CHAPTER 1

Introduction and Summary

INTRODUCTION AND SUMMARY

Cigarette smoking continues to be a major health problem in the United States today. It is still too early to tell whether the increasing rate of giving up smoking by adults during the years 1967, 1968, 1969, and early 1970 and the plateauing of this effect during the past year have had any measurable effect on the morbidity and mortality associated with smoking. At the same time that the major health professions, voluntary health agencies, and public service agencies concerned have joined with government agencies to reduce the magnitude of this problem through education, research efforts devoted to understanding how cigarette smoking affects biological function to produce disease continue at a high level.

This report is largely concerned with reviewing the research reports which have become available in the past year. In this chapter, brief summary statements are presented of the state of knowledge in several areas. These are followed, where appropriate, by a "highlight" statement of significant additions to knowledge made as a result of the new research presented in greater detail in the body of the report.

The state of knowledge in three areas, which have not been reviewed previously, is also presented in the report. These areas are: Allergy, Public Exposure to Air Pollution from Tobacco Smoke, and the Harmful Constituents of Cigarette Smoke.

SUMMARY: CORONARY HEART DISEASE

Cigarette smokers have higher death rates from coronary heart disease (CHD) than nonsmokers. This relationship is stronger for men than women. Cigarette smoking markedly increases an individual's susceptibility to earlier death from CHD. Cigarette smoking, hypertension, and elevated serum cholesterol are major risk factors contributing to the development of CHD; cigarette smoking acts both independently and conjointly with these other factors to increase the risk of developing CHD. Cigarette smoking may contribute both to the development of CHD and to the exacerbation of preexistent CHD; both nicotine and carbon monoxide are thought to contribute to these abnormal processes. Cigarette smoking is associated with a significant increase in atherosclerosis of the aorta

and coronary arteries. Cessation of smoking is associated with a decreased risk of death from CHD. The risk of CHD incurred by pipe and cigar smokers is appreciably less than that incurred by cigarette smokers.

Highlights of 1972 Report: Coronary Heart Disease

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.

2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.

3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.

4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic non-neoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

SUMMARY: CEREBROVASCULAR DISEASE

Cigarette smokers have higher death rates from cerebrovascular disease than nonsmokers.

SUMMARY: NONSYPHILITIC AORTIC ANEURYSM*

Cigarette smokers have higher death rates from nonsyphilitic aortic aneurysm than nonsmokers.

SUMMARY: PERIPHERAL VASCULAR DISEASE

Cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking appears to aggravate preexistent peripheral vascular disease.

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* This summary statement is the same as that appearing in previous reports, because new studies adding to the understanding of this area have not appeared. Consequently, the literature in this area is not reviewed and the statement is only included to complete this summary chapter.

SUMMARY: NON-NEOPLASTIC BRONCHOPULMONARY DISEASES

Cigarette smoking is the most important cause of chronic obstructive bronchopulmonary disease (COPD) in the United States. Cigarette smokers have higher death rates from pulmonary emphysema and chronic bronchitis and more frequently have impaired pulmonary function and pulmonary symptoms than nonsmokers. Ex-cigarette smokers have lower death rates from COPD than do continuing smokers. Cessation of smoking is associated with improved ventilatory function and decreased pulmonary symptom prevalence. For most of the United States population, cigarette smoking is a more important cause of COPD than air pollution or occupational exposure; cigarette smoking may also act conjointly with occupational or environmental exposure to produce greater COPD morbidity and mortality. An infrequent genetic error, homozygous alpha$_1$-antitrypsin deficiency, has been commonly associated with the early development of severe, panacinar emphysema. Whether or not cigarette smoking acts together with the homozygous or heterozygous deficiency states to increase the risk of developing either panacinar emphysema or the more common forms of COPD has not been adequately studied. Cigarette smoking exerts an adverse effect on the pulmonary clearance mechanism. Respiratory infections are more prevalent and severe among cigarette smokers, particularly among heavy smokers, than among nonsmokers. The risk of developing or dying from COPD among pipe or cigar smokers is probably higher than that among nonsmokers but is clearly less than that among cigarette smokers.

Highlights of the 1972 Report:
Non-neoplastic Bronchopulmonary Diseases

1. Recent epidemiological and clinical studies from several countries confirm that men and women cigarette smokers have an increased prevalence of respiratory symptoms and have diminished pulmonary function compared to nonsmokers.

2. Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers.

3. Recent occupational studies confirm that cigarette smoking is an important cause of COPD, acting both independently and in combination with occupational exposure.

4. Recent experimental studies confirm that cigarette smoking exerts an adverse effect on pulmonary clearance and macrophage function.

5. Pulmonary macrophages obtained from cigarette smokers exhibit characteristic morphologic differences when compared to those obtained from nonsmokers.

SUMMARY: CANCER

Cigarette smoking is the major cause of lung cancer in men and a significant cause of lung cancer in women. The risk of developing lung cancer in both men and women is directly related to an individual's exposure as measured by the number of cigarettes smoked, duration of smoking, earlier initiation, depth of inhalation, and the amount of "tar" produced by the cigarette. The risk of developing lung cancer diminishes with cessation of smoking. Smokers of pipes or cigars have a lower risk of developing lung cancer than cigarette smokers. Certain occupations are associated with an increased risk of developing lung cancer. In these occupational settings cigarette smoking appears to exert an effect that produces much higher lung cancer rates than those resulting either from the occupational exposure alone or from smoking alone. Factors associated with urban living result in an increase in the risk of developing lung cancer; this effect, however, is minor compared to the overriding effect of cigarette smoking.

The smoking of cigarettes, pipes, and cigars is a significant factor in the development of cancers of the larynx and oral cavity. Pipe smoking is causally related to cancer of the lip. The significant association between smoking and the development of cancer of the esophagus is somewhat stronger for cigarettes than for pipes or cigars and the combined exposure to alcohol and cigarettes is associated with especially high rates of cancer of the esophagus. Cigarette smoking is associated with cancer of the urinary bladder in men. There is also an association between cigarette smoking and cancer of the pancreas.

Highlights of the 1972 Report: Cancer

1. Preliminary results from a major prospective epidemiological study in Japan demonstrate a strong association between cigarette smoking and lung cancer. A dose-response relationship was demonstrated for the number of cigarettes smoked. These findings in an Asian population with distinct genetic and cultural characteristics confirm the major importance of cigarette smoking in the causation of lung cancer, a conclusion which up to now has been based largely on studies of Caucasian populations in the United States, Canada, and Europe.

2. Ex-smokers have significantly lower death rates for lung cancer than continuing smokers. The decline in risk following cessation appears to be rapid both for those who have smoked for long periods of time and for those with a shorter smoking history, with the sharpest reductions taking place after the first two years of cessation.

3. The risk of developing lung cancer appears to be higher for smokers who have chronic bronchitis. Though both conditions are directly related to the amount and duration of smoking, an additional risk for lung cancer appears to exist for cigarette smokers with chronic bronchitis which is independent of age and number of cigarettes consumed.

4. Experimental studies on animals have demonstrated that the particulate phase of tobacco smoke contains certain chemical compounds which can act as complete carcinogens, tumor initiators, or tumor promoters. Recently, other compounds have been described that have no independent activity in two-stage carcinogenesis but *accelerate* the carcinogenic effects of polynuclear aromatic hydrocarbons in the initiator-promoter system.

5. Additional epidemiological evidence confirms a significant association between the combined use of cigarettes and alcohol, and cancer of the esophagus.

6. Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder cancer increases with inhalation and the number of cigarettes smoked.

7. Epidemiological evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas.

SUMMARY: PREGNANCY

Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight. There is increasing evidence to support the view that women who smoke during pregnancy have a significantly greater risk of an unsuccessful pregnancy than those who do not.

SUMMARY: GASTROINTESTINAL DISORDERS

Cigarette smoking males have an increased prevalence of peptic ulcer disease as compared to nonsmoking males and a greater peptic

ulcer mortality ratio. These relationships are stronger for gastric ulcer than for duodenal ulcer. Smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of ulcer healing.

Highlights of the 1972 Report: Gastrointestinal Disorders

1. A possible link between cigarette smoking and peptic ulcer has been demonstrated in dogs in which nicotine was found to inhibit pancreatic and hepatic bicarbonate secretion. This could lead to peptic disease by depriving the duodenum of sufficient alkaline secretion to neutralize gastric acidity.

2. An investigation in human volunteers has suggested that cigarette smoking decreases the effectiveness of the lower-esophageal sphincter as a barrier against gastro-esophageal reflux.

SUMMARY: TOBACCO AMBLYOPIA*

Tobacco amblyopia is presently a rare disorder in the United States. The evidence suggests that this disorder is related to nutritional or idiopathic deficiencies in certain detoxification mechanisms, particularly in the metabolism of the cyanide component of tobacco smoke.

SUMMARY: NON-NEOPLASTIC ORAL DISEASE*

Ulceromembranous gingivitis, alveolar bone loss, and stomatitis nicotina are more commonly found among smokers than among nonsmokers. The influence of smoking on periodontal disease and gingivitis probably operates in conjunction with poor oral hygiene. In addition, there is evidence that smoking may be associated with edentulism and delayed socket healing. While further experimental and clinical studies are indicated, it would appear that nonsmokers have an advantage over smokers in terms of their oral health.

The information contained in the following three summary statements: Allergy, Public Exposure to Air Pollution from Tobacco Smoke, and Harmful Constituents of Cigarette Smoke, is new and appears for the first time.

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* This summary statement is the same as that appearing in previous reports, because new studies adding to the understanding of this area have not appeared. Consequently, the literature in this area is not reviewed and the statement is only included to complete this summary chapter.

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SUMMARY OF THE 1972 REPORT: ALLERGY

1. Tobacco leaf, tobacco pollen, and tobacco smoke are antigenic in man and animals.

2. (a) Skin sensitizing antibodies specific for tobacco antigens have been found frequently in smokers and nonsmokers. They appear to occur more often in allergic individuals. Precipitating antibodies specific for tobacco antigens have also been found in both smokers and nonsmokers.

   (b) A delayed type of hypersensitivity to tobacco has been demonstrated in man.

   (c) Tobacco may exert an adverse effect on protective mechanisms of the immune system in man and animals.

3. (a) Tobacco smoke can contribute to the discomfort of many individuals. It exerts complex pharmacologic, irritative, and allergic effects, the clinical manifestations of which may be indistinguishable from one another.

   (b) Exposure to tobacco smoke may produce exacerbation of allergic symptoms in nonsmokers who are suffering from allergies of diverse causes.

4. Little is known about the pathogenesis of tobacco allergy and its possible relationship to other smoking-related diseases.

SUMMARY OF THE 1972 REPORT: PUBLIC EXPOSURE TO AIR POLLUTION FROM TOBACCO SMOKE

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various

concentrations to affect adversely animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

SUMMARY OF THE 1972 REPORT: HARMFUL CONSTITUENTS OF CIGARETTE SMOKE

A number of substances or classes of substances found in cigarette smoke are identified as those which are judged to be contributors to the health hazards of smoking. These constituents are further divided into the *most likely* contributors to these health hazards (carbon monoxide, nicotine, and tobacco "tar"), substances which are *probable* contributors, and those which are *suspected* contributors. The recommendations for control in this area are to seek progressive reduction of all harmful constituents in cigarette smoke with priority being given first to the most likely contributors named and second to the probable contributors to the health hazards of smoking. These judgments represent the consensus of experts based on current knowledge and are subject to modification and further elaboration as more knowledge becomes available.

CHAPTER 2

Cardiovascular Diseases

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INTRODUCTION

In the United States more people die from coronary heart disease (CHD) than from any other disease; furthermore, CHD is the single most important cause of excess death among cigarette smokers (*54, 57*). The 1971 report, "The Health Consequences of Smoking" (*56*), outlined the growing magnitude of this problem and summarized the relationship between smoking and coronary heart disease as follows:

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.

3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.

4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.

5. The cessation of smoking is associated with a decreased risk of death from CHD.

6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:

   a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.

c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.

d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.

e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Recent epidemiological, pathological, and experimental studies add to the understanding of the relationship between smoking and CHD. These studies point to cigarette smoking as one of the major risk factors leading to CHD and help clarify some of the biomechanisms through which this occurs.

EPIDEMIOLOGICAL STUDIES

A prospective study of 973 men born in 1913 in Göteborg, Sweden, was undertaken in 1963 (51, 52). The proportion of myocardial infarctions among cigarette smokers was significantly greater than among nonsmokers (P < .05), and the incidence of myocardial infarction rose with increasing cigarette consumption (table 1). Of the 35 individuals who experienced a myocardial infarction between 1963 and 1970, only two had been nonsmokers; in the whole population of men born in 1913, 56 percent were smokers.

Although angina pectoris was more common in smokers than nonsmokers, the difference was smaller than for myocardial infarction and was not statistically significant (52).

Paffenbarger, et al. (42) reported on the health experience of 3,263 longshoremen studied over the past 18 years. During this interval 1,098 were known to have died, 350 dying from CHD. Longshoremen who smoked more than 20 cigarettes a day faced a risk of coronary death which was more than twice as great as that of the group made up of both nonsmokers and smokers of less than 20 cigarettes a day (P < .01).

Keys, et al. (30) analyzed the 20-year CHD incidence among 279 Minnesota men aged 47 through 57 years who were CHD free at entry into the study. The relationship of cigarette smoking habits at the start of the study to the subsequent incidence of CHD was examined. The originally published table of results was incorrect

and the authors have supplied a corrected table which appeared in a later issue of the same journal (table 2). The morbidity ratio for "hard CHD" (CHD deaths plus myocardial infarctions not resulting in death) among those smoking more than 10 cigarettes a

TABLE 1.—*Incidence (1963–1970) of heart infarct in relation to tobacco consumption in "The Men Born in 1913," Göteborg, Sweden.*

n = 855

Smoking classification	Heart infarct Number	Percent
Never smoked n = 207	(2)	1.0
Stopped smoking n = 168	(2)	1.0
Cigarette smokers 1–14 cig/day n = 234	(13)	6.0
15–24 cig/day n = 138	(9)	7.0
≧25 cig/day n = 33	(4)	12.0
Pipe/cigar n = 75	(5)	7.0

SOURCE: Tibblin, G., Wilhelmsen, L. (51).

TABLE 2.—*Cigarette smoking at entry and subsequent 20-year CHD incidence among Minnesota men.*[1]

Age	Number of men	Item	Never	Smoking habit (cigarettes/day) Stopped	<10	10–19	>20
47, 48	53	% with habit	23	19	9	19	30
49, 50	51	% with habit	33	20	14	10	23
51, 52	69	% with habit	33	26	14	14	13
53, 54	53	% with habit	36	30	8	13	13
55–57	51	% with habit	24	33	8	18	17
47–57	277	Number of men	83	71	30	41	52
47–57	277	Hard CHD rate (%)	12.0	15.5	10.0	17.1	21.2
47–57	277	Hard CHD rate (SE)	± 3.6	+ 4.3	± 5.5	± 5.9	± 5.7
47–57	277	Hard CHD Morbidity Ratio	1.00	1.29	.83	1.43	1.77
47–57	277	All CHD rate (%)	±21.7	±21.1	±16.7	±19.5	±26.9
47–57	277	All CHD rate (SE)	± 4.5	± 4.8	± 6.8	± 6.2	± 6.1
47–57	277	All CHD Morbidity Ratio	1.00	.97	.77	.90	1.24

[1] Cigarette smoking habits, by age at start of the 20-year follow-up. 20-year incidence rates (per 100 men), and standard errors (SE) of the rates. "Hard CHD"—CHD death and myocardial infarcts. "All"—angina pectoris and other CHD diagnoses. "Deaths"—from all causes except violence.

SOURCE: Modified from Keys, A., et al. (30).

day is similar to that reported from the large prospective studies. However, with the small number of cases in each smoking category, there are no statistically significant differences in the incidence of CHD between the categories, either singly or combined.

Retrospective studies of CHD have recently been reported from Czechoslovakia, Sweden, Norway, and India which corroborate earlier studies linking cigarette smoking with excess CHD morbidity and mortality.

The Prague study (19) included 443 men between the ages of 60 and 64 years. Significantly more (P < .05) individuals with a "probable" myocardial infarction were found among cigarette smokers than among nonsmokers or pipe and cigar smokers.

The smoking habits of 120 patients with myocardial infarction who were hospitalized in Göteborg were compared with those of the entire "men born in 1913" population sample (17, 62). A significantly (P < .01) greater number of smokers and heavy smokers (more than 15 cigarettes a day) were found in the myocardial infarction group than in the population sample.

The Bergen, Norway, cross sectional study of 2,117 women and 2,472 men documented a relationship between smoking and CHD in men, which was most marked in the 50 to 59 year old age group (16). No effect of smoking on the prevalence of CHD in women was demonstrable in this study, and the effect in men did not appear to be related to the daily number of cigarettes smoked.

In New Delhi, 100 "well documented" cases of ischemic heart disease were compared with an equal number of control cases (8). In this study, significantly more (P < .01) of the case group smoked cigarettes regularly than the control group (Morbidity Ratio = 2.1).

Mulcahy, et al. (40) recently found a positive association between coronary heart disease mortality rate and calculated per capita cigarette consumption in 21 countries. He interpreted the results as being consistent with the hypothesis that cigarette smoking is a significant risk factor in CHD mortality.

Stamler, et al. (50) found that for both men and women the 1964 CHD mortality rates in 17 developed countries were related to average annual per capita cigarette consumption.

INTERACTION OF SMOKING AND OTHER RISK FACTORS

The Report of the Inter-Society Commission for Heart Disease Resources summarized the evidence indicating that three risk factors (hypercholesterolemia, hypertension, and cigarette smoking) are properly designated major risk factors for premature CHD (28). Other possible risk factors including obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, electrocardio-

graphic abnormalities, a positive family history of premature CHD, and psychologic and social factors have also been described (*54, 55, 56*).

In the study of 973 men born in 1913 in Göteborg, Sweden, several coronary risk factors including elevated serum cholesterol, elevated serum triglyceride, low physical activity at work, and smoking were found to be related to an increased risk for the development of coronary heart disease during the subsequent years of the study. Failure to find a relationship between hypertension and an increased risk of CHD may have been due to the fact that all patients with hypertension in 1963 have been under treatment since that time.

Tibblin and Wilhelmsen (*52*) found that as a patient accumulated more risk factors his chance of developing CHD became substantially greater. Werkö (*61*) reported from the same Göteborg study that patients who were smokers, had sedentary jobs, and had both elevated cholesterol and triglycerides experienced a 4-year incidence of new coronary events of about 20 percent; the 4-year incidence among those who exhibited only one or two risk factors was much lower, ranging from 0 to 3 percent. ECG changes and anginal pain were included in the definition of new coronary events.

Paffenbarger, et al. (*42*) evaluated coronary risk factors in the study of 3,263 longshoremen. They found that, with the exception of diagnosed heart disease, smoking was the most important factor predictive of high risk for coronary mortality.

Keys, et al. (*30*) in the study of 279 Minnesota men, concluded that a positive cold pressor test, elevated serum cholesterol, and elevated systolic blood pressure had major predictive power for CHD death or infarction; in their analysis smoking seemed less important.

Stamler (*49*) has analyzed the data on 13 deaths occurring during the first years of the Chicago Coronary Prevention Evaluation Program, which originally consisted of 519 coronary-prone male volunteers aged 40 to 59 who were free from clinical CHD. Eleven of the 13 decedents had three or more coronary risk factors at entry into the program, and at least 8 were cigarette smokers at the time of death. Forty-three men, who were cigarette smokers at entry into the Coronary Prevention Evaluation Program, gave up smoking and have remained active in the program. There have been no deaths from cardiovascular causes in this group. Stamler (*49*) commented: "Even though the number of decedents was small, these data strongly suggest that continued cigarette smoking is associated with very high risk of premature death for very coronary-prone men, and that other preventive measures are by themselves of limited value for them as long as they fail to give up cigarette smoking."

As described in the 1971 report, "The Health Consequences of Smoking" (56), some studies have indicated that smokers show increased levels of serum lipids while others have not. Such contradictory results are also present in recent studies from Germany, Poland, and Sweden (21, 39, 53).

After a patient suffers a myocardial infarction, he frequently gives up smoking (17, 26). Only fragmentary data are available on what effect the cessation of cigarette smoking might have on the likelihood of a recurrent myocardial infarction (9, 34, 43). Ninety-two survivors of a first myocardial infarction were studied over a 3-year period by Parás Chavero, et al. (43). During this time, 37 patients continued smoking, and 12 of them (32 percent) experienced a second myocardial infarction. The 51 patients who did not smoke during this 3-year period included 39 ex-smokers and 12 patients who had never smoked. Eight of the nonsmokers (16 percent) experienced a second myocardial infarction. The smoking habits of four of the patients were not known. Although the continuing smokers experienced a greater rate of recurrent myocardial infarction than the nonsmokers, the difference was not statistically significant (P = .07).

The role of genetic factors in the development of CHD and the difficulties associated with the use of twin studies were discussed in the 1971 report, "The Health Consequences of Smoking" (56). Mailed questionnaires were used to establish the diagnosis of angina pectoris in a study by Lundman, et al. of twin pairs discordant with respect to smoking habits and in a study by Liljefors of twins with CHD. Lundman, et al. (36) recently investigated 69 male twins with the diagnosis of angina pectoris established by questionnaire. Only 22 percent of these diagnoses could be verified by clinical examination.

In a study of CHD, Liljefors (35) studied 91 pairs of twins from the Swedish Twin Registry of 1967. The twins ranged in age from 42 to 67 years, and 51 pairs were monozygotic. Smoking habits were not significantly different in pairs discordant for the probable presence of CHD. However, Liljefors noted that ". . . in many pairs the smoking habits were similar and that the material included few pairs discordant with respect to smoking, so that it does not provide a suitable basis for conclusions as to the causal importance of smoking for CHD." As observed in the 1971 report, "The Health Consequences of Smoking" (56), it would be surprising if genetic factors did not play a role in heart disease; however, it is open to question whether findings from twin studies can be used to distinguish between ". . . the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors 'cause' both heart disease and smoking."

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AUTOPSY STUDIES

In previously reported autopsy studies, Auerbach, et al. found that aortic and coronary atherosclerosis in man were more common and severe among smokers than among nonsmokers (5). They have now extended their investigations to the myocardial arterioles of men and beagle dogs (6). In a study of 1,184 men, they found that the thickness of myocardial arteriole walls was greater, on the average, in smokers than nonsmokers (table 3). The thickness increased with the number of cigarettes smoked per day and with age. The thickness was less, on the average, among cigar and pipe smokers than among cigarette smokers, but it was greater than in men who had never smoked regularly.

TABLE 3.—*Human autopsy study. Comparison of the thickness of myocardial arteriole walls in smokers and nonsmokers.*[1]

Age (year)	Smoking	Total	Number of Men				Percent of Men		
			‡Grade 0	‡Grade 1	‡Grade 2, 3	‡Grade Total	‡Grade 0	‡Grade 1	‡Grade 2,3
< 45	None	22	2	19	1	100.0	9.1	85.4	4.5
	Cigar, pipe	4	—	1	3	100.0	—	†25.0	†75.0
	Cig. 1–19	50	1	31	18	100.0	2.0	62.0	36.0
	Cig. 20–39	85	4	35	46	100.0	4.7	41.2	54.1
	Cig. ≧40	29	—	10	19	100.0	—	34.5	65.5
45–59	None	15	1	12	2	100.0	6.7	80.0	13.3
	Cigar, pipe	13	—	8	5	100.0	—	61.5	38.5
	Cig. 1–19	33	—	17	16	100.0	—	51.5	48.5
	Cig. 20–39	99	—	35	64	100.0	—	35.4	64.6
	Cig. ≧40	50	—	11	39	100.0	—	22.0	78.0
60–69	None	56	4	36	16	100.0	7.1	64.3	28.6
	Cigar, pipe	35	—	22	13	100.0	—	62.9	37.1
	Cig. 1–19	92	—	44	48	100.0	—	47.8	52.2
	Cig. 20–39	193	—	58	135	100.0	—	30.1	69.9
	Cig. ≧40	87	—	21	66	100.0	—	24.1	75.9
≧ 70	None	32	2	18	12	100.0	6.3	56.2	37.5
	Cigar, pipe	40	—	19	21	100.0	—	47.5	52.5
	Cig. 1–19	30	—	12	18	100.0	—	40.0	60.0
	Cig. 20–39	46	—	12	34	100.0	—	26.1	73.9
	Cig. ≧40	9	—	3	6	100.0	—	†33.3	†66.7

[1] In the right ventricular wall of 1,020 men by age and smoking habits.
† Percentages based on less than ten cases.
‡ Four Point Scale for the Thickness of Myocardial Arteriole Walls:
    0—normal thickness; 1—slight thickness; 2—moderate thickness; 3—great thickness.
SOURCE: Auerbach, O., et al. (6).

In one experiment, beagle dogs inhaled cigarette smoke daily through tracheostomae. Twenty-eight dogs that died between days 57 and 875 formed one group; 32 dogs that were killed after 875 days formed another group. Eight control dogs were not exposed. Beagle myocardial arteriole walls were found to be thicker in smoking than nonsmoking dogs, in dogs smoking many cigarettes than in dogs smoking fewer cigarettes, and in dogs smoking nonfilter cigarettes than in dogs smoking filter-tip cigarettes (figure 1). Also, the thickness of arteriole walls increased with the duration of smoking.

Group N No smoking 8 Dogs	:	dots	
Group L Nonfilter Cigarettes (½ as many cigarettes) 10 Dogs		dots	dots
Group F Filter-Tip Cigarettes 10 Dogs		dots	dots
Group H Nonfilter Cigarettes 12 Dogs			dots
Grade of Thickness	0	1	2

Each dot represents one section. The three dots on a line represent the three sections from a particular dog.

FIGURE 1.—Canine autopsy study. Comparison of the thickness of myocardial arteriole walls in 32 smoking dogs killed after 875 days and 8 nonsmoking dogs.

SOURCE: Auerbach, O., et al. (6).

EXPERIMENTAL STUDIES

NICOTINE AND CIGARETTE SMOKE

Schievelbein, et al. (47) investigated the effect of oral nicotine administration over a 20-month period on lipid metabolism in 35 rabbits. Even though lipoprotein lipase levels and calcium content of the aorta were significantly greater in the group given nicotine than in the control group, the histological changes of arteriosclerosis were found with equal frequency in both groups. The authors concluded that the epidemiological correlations between CHD and cigarette smoking could not be explained by the pharmacologic effect of nicotine alone.

A study of the interaction of chronic nicotine administration and acute hypoxia in 280 rats was performed by Wenzel and Richards (60). Pretreatment of the rats with nicotine increased the mortality during hypoxia, but the difference was not statistically significant. Pretreatment with the nicotine also was associated with marked variability of regression of hypoxic heart lesions. The interaction of nicotine pretreatment and the hypoxic insult produced variable effects on myocardial enzymes.

Aronow (1) recently studied the effect of cigarette smoking on the A wave of the apexcardiogram in 20 men with CHD. The A wave reflects the left ventricular filling wave associated with the impact of blood upon the ventricular wall during left atrial contraction. He found that the mean maximum increase in A wave ratio after smoking was 34 percent for high-nicotine cigarettes, 13 percent for the low-nicotine cigarettes, and 6 percent for the non-nicotine cigarettes. He ascribed these changes to increased myocardial ischemia produced by cigarette smoking, which was reflected by a larger A wave ratio in the apexcardiogram. While nicotine appears to have produced most of these changes, the observation that a 6 percent increase occurred in the absence of nicotine suggests the possibility that carbon monoxide plays a role in this effect.

CARBON MONOXIDE

Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (13, 20, 24, 63). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (4, 20, 56). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (20).

Haebisch (24) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar

CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (*14, 18, 23, 24*).

Cohen, et al. (*13*) and Aronow, et al. (*2*) have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (*20*), CO intoxication has been reported in cigar smokers (*25*).

CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (*56*). CO has also been implicated in experimental atherogenesis in animals (*56*).

Ayres, et al. (*7*) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery O_2 extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

Brewer and his colleagues (*11*) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial pO_2 of 8 smokers was significantly lower (P < .05) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on O_2 transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced O_2 tensions (*11, 12*).

Kjeldsen (*31, 32*) examined 993 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

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The diseased smokers had significantly higher carboxyhemoglobin and serum cholesterol levels than either smoking or nonsmoking control patients. This was true after standardizing for differences in levels of smoking between controls and diseased patients. As expected, there was a gradient in carboxyhemoglobin levels from lower levels in light smokers to higher levels in heavy smokers (table 4).

TABLE 4.—*Average values of carboxyhemoglobin and serum cholesterol in Danish smokers and nonsmokers in control group and group of patients with arteriosclerotic cardiovascular disease.*

Smoking category	Carboxyhemoglobin (saturation percentage)			Serum cholesterol (mg/100 ml)		
	controls M±S.D.	patients M±S.D.	signifi- cance	controls M±S.D.	patients M±S.D.	signifi- cance
Smokers	4.2±3.1 (738)[a]	7.0±3.7 (57)	$p<0.001$ $t=5.52$	247±44 (738)	290±33 (57)	$p<0.001$ $t=4.89$
Nonsmokers	0.4±0.9 (196)	0.5±0.7 (2)	n.s. $t=0.16$	236±49 (196)	284±56 (2)	$p<0.02$ $t=2.32$
Light smokers	2.5±2.5 (121)	3.7±2.5 (3)	n.s. $t=0.76$	245±38 (121)	279±67 (3)	n.s. $t=1.45$
Moderate smokers	4.1±3.0 (463)	7.3±3.6 (34)	$p<0.001$ $t=4.95$	246±45 (463)	286±50 (34)	$p<0.001$ $t=4.52$
Heavy smokers	5.7±3.0 (154)	7.0±4.0 (20)	n.s. $t=1.45$	253±45 (154)	298±53 (20)	$p<0.05$ $t=2.18$

p = Probability that difference is not due to chance.
t = Student's t calculation.
n.s. = not significant.
[a] The number of subjects in each category is enclosed in parentheses beneath the mean (M) and standard deviation (S.D.).
SOURCE: Kjeldsen, K. (31).

Kjeldsen also observed that the COHb levels of 8 to 19 percent seen in 40 percent of the patients with arteriosclerosis were of the same magnitude as those provoking experimental atherosclerosis and cardiac necrosis in animals.

SMOKING AND THROMBOSIS

Previous reports of the Surgeon General on smoking and health have reviewed the effects of smoking on thrombus formation (*54*, *55*, *56*). The role of thrombosis in CHD remains an active area of investigation. Recent studies have not thus far yielded a unifying concept of the effect of smoking on thrombosis (*33*, *41*, *48*).

Cholesterol glucoside has not previously been reported in tobacco, or in any other plant (10). Bolt and Clarke (10) investigated the sterolin and sterol fraction of flue-cured tobacco and found that cholesterol is one of the major components of the sterol fraction.

More recently, Grunwald, et al. (22) have confirmed that cholesterol accounts for 10 percent of the total sterol in cigarette tobacco. They also found that 8.6 percent of the total sterol content of cigarette smoke condensate was cholesterol. Thirteen percent of the cholesterol present in cigarette tobacco was transferred to the condensate.

The biological significance of these findings remains to be determined.

COR PULMONALE (PULMONARY HEART DISEASE)

The relationship between cigarette smoking and chronic obstructive bronchopulmonary disease (COPD) with cor pulmonale was discussed in the 1968 Supplement to "The Health Consequences of Smoking" (55).

Although the extent of morbidity and mortality due to cor pulmonale and right heart failure is difficult to determine, COPD is often complicated by these conditions (27).

The Pulmonary Heart Disease Study Group of the Inter-Society Commission for Heart Disease Resources recently summarized the evidence linking cigarette smoking with COPD and concluded: "Cigarette smoking is the major cause of pulmonary heart disease in that it is the most important cause of the chronic non-neoplastic bronchopulmonary diseases in the United States" (28).

CEREBROVASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (56), summarized the data linking smoking to cerebrovascular disease as follows:

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.

2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

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In the interim, additional reports have been published.

Dyken (*15*) performed a retrospective study on 285 patients with cerebrovascular disease in Elkhart, Indiana. Even though low cigarette consumption was noted in all groups, males who had cerebral infarctions smoked significantly more than controls.

Paffenbarger, et al. (*42*) found that smokers of more than 20 cigarettes a day faced a slightly increased but not significantly greater risk of dying from a stroke than those smoking lesser amounts.

After 16 years follow-up, male cigarette smokers in the Framingham study had more than three times the nonsmokers' risk of developing a cerebral infarction (*29*). However, Kannel commented: "It is not clear that smoking actually affects the rate of cerebral atherogenesis, and some other mechanism may be involved."

PERIPHERAL VASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data relating smoking to peripheral vascular disease as follows:

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

Newly published studies add to our understanding of the effect of nicotine or tobacco smoke on the peripheral circulation and of the significance of smoking in peripheral vessel atherogenesis.

Martz, et al. (*37*) observed that some of the apparently conflicting data on the effects of nicotine upon the peripheral vasculature may result from interpretations based upon indirect measurements of microcirculatory variables. Hence, they studied vascular changes in a bat wing under direct microscopic observation. They noted a marked increase in the diameter of innervated, minute arteries with intraperitoneal nicotine administration, but this effect was abolished with sympathetic denervation.

Asano and Branemark (*3*) installed a direct, microscopic observation chamber in the connective tissue of two human volunteers. One volunteer was a "healthy" 20-year-old male nonsmoker. The other volunteer was a diabetic who had been a smoker for five years and who "... had no apparent diabetic vasculopathy." The effects of tobacco smoking on the microcirculation of these volunteers in-