were given up.

The results of the ischemic heart disease study by Kahn, et al. (*34*) raise additional questions about Seltzer's data. Kahn followed 10,000 Israeli male civil service employees for 5 years to determine what factors were associated with an increased incidence of hypertension. He presented no data concerning persons who stopped smoking, but he did show that the incidence of hypertension increased with age and that the age-adjusted incidence of hypertension in smokers was over twice that of nonsmokers (76.9/1000 for smokers versus 35.4/1000 for nonsmokers). Seltzer reported no

TABLE 1. – *Age-standardized blood pressure changes (mm Hg)[1] at followup for continuing cigarette smokers and quitters according to weight changes*

Smoking Class	Weight Change (LB)							
	Significant Wt Loss		No Significant Wt Change		Moderate Wt Gain		Significant Wt Gain	
	No.	lb -25 to -5	No.	lb -4 to +4	No.	lb +5 to +12	No.	lb +13 to +30
Mean systolic BP changes:								
Continuing smokers	32	−4.00	84	−1.52	71	2.85	24	1.50
Quitters	13	1.77	27	2.22	27	4.04	32	3.69
Mean diastolic BP changes:								
Continuing smokers	32	−3.28	84	−2.04	71	0.73	24	−0.04
Quitters	13	−0.31	27	−1.96	27	4.30	32	3.94

[1]Standardized on basis of age distribution of current cigarette smokers.

Source: Seltzer, C.C. (*55*).

TABLE 2. – *Number of subjects who had developed hypertension at followup for continuing cigarette smokers and quitters*

Blood pressure levels	Continuing cigarette smokers		Quitters	
	Number	Percent	Number	Percent
Systolic blood pressure 150+	6	2.8	9	8.7
Systolic blood pressure 160+	2	0.9	5	4.8
Diastolic blood pressure 95+	3	1.4	5	4.8

Source: Seltzer, C.C. (*55*).

data on the incidence of hypertension in nonsmokers, and the age distribution for his group of smokers (the original source of the quitters) is heavily weighted toward younger age groups (with only 33 of 214 men age 50 years or over). According to Kahn's data, this age group would be expected to have a lower incidence of hypertension, and, in fact, Seltzer found only small numbers of men who developed hypertension (eight with diastolic hypertension) (Table 2). Making interpretations based on such small numbers is hazardous; for example, the difference between current smokers and quitters in the incidence of diastolic hypertension could have been produced by only three men quitting smoking because they developed hypertension.

Coffee Drinking

The Boston Collaborative Drug Study (*12*) recently reported a correlation between coffee drinking ($\geq$ 6 cups per day) and myocardial infarction that persisted after controlling for the effect of cigarette smoking. This was a retrospective study of 276 patients with a hospital discharge diagnosis of myocardial infarction and 1,104 age, sex, and hospital-matched controls discharged with other diagnoses. In addition to the usual limitations of retrospective studies, this study has several characteristics that make interpretation difficult. In controlling for the effect of cigarette smoking, the investigators divided the smokers into those who smoked one pack or less per day and those who smoked more than one pack per day. Because cigarette consumption is highly correlated with coffee consumption (*29, 39*), it can be expected that within such broad smoking categories those who were heavy coffee drinkers tended to be heavier smokers than those who consumed smaller amounts of coffee. It is also possible that the hospitalized controls represented persons who drank less coffee than the general population because of serious chronic illnesses. These characteristics of the study design do not allow firm conclusions to be made concerning the extent to which the relationship between coffee drinking and myocardial infarction is independent of the relationship of both variables to cigarette smoking.

The question of the independent nature of this relationship is also dealt with in a prospective study by Klatsky, et al. (*39*) of 464 patients with myocardial infarction who previously had had multiphasic health checkups. Both ordinary controls and CHD risk factor-matched controls were drawn from 250,000 people who had undergone the same multiphasic health checkups. The investigators did not find an independent correlation between coffee drinking and myocardial infarction when risk-matched controls were used.

The Framingham Study (*18*) recently published data on coffee drinking based on a 12-year followup of 5,209 men and women ages 30-62. An increased risk of death from all causes was demonstrated in coffee drinkers, but this relationship was accounted for by the association between coffee consumption and cigarette smoking. No association between coffee drinking and myocardial infarction or between coffee drinking and the development of CHD, stroke, or intermittent claudication was demonstrated. Heyden, et al. (*29*) also found no relationship between excessive coffee consumption (> 5 cups per day) and atherosclerotic vascular disease.

Ventricular Premature Beats

Ventricular premature beats have been shown to be a risk factor for sudden death from CHD. Vedin, et al. (*69*), in a study of 793 men in Goteborg, Sweden, examined the frequency of rhythm and conduction disturbances at rest and during exercise. They found no statistically significant correlation between cigarette smoking habits and the presence of supraventricular or ventricular premature beats at rest or during exercise.

CARBON MONOXIDE

Introduction

Carbon monoxide has long been recognized as a dangerous gas, but until recently concentrations which produced carboxyhemoglobin levels below 15 to 20 percent were thought to have little effect on humans. Currently there is considerable interest in determining the effect of chronic exposure to low levels of carbon monoxide (*65, 66, 67, 68*).

Carbon monoxide is present in concentrations of 1 to 5 percent of the gaseous phase of cigarette smoke (*11, 45*). The concentration varies with temperature of combustion as well as with factors which control the oxygen supply such as the porosity of the paper and packing of the tobacco. The amount of carbon monoxide produced increases as the cigarette burns down. Carboxyhemoglobin levels in smokers vary from 2 to 15 percent depending on the amount smoked, degree of inhalation, and the time elapsed since smoking the last cigarette.

Carbon monoxide, which has 230 times the affinity of oxygen for hemoglobin, impairs oxygen transportation in at least two ways:

First, it competes with oxygen for hemoglobin binding sites. Second, it increases the affinity of the remaining hemoglobin for oxygen, thereby requiring a larger gradient in Po_2 between the blood and tissue to deliver a given amount of oxygen; this increased gradient is usually produced by a lowering of the tissue Po_2.

Carbon monoxide also binds to other heme-containing pigments, most notably myoglobin, for which it has even a greater affinity than for hemoglobin under conditions of low Po_2. The significance of this binding is unclear, but may be important in tissues, such as the heart muscle, which have both high oxygen requirements and large amounts of myoglobin.

Sources of Carbon Monoxide Exposure and Human Absorption

Several researchers (*13, 32, 35, 57, 60, 70*) have estimated the relative contribution of cigarette smoking and air pollution to the human carbon monoxide burden as measured by carboxyhemoglobin levels (COHb). Kahn, et al. (*35*), in a study of 16,649 blood donors, determined that smoking was the most important contributing factor, followed by industrial work exposure. Nonsmoking industrial workers had COHb levels of 1.38 percent, and nonsmokers without industrial exposure had levels of .78 percent. Cigarette smokers, on the other hand, had very high levels. Smokers with industrial exposure had levels of 5.01 percent, while smokers without industrial exposure had levels of 4.44 percent (Tables 3 and 4). Stewart, et al. (*57*) found similar results in a nationwide survey of blood donors and noted marked variation in mean COHb levels in residents of different cities measured at different times of the year (Table 5). However, in all areas, smokers still had COHb levels two to three times higher than nonsmokers and had increasing COHb levels with increasing level of cigarette consumption (Table 6). Similar findings were reported by Torbati, et al (*60*) in a study of 500 male Israeli blood donors.

Nonsmoking workers exposed to automobile exhaust – London taxi drivers (*32*) and garage and service station operators (*13*) – have higher baseline levels of carboxyhemoglobin than nonsmokers of the general population. But even in these high exposure occupations smokers have markedly higher COHb levels (8.1 and 10.8 percent) than nonsmokers (6.3 and 5.5 percent). An extreme is represented by New York City tunnel workers who are exposed to an average of 63 ppm CO with peak exposure levels as high as 217 ppm CO; cigarette smokers still maintained much higher COHb levels (5.01 percent) than nonsmokers (2.93 percent) (*8*).

TABLE 3. – *Mean percent of carboxyhemoglobin saturation in smokers and nonsmokers by sex and race*

	Total Sample		Nonsmokers		Smokers[1]	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Total Sample	16,649	2.30 ± 0.02	10,157	0.85 ± 0.01	6,492	4.58 ± 0.03
Male	10,542	2.66 ± 0.03	5,888	1.00 ± 0.01	4,654	4.76 ± 0.04
Female	6,107	1.68 ± 0.03	4,269	0.64 ± 0.01	1,838	4.10 ± 0.06
White	15,167	2.28 ± 0.02	9,474	0.85 ± 0.01	5,693	4.66 ± 0.04
Male	9,669	2.65 ± 0.03	5,508	1.00 ± 0.01	4,161	4.83 ± 0.04
Female	5,498	1.63 ± 0.03	3,966	0.64 ± 0.01	1,532	4.19 ± 0.06
Black	1,429	2.59 ± 0.06	641	0.86 ± 0.03	788	4.00 ± 0.08
Male	829	2.91 ± 0.10	347	1.07 ± 0.05	482	4.24 ± 0.10
Female	600	2.15 ± 0.09	294	0.62 ± 0.04	306	3.63 ± 0.12

[1]Smokers are defined as those who smoked on the day of giving blood.

NOTE. – $\bar{X}$ = mean percent; $S_{\bar{X}}$ = standard error of mean percent.

Source: Kahn, A., et al. (*35*).

TABLE 4. – *Mean percent of carboxyhemoglobin saturation in smokers and nonsmokers by employment status*

	Nonsmokers		Smokers[1]	
	No.	$\bar{X} \pm S_{\bar{X}}$	No.	$\bar{X} \pm S_{\bar{X}}$
Persons employed	8,478	0.89 ± 0.01	5,962	4.61 ± 0.03
Classed as industrial workers[1]	1,523	1.38 ± 0.04	1,738	5.01 ± 0.06
Classed as workers other than industrial	6,955	0.78 ± 0.01	4,224	4.44 ± 0.04
Persons not employed	1,678	0.63 ± 0.02	531	4.24 ± 0.11

[1]Industrial workers are employed in either durable or nondurable goods manufacturing (craftsmen, operatives, or laborers). Smokers are defined as those who smoked on the day of giving blood.

NOTE. – $\bar{X}$ = mean percent; $S_{\bar{X}}$ = standard error of mean percent.

Source: Kahn, A., et al. (*35*).

TABLE 5. – *Median percent carboxyhemoglobin (COHb) saturation and 90 percent range for smokers and nonsmokers by location*

Location	Cigarette Smokers		Nonsmokers	
	Median	Range	Median	Range
Anchorage	4.7	0.9 – 9.5	1.5	0.6 – 3.2
Chicago	5.8	2.0 – 9.9	1.7	1.0 – 3.2
Denver	5.5	2.0 – 9.8	2.0	0.9 – 3.7
Detroit	5.6	1.6 – 10.4	1.6	0.7 – 2.7
Honolulu	4.9	1.6 – 9.0	1.4	0.7 – 2.5
Houston	3.2	1.0 – 7.8	1.2	0.6 – 3.5
Los Angeles	6.2	2.0 – 10.3	1.8	1.0 – 3.0
Miami	5.0	1.2 – 9.7	1.2	0.4 – 3.0
Milwaukee	4.2	1.0 – 8.9	1.2	0.5 – 2.5
New Orleans	5.5	2.0 – 9.6	1.6	1.0 – 3.0
New York	4.8	1.2 – 9.1	1.2	0.6 – 2.5
Phoenix	4.1	0.9 – 8.7	1.2	0.5 – 2.5
St. Louis	5.1	1.7 – 9.2	1.4	0.9 – 2.1
Salt Lake City	5.1	1.5 – 9.5	1.2	0.6 – 2.5
San Francisco	5.4	1.6 – 9.8	1.5	0.8 – 2.7
Seattle	5.7	1.7 – 9.6	1.5	0.8 – 2.7
Vermont, New Hampshire	4.8	1.4 – 9.0	1.2	0.8 – 2.1
Washington, DC	4.9	1.2 – 8.4	1.2	0.6 – 2.5

Source: Stewart, R.D., et al. (57).

TABLE 6. – *Mean percent carboxyhemoglobin (COHb) saturation in cigarette smokers 1 hour after last cigarette*

Location	Nonsmoker	Packs of Cigarettes Smoked Per day				
		< ½	½-1	1	1½	2
Milwaukee	1.3	3.0	4.2	5.3	6.2	4.7
New Hampshire, Vermont	1.4	3.3	4.4	5.7	6.7	5.3
New York City	1.4	3.1	4.3	4.7	5.8	6.3
Washington, DC	1.4	3.8	4.6	5.2	5.8	6.6
Los Angeles	2.0	4.0	5.2	6.0	7.4	7.5
Chicago	2.0	4.8	5.4	6.3	7.1	7.7

Source: Stewart, R.D., et al. (57).

Studies on the CO burden of each cigarette have determined the body burden of CO per cigarette to be 7.10-8.66 ml (*40*), and the increase in COHb level produced by smoking one cigarette to be .94 to 1.6 percent after 12 hours of abstinence (*40, 53*). The half-life for the washout of CO in healthy college smokers (*40*) was calculated to be from 3 to 5 hours.

Effects on Healthy Individuals

Several studies have been published on the effects of carbon monoxide on healthy individuals. Small doses of CO (COHb levels 2.4-5.4 percent) were found to have no effect on heart rate (*56*). Raven, et al. (*51*), in a study of young men exposed during exercise on a treadmill to 50 ppm CO (COHb levels 2.5 percent in nonsmokers and 4.1 in smokers), found no decrease in maximum aerobic capacity when the subjects were tested at 25° C. In a similar experiment conducted at 35° C by the same researchers (*20*), there was a decrease in maximum aerobic capacity in nonsmokers exposed to 50 ppm CO, but not in smokers despite an increase in the carboxyhemoglobin levels of 1.5 percent in both groups. They postulated a possible physiologic adaptation of smokers to carbon monoxide. Ekblom and Huot (*22*) studied five young men who inhaled CO to reach given COHb levels. They reported that as COHb levels increased, there was a decrease in maximal oxygen uptake and lower heart rates at maximal treadmill exercise.

Sagone, et al. (*54*), in a study of 9 cigarette smokers and 18 nonsmokers ages 20-32, showed significantly higher values for COHb, red cell mass, hemoglobin, and hematocrit in the smokers. Levels of 2,3 DPG were unaltered while oxyhemoglobin affinity P50 and ATP levels were significantly lower in the smokers. The three smokers with highest red cell mass had normal arterial blood gases and one smoker had very high values of red cell mass which returned to normal after he stopped smoking. The authors interpret these data as evidence of tissue hypoxia.

Millar and Gregory (*43*), in a study of both fresh heparinized blood and ACD-stored blood from a blood bank, showed a reduction in the oxygen carrying capacity of up to 10 percent in the blood of cigarette smokers; this reduction persisted for the full 21-day storage life of blood bank blood.

Cole, et al. (*16*), in a study of pregnant women, found COHb levels in the fetus to be 1.8 times as great as those in the

simultaneously measured blood of the mother. Fetal blood was exposed to carbon monoxide in vitro, and fetal hemoglobin was found to have a shift of the oxyhemoglobin disassociation curve to the left as occurs with adult hemoglobin. The higher fetal COHb levels were attributed to the lower fetal Po_2 and a resultant decrease in the ability of oxygen to compete for the fetal hemoglobin. It was felt by the authors that the high COHb levels may be responsible for the lower birth weight of infants born to mothers who smoke.

Effects on Persons with Atherosclerotic Cardiovascular Disease

Aronow and Isbell (*5*) and Anderson, et al. (*1*) have shown a decrease in the mean duration of exercise before the onset of pain in patients with angina pectoris exposed to low levels of carbon monoxide (50 and 100 ppm). Carboxyhemoglobin levels were significantly elevated (2.9 percent after 50 ppm; 4.5 percent after 100 ppm) and the systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate (a measure of cardiac work) were all significantly lower at onset of angina pectoris.

In a continuation of this work, Aronow, et al. (*2, 3*) studied eight patients during two separate cardiac catheterizations, one during which each patient smoked three cigarettes and one during which each patient inhaled carbon monoxide until the maximal coronary sinus COHb level equalled that produced by smoking during the first catheterization. All eight had angiographically demonstrated CHD (> 75 percent obstruction of at least one coronary artery). Smoking increased the systolic and diastolic blood pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and coronary sinus, arterial, and venous CO levels. No changes were noted in left ventricular contractility (dp/dt), aortic systolic ejection period, or cardiac index, and decreases were found in stroke index and coronary sinus, arterial, and venous Po_2. When carbon monoxide was inhaled, increased LVEDP and coronary sinus, arterial, and venous CO levels were noted; there were no changes in systolic and diastolic blood pressure, heart rate, or systolic ejection period; and decreases in left ventricular dp/dt, stroke index, cardiac index and coronary sinus, arterial, and venous Po_2 were found. These data suggest that carbon monoxide has a negative inotropic effect on myocardial tissue resulting in the decrease in contractility (dp/dt) and stroke index. When the positive effect of nicotine on contractility and heart rate is added by cigarette smoking, the net effect is increased cardiac work for the same cardiac output. In the heart with

coronary artery disease there is a greatly restricted capacity to increase blood flow in response to this increase in cardiac work. The result is early cardiac decompensation manifested by elevation in LVEDP and angina pectoris.

Aronow, et al. have also shown decreased exercise time prior to onset of angina pectoris in persons exercised after riding for 90 minutes on the Los Angeles Freeway (*4*). In a related study, they demonstrated a decrease in exercise time before claudication in a group of patients with intermittent claudication who were exposed to 50 ppm CO (*6*).

Studies on the Pathogenesis of Cardiovascular Disease

In a review of some of their work on carbon monoxide, Astrup and Kjeldsen (*7*) noted that in cholesterol-fed rabbits exposed to 170 ppm carbon monoxide for 7 weeks (COHb 16 percent) and then to 340 ppm for 2 weeks, the cholesterol content of the aorta was 2.5 times higher than that of cholesterol-fed, air breathing controls. Groups of cholesterol-fed rabbits intermittently exposed to carbon monoxide for 12 or 4 hours per day produced three- to fivefold increases in the cholesterol content of their aortas. Cholesterol-fed rabbits made hypoxic at 10 and 16 percent oxygen had 3 to 3.5 times the aortic cholesterol content, while those exposed to 26 and 28 percent oxygen had a considerable decrease in cholesterol accumulation.

Theodore, et al. (*58*) studied the aortas of monkeys, baboons, dogs, rats, and mice fed a normal diet but exposed to very high levels of CO (COHb levels 33 percent) and found no atheromatous changes in their aortas.

Further work by Astrup and Kieldsen (*38*) revealed that in rabbits fed normal diets but exposed to 180 ppm carbon monoxide for 2 weeks, there were local areas in their hearts of partial or total necrosis of myofibrils; in the arteries there was endothelial swelling, formation of subendothelial edema, and degeneration of the myocytes. When the aortas of these rabbits were examined (*37*), the luminal coats showed pronounced changes characterized by severe edematous reaction with extensive swelling and formation of subendothelial blisters and plaques. The authors postulate that carbon monoxide increases endothelial permeability to albumin which results in formation of edema leading to changes indistinguishable from early atherosclerosis.