factors, such as hypercholesterolemia or excessive doses of vitamin D, can damage the arterial wall, and arterial injury is widely accepted as one mechanism for predisposing to or accelerating lesions in animal models of atherosclerosis.

Carbon monoxide is another major component of cigarette smoke for which there are some data supporting a possible atherogenic role; however, a review of recent literature on the role of carbon monoxide in arterial injury and atherogenesis leads to no consensus. Early studies by Astrup and coworkers (*3*) on the effect of carbon monoxide in rabbits suggested the theory that carbon monoxide causes endothelial damage, which might promote atherogenesis. Later studies by Astrup's group (*2, 32*) indicated that the duration of exposure of rabbits to carbon monoxide did not influence the intimal morphology of the coronary arteries or the aorta. They felt that these new data contradicted the theory of carbon-monoxide-mediated endothelial damage as a cause of atherosclerosis.

Recent experimental studies have produced a variety of results regarding the effects of carbon monoxide on the development of arterial lesions. Malinow et al. (*40*) exposed cynomolgus monkeys, fed a standard laboratory diet or a semipurified high cholesterol diet, to carbon monoxide or to room air for 14 months. None of the animals developed a myocardial infarction, and there was no difference in plasma cholesterol levels or in aortic or coronary atherosclerosis attributable to carbon monoxide exposure. Davies et al. (*17*) studied the effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit and found there was an increase in coronary artery atherosclerosis in the carbon-monoxide-exposed animals, but they did not find significant differences in the lipid content of the aortas. Armitage et al. (*1*) studied the effect of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon and found that the severity of coronary atherosclerosis was significantly greater in birds exposed to carbon monoxide than in nonexposed birds after 52 weeks of exposure, but not after 84 weeks. The severity of atherosclerosis was related to the degree of hypercholesterolemia. They suggested that in the White Carneau pigeon, exposure to carbon monoxide elevates plasma cholesterol levels, and thereby increases the extent of experimentally induced atherosclerotic lesions. They further suggested that compensatory mechanisms may reduce the effect of carbon monoxide exposure on hypercholesterolemia over time.

Two reviews in 1979 came to different conclusions concerning the relationship of carbon monoxide and arteriosclerosis. Astrup and Kjeldsen (*2*) surveyed the cardiovascular effects of exposure of animals to carbon monoxide and concluded that carbon monoxide produces myocardial effects that can lead to decreased myocardial oxygen tension with compensatory increases in coronary blood flow.

They stated that their previous findings of arterial intimal changes had not been confirmed. Turner (*78*) reviewed studies involving carbon monoxide, tobacco smoking, and the pathogenesis of atherosclerosis, and concluded that carbon monoxide exposure enhances the extent of coronary atherosclerosis in pigeons that have been made hypercholesterolemic by adding dietary cholesterol. Carbon monoxide was without effect on normocholesterolemic birds. They indicated that the level of carbon monoxide exposure, the duration of exposure, and the level of dietary cholesterol are critically interdependent factors that can influence the pathogenesis of the disease.

Studies by Sarma et al. (*62*) on the effect of carbon monoxide on lipid metabolism of human coronary arteries provide some support for the idea that carbon monoxide increases endothelial permeability. They perfused human coronary arteries under sterile conditions in vitro with blood containing high and low concentrations of carbon monoxide. They found no effect of carbon monoxide on lipid synthesis in the arterial wall; however, the arteries that were exposed to carbon monoxide showed a higher uptake of cholesterol from the perfusate as compared with their corresponding controls. Thus, the results of Sarma et al. (*62*) were in agreement with those of other investigators who have found that carbon monoxide significantly increases the permeability of endothelial membranes.

Schneiderman and Goldstick (*67*) used a computer simulation of the oxygen transport system of the arterial wall to evaluate the extent of carbon-monoxide-induced hypoxia of the arterial wall under various conditions; the results suggested that the moderate to high carboxyhemoglobin levels found in some smokers may result in a significant reduction in the oxygen tension of the arterial wall.

Hugod (*31*) reported no morphological change in the coronary arteries and aortas of rabbits exposed to low doses of hydrogen cyanide, alone or in combination with 200 ppm carbon monoxide, and nitric oxide for 2 weeks.

McMillan (*46*) reviewed the many substances that may enter the body from tobacco smoke and that have been conjectured as having a role in cardiovascular disease. He concentrated on those substances other than carbon monoxide and nicotine, such as cadmium, zinc, chromium, carbon disulfide, carbon dioxide, tobacco antigens, hydrogen cyanide, nitric oxide, and polonium-210. He concluded that these substances provide interesting ground for speculation as to their possible role in cardiovascular disease, but that only carbon monoxide and nicotine offer both data and a rational conceptualization for a role in cardiovascular disease.

Studies of Whole Tobacco Smoke

McGill (*42*) reviewed potential mechanisms for the augmentation of atherosclerosis and atherosclerotic disease by cigarette smoking.

On the basis of his review of the evidence concerning smoking and serum lipid and lipoprotein concentrations, he suggested that cigarette smoking often causes a slight to moderate elevation of total serum cholesterol concentration, and that smoking may depress HDL concentrations and elevate LDL concentrations. These changes might have the effect of increasing atherosclerosis because increased levels of LDL and decreased levels of HDL have been shown to be related to increased amounts of atherosclerosis as well as to an increased risk of coronary heart disease.

Hojnacki et al. (*28*) studied the effect of acute inhalation of cigarette smoke and consumption of dietary cholesterol on plasma lipoprotein composition in atherosclerosis-susceptible White Carneau pigeons. They concluded that cigarette smoking can mediate alterations in lipoprotein composition independent of changes induced by dietary cholesterol and saturated fat.

Sieffert et al. (*69*) demonstrated endothelial damage and focal platelet aggregation after exposing Sprague-Dawley rats to tobacco smoke for 15-minute periods three times a day for 6 and 12 weeks. Scanning electron microscopic examination of perfusion-fixed thoracic aortas disclosed elongation of endothelial cells, uplifting of endothelial cells from the basement membrane, areas of endothelial loss, pitting, crater formation, and white blood cell invasion of the underlying intima. They also found platelet aggregation on damaged intima. They did not indicate which one of the constituents of tobacco smoke they suspected as being the cause of these changes.

Rogers et al. (*58*) recently completed an investigation of cigarette smoking, diet-induced hyperlipidemia, and experimental atherosclerosis in baboons. The design of the study and interim results are contained in a report by Rogers et al. (*57*). The baboons in this controlled experiment consumed a diet enriched in cholesterol and saturated fat for 3.3 years and puffed on lighted cigarettes or shams for 2.8 years. The study was designed to determine whether cigarette smoking interacts with diet-induced hyperlipidemia to accelerate the development of atherosclerosis. This hypothesis was based on a report by Keys (*35*), who found that populations with high total serum cholesterol concentrations and a high incidence of atherosclerotic disease have a dose-related relationship between cigarette smoking and the incidence of atherosclerotic disease. However, in populations with low total serum cholesterol levels and a low incidence of atherosclerotic disease, cigarette smoking is not associated with the incidence of atherosclerotic disease. Thus, cigarette smoking might augment atherosclerosis only when it interacts with an atherogenic diet. The investigation by Rogers et al. (*57, 58*), used nonhuman primates—baboons—as experimental animals, and the animals were trained by operant conditioning techniques to smoke cigarettes in a human-like manner. The diet induced a moderate

hypercholesterolemia, which attained a peak of 235 mg/dl 5 months after initiation and declined thereafter to 160 mg/dl at termination. The early report of Rogers et al. (*57*) disclosed no significant differences in serum lipids or lipoproteins between smokers and shams after 1.6 years of smoking; however, there were some differences that would be expected to accompany the augmentation of atherosclerosis, namely higher LDL/HDL ratios in smokers than in shams. At the completion of the experiment, these trends of differences in lipoprotein concentrations were not present, and the mean serum total cholesterol, serum triglyceride, LDL cholesterol, and HDL cholesterol concentrations of smokers and shams were not significantly different. The LDL/HDL cholesterol ratios of smokers and shams were almost identical. Their observations on LDL/HDL cholesterol ratios in the midcourse of the experiment and again at the end suggested that cigarette smoking either increases the LDL/HDL cholesterol ratio only during hypercholesterolemia or increases the LDL/HDL ratio only in some animals.

At autopsy of these baboons, the mean extent of fatty streaks was not significantly different for smokers versus shams in the aorta, femoral, iliac, and innominate arteries. The mean extent of fatty streaks in smokers was significantly greater than in shams for the carotid arteries. The variability in extent of lesions was greater in smokers than in shams, suggesting the possibility that a subset of smokers may have responded positively to smoking by developing increased lesions. This difference in variability of lesions was statistically significant for the thoracic aorta, carotid, and innominate arteries. The authors suggest that the "compensatory" decline in mean serum cholesterol concentration that occurred in the latter part of the experiment could have led to regression of experimentally induced lesions.

The authors indicate that their results do not support the hypothesis that cigarette smoking, at a level approximately equivalent to that of the average human cigarette smoker, augments experimental atherosclerosis in the presence of a moderate level of diet-induced hypercholesterolemia. They did, however, find a significantly greater extent of fatty streaks in the carotid arteries for the smokers and significantly more variability in the extent of lesions in the smokers. Also, among the small number of animals that died during the course of the experiment, the smoking animals had more extensive involvement with lesions than did the shams. Nevertheless, there were no dramatic, clear-cut, across-the-board differences between the smoking and nonsmoking animals. The authors conclude that this experiment cannot be regarded as a conclusive test of the hypothesis that cigarette smoking can augment the formation of fatty streaks associated with dietary-induced hyperlipidemia.

McGill's review (*42*) indicated that smokers have slightly increased erythrocyte counts, hematocrit, and hemoglobin concentrations, but he doubted that the slight changes observed would increase the risk of atherosclerosis. In the experiments with baboons, smokers also had elevated leukocyte counts owing to both increased polymorphonuclear leukocytes and increased lymphocytes. These changes might be one manifestation of an altered immune system that might deserve attention as a possible mechanism for accelerating atherogenesis. The smoking baboons had slightly elevated blood glucose levels; it is not known if this change would contribute to atherosclerosis. Body weight and blood pressure are slightly lower in smokers than in nonsmokers, and this response to smoking is in the opposite direction with regard to risk of atherosclerotic disease.

Smoking and the Hemostatic System

McGill indicated that the limited number of recent studies of the effects of smoking on the hemostatic system show little or no effect on clotting action, but marked effects on platelets. Platelet counts are not different in smokers and nonsmokers, but smokers have a decrease in survival time and an increase in platelet turnover (*50*), increased adhesiveness (*49*), and increased tendency for aggregation (*24, 27, 36*).

Ogston et al. (*52*) found that chronic smoking led to an increased plasma fibrinogen concentration, but acute smoking did not. Janzon and Nilsson (*33*) found that chronic smoking was associated with increased fibrinolytic activity of the blood.

Davis and Davis (*18*) studied the effect of cigarette smoking on circulating platelet aggregates as detected by the platelet-aggregate ratio in volunteer subjects. The platelet-aggregate ratios were lower in the smokers, indicating increased circulating platelet aggregates. The authors indicated that the decrease in platelet-aggregate ratio was not mediated through the elevation of plasma nonesterified fatty acid concentration.

Fuster et al. (*21*) found a shortened platelet survival half-life in apparently normal persons who smoked and in persons with a strong family history of coronary disease. Their study suggested a possible relationship among cigarette smoking, strong family history of coronary disease, and platelet activation in the process of coronary atherogenesis in the young adult.

Smoking and the Immune System

McGill (*42*) suggested that the leukocytosis observed in smokers may represent in part a manifestation of an immune disorder. Immune complex disease markedly aggravates atherogenesis in rabbits (*48*) and in baboons (*30*). Becker and Dubin (*10*) and Becker et al. (*11*) have identified a low molecular weight glycoprotein in

tobacco smoke that is highly antigenic in man. McGill (*42*) suggests that differences in sensitivity to antigenic materials could account for the great variation in response to cigarette smoking. He also suggests endothelial injury and increased endothelial permeability as a mechanism for cigarette smoking effects on cardiovascular disease. Becker (*9*), in summarizing a workshop on immunologic injury and the thrombotic process in atherogenesis, postulated that the capacity of tobacco glycoprotein to activate the intrinsic pathway of coagulation might contribute to the growth of arteriosclerotic plaques and to more lethal complications by initiating thrombus formation. Denburg et al. (*19*) studied the reactivity of 164 patients with peripheral vascular disease to purified tobacco glycoprotein; they suggested that reactivity to tobacco glycoprotein may be causally related to the development of atherosclerotic vascular disease.

Conclusions

1. A preponderance of evidence both from prospective studies with autopsy followup and from autopsy studies with retrospective smoking data indicates that cigarette smoking has a significant positive association with atherosclerosis. This evidence suggests that cigarette smoking has the effect of aggravating and accelerating the development of atherosclerotic lesions in the artery wall and that its effect is not limited to those events related to the occlusive episode. The effects are most striking for aortic atherosclerosis; a significant positive relationship also exists between cigarette smoking and atherosclerotic lesions in the coronary arteries, at least for most high risk populations. Cigarette smoking could also be associated with other factors that precipitate thrombosis, hemorrhage, or vasoconstriction leading to occlusion and ischemia.
2. Some evidence exists that cigarette smoke alters total serum cholesterol concentrations and lipoprotein composition in ways that would be expected to increase the development of atherosclerosis. Recent studies of the effects of smoking on the hemostatic system indicate effects of smoking on platelet function.
3. Although the specific mechanisms by which tobacco smoke affects arteriosclerosis have not been clearly delineated, the effects of cigarette smoking on the atherosclerotic lesions that underlie cardiovascular disease seem well established.

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SECTION 3. CORONARY HEART DISEASE

Introduction

Higher rates of disease and earlier mortality in cigarette smokers than in nonsmokers have been documented in a large number of investigations. Of the several disease manifestations that account for the excess disability and death in cigarette smokers, coronary heart disease (CHD) is the leading cause in North America and northern Europe (*18, 40, 43, 45, 67, 94, 96, 134, 143, 189, 214, 224, 257*). CHD is related to several risk factors, including cigarette smoking. Estimates indicate that up to 30 percent of all CHD deaths in the United States are attributable to the cigarette smoking habit (*189*).

Three of the major prospective studies have reported estimates of cigarette-related CHD mortality based on the number of observed versus expected CHD deaths in smokers and nonsmokers. In the ACS 25-State study, involving more than 1 million men and women, Garfinkel (*73*) estimated that of the 12,724 CHD deaths that occurred among all males followed prospectively for 6 years, 5,358 (46 percent) would not have occurred if all male cigarette smokers had the same CHD death rates as did nonsmoking males. Among females, a similar percentage of excess deaths (40 percent) attributed to smoking was noted; however the total number of CHD deaths was not large. Rogot and Murray (*224*) followed 290,000 U.S. veterans over a period of 16 years. During this time 13,845 CHD deaths were observed among cigarette smokers, whereas only 8,787 were expected. This represents an approximately 40 percent greater observed-to-expected ratio. In the British physicians study, in which 34,000 male British physicians were followed for 22 years, it was reported that cardiovascular disease accounted for 52 percent of all excess deaths in smokers, including 31 percent arising from CHD. By contrast, lung cancer was responsible for 19 percent of the cigarette-related excess deaths (*232*).

Whyte (*277*), using the "attributable fraction" method as advocated by Miettinan (*179*), reanalyzed data from the Pooling Project study and estimated that 24 percent of first major coronary events were cigarette related and independent of other risk factors. When all three major risk factors were considered together, the proportion of attributable risk increased to 70 percent.

Both Luce and Schweitzer (*163, 164*) and Boden (*21*) attributed 25 percent of all circulatory diseases to smoking. Both used data derived from estimates provided by the NIH Task Force Report on Preventive Medicine (*63*). These estimates are in close agreement with that published by Richter and Gori (*219*) that attributed 30 percent of heart disease to smoking; they also estimated that 33 percent of all arteriosclerosis was cigarette related. The latter estimate is identical to those published by the National Cancer Institute and the National Heart, Lung, and Blood Institute in the final report on the program to reduce the risk of disease in smokers (*189*).

In young people—including young women who are otherwise at very low risk for CHD—as many as three-quarters of the cases may be attributable to the cigarette smoking habit (*244, 257*). During the period 1965–1977, there were an estimated 2.8 million premature deaths from heart disease, primarily CHD, in American men and women attributable to the use of tobacco. Furthermore, unless smoking habits of Americans change, over 10 percent of all those now alive may die prematurely of heart disease that will be attributable to the use of tobacco. The number of such deaths may exceed 24 million (*189*).

Annually during recent years, more than one and a quarter million Americans have suffered fatal or nonfatal heart attacks (*2, 101, 198*). The deaths from CHD have numbered over 500,000 and have exceeded the deaths from any other cause; half or more of these deaths are sudden (*139*). In addition to these acute manifestations of CHD, more than 5 million Americans are under treatment for chronic manifestations of CHD (*2, 198*). Millions of others have significant CHD that is undiagnosed. Of those currently undiagnosed, approximately one-quarter will manifest sudden, unanticipated death as the first clinical indication of CHD (*110, 137, 153*).

Scientific Investigation of the Relationship Between Coronary Heart Disease and Smoking: Objectives of the Present Review

The scientific basis for the judgment that cigarette smoking is a major contributor to CHD in Americans has been presented in the Reports of the Surgeon General beginning in 1971 (*264*) and emphasized recently in the Reports of 1979 (*263*) and 1980 (*261*). A large number of epidemiologic, clinical, and experimental studies using a variety of methods and research designs have accumulated overwhelming evidence of the strong relationship between cigarette smoking and CHD. The possibilities of sample selection bias or confounding of this association by other factors as explanation for this association have been examined exhaustively and do not explain the relationship between cigarette smoking and CHD.

In this section, emphasis is placed on critical examination of the relationship between cigarette smoking and CHD incidence and mortality. The independence of cigarette smoking as a predictor of CHD is considered in the context of those other risk factors that also predict the occurrence of CHD. This includes evaluation of the consistency of the relationships between risk factors and subsequent CHD, including those mathematical models for prediction of CHD that have been applied widely among diverse population groups. The examination takes into account sample size, effects of multiple risk factors acting simultaneously, and secular trends in risk factor

prevalence. Areas of opportunity for expansion of knowledge are discussed.

Mortality studies are summarized with respect to the relationship of smoking and CHD. The large prospective mortality studies provide evidence of the influence of cigarette smoking in large and varied populations, and they provide sufficient numbers of cases for detailed analyses of the influence of smoking intensity and duration, age, sex, race, and smoking cessation on CHD.

Coronary Heart Disease Manifestations

The major clinical manifestations of CHD are myocardial infarction (MI), which may be fatal or nonfatal; other death from CHD, which may be sudden or not; and angina pectoris, which is the first clinical manifestation in about one-third of new cases (*40*).

In most cases, obstruction to blood flow in the coronary arteries is caused by arteriosclerotic narrowing (*34, 39*). Some cases are associated with coronary artery spasm with or occasionally without atherosclerotic change in the coronary arteries (*39, 87, 174, 202*). When there is thrombosis superimposed on the coronary narrowing, myocardial infarction typically results (*34*). The aggregation of platelets and formation of fibrin thrombi are related to the acute clinical manifestations of coronary heart disease, and may also play a role in the development of coronary atherosclerosis (*187, 230*). Several autopsy studies in the United States and elsewhere have shown that atherosclerosis of the coronary arteries is more common in cigarette smokers than in nonsmokers (*3, 7, 8, 9, 220, 245, 247*). This topic is discussed elsewhere in this Report.

Clinical Manifestations and Epidemiologic Criteria for Coronary Heart Disease Events

Myocardial Infarction

Myocardial infarction (MI) denotes necrosis of a discrete volume of heart muscle resulting from prolonged, severe ischemia following interruption of coronary blood flow. The characteristic symptom is unremitting chest pain that may be associated with sweating, nausea, shortness of breath, dizziness, or loss of consciousness. The role of coronary thrombosis in the evolution of acute myocardial infarction (AMI) has been debated in the past; recently, coronary angiography has been performed in large numbers of patients with AMI. In the majority, coronary thrombosis has been found to be superimposed upon preexisting arteriosclerotic narrowing. In a small proportion of cases, but more commonly in young men and women, MI has been observed in patients with little or no coronary

atherosclerosis who have had coronary artery spasm or coronary thrombosis or both (*1*).

Loss of consciousness in acute myocardial infarction is an ominous sign because it often reflects inadequate pumping action of the heart owing either to catastrophically abnormal cardiac rhythm or to severe deterioration of cardiac muscle function. A broad range of cardiac rhythm disturbances may occur, but the most characteristic catastrophic one accompanying myocardial infarction is a chaotic irregularity of muscle fiber contraction (ventricular fibrillation) that results in a cessation of effective pumping by the heart. In such instances, death occurs within several minutes after cessation of blood flow to the brain if the rhythm disturbance is not reversed.

In patients who survive long enough to be admitted to the hospital, the diagnosis of AMI may be made from changes in the electrocardiogram and increases in serum enzymes (*1*). In comprehensive clinical epidemiologic studies, the criteria for identifying cases of MI include specific presenting symptoms, electrocardiographic changes, and serum enzyme elevations (*40, 214*).

Death from CHD

In fatal cases, evidence of CHD may be provided by clinical or autopsy information (*40, 214*). In the absence of adequate clinical or autopsy evidence, diagnosis of death from CHD is based on documentation of a sufficiently short interval from onset of symptoms until death and the absence of another potentially lethal condition (*153*).

Sudden Cardiac Death

A large proportion of deaths certified as due to CHD have been sudden, and a significant fraction of these sudden cardiac deaths (SCD) have occurred in persons with no prior history of CHD (*68, 109, 139, 152, 154, 220*). The incidence of SCD increases with age, and it is substantially more frequent in men than in women; in women the incidence of SCD lags behind that of men by 20 years (*139*).

Epidemiologic investigations have shown that the majority of deaths in ambulatory adults that are sudden and unanticipated are associated with severe CHD. In the Baltimore study by Kuller et al. (*153*), 71 percent of the deaths (excluding trauma) that occurred within 24 hours of the onset of terminal illness in individuals who had been able to function in the community were from CHD. In those with other causes, more than half were associated with fatty liver. Alcohol consumption appears to have a complex relationship to CHD, and heavy alcohol consumption has been identified as a factor in sudden death in several studies. This relationship has been shown to be independent of the relationship with cigarette smoking (*38, 64, 148, 158, 173, 188, 209, 216*). Although some difficulty may arise in

appropriate designation of unwitnessed deaths, the less frequent and rare conditions are usually differentiated easily from SCD.

Criteria for SCD have varied in different studies. Among ambulatory adults considered to be well who die suddenly, the probability of severe CHD has been shown to be very high both by autopsy data and by clinical data (*40, 109, 139, 157, 200, 248*). In large population studies, however, information for some cases is often not available to determine the exact interval from onset of symptoms until death; therefore, criteria for sudden death have often included intervals up to 24 hours (*153, 156, 200*). In a high proportion of such cases, severe CHD has been observed by autopsy examination (*10, 12, 50, 68, 109, 153, 160, 200, 208*).

The physiologic disorders responsible for sudden collapse and cardiac arrest in ambulatory adults have been well documented. In the overwhelming fraction, ventricular fibrillation is the terminal ventricular rhythm disorder; however, profound cardiac bradycardia or cardiac standstill can be the mechanism as well. Ventricular fibrillation may further degenerate into cardiac standstill (*33, 47, 55, 56, 145, 202*). Among patients resuscitated following cardiac arrest, AMI has been documented during the subsequent hospital course in one-quarter to one-half of the cases; in the others, severe, multivessel coronary atherosclerosis, with or without old MI, has been observed by coronary angiography in three-quarters or more (*33, 56, 273*).

Ascertainment of CHD From Death Certificates

In large-scale mortality studies the underlying cause of death on death certificates has usually been used to identify the deaths from coronary heart disease. [In recent editions of the *International Classification of Diseases,* the term ischemic heart disease is preferred over the older term coronary heart disease. Some authors prefer the term arteriosclerotic heart disease. For uniformity, coronary heart disease (CHD) is used throughout this section regardless of the usage in the publications reviewed.] The accuracy of death certificate data has been evaluated through review of available clinical data and retrospective analyses and from available pathological data. Coronary heart disease has been confirmed as probable or likely in the vast majority of cases (*183, 184, 236, 284*).

In a random sample of 1,362 U.S. death certificates in 1960, pertinent clinical and pathological information to determine the cause of death was investigated by Moriyama et al. (*182*). In the 87 percent of cases for which responses from medical certifiers were obtained, only 7 percent of those certified to be CHD were judged to be incorrect or probably incorrect. The information for diagnosis of CHD was judged to be reasonable or well established in 74 percent and inadequate to determine the cause of death in 19 percent.

In recent years, cardiac evaluation has become more prevalent with widespread use of objective diagnostic tests. This should result in even greater accuracy of CHD case ascertainment from death certificates.

Angina Pectoris

Angina pectoris is the first clinical manifestation in about one-third of the new cases of CHD (*133*). In the typical form, observed in about 90 percent of clinically diagnosed patients, chest pain or tightness occurs with exertion or excitement and is relieved promptly by rest or nitroglycerin. Such patients usually have fixed obstruction to blood flow due to arteriosclerosis in one or more of the coronary arteries (*34, 174, 237*). Patients with typical angina pectoris are at increased risk for the more serious manifestations of CHD, myocardial infarction, and death from CHD (*34, 133, 174, 175, 241*).

In the atypical form, chest discomfort usually occurs at rest, although it may also occur with exertion, and it is usually relieved by nitroglycerin (*87, 174, 175, 237, 241*). This atypical or variant form of angina pectoris has been shown to result from coronary artery spasm that occurs at the site of atherosclerosis in many cases, but in otherwise normal-appearing coronary arteries in others (*87, 175, 202*). Sudden death is a rather common complication of variant angina (*39, 110, 175, 202, 241*).

Conditions other than CHD may cause symptoms that mimic angina pectoris, and definitive diagnosis may require clinical observation over time and the performance of ancillary diagnostic procedures (*34, 40*). However, in large-scale epidemiologic studies, complete diagnostic evaluation is usually not feasible, and the proportion of cases with underlying severe coronary atherosclerosis has probably varied among the different studies (*40, 121, 273*).

In addition to those in the population who have symptoms of CHD, there are many with significant coronary atherosclerotic obstruction who are undiagnosed. The frequency of clinically silent but physiologically significant coronary artery disease is unknown; it is estimated that in one-quarter of the cases with a new myocardial infarction, the infarction is silent and detected only on followup by electrocardiographic (ECG) examination (*172*).

In prospective epidemiologic studies with clinical followup, cases may be classified only by the most severe CHD manifestation, in this order: death from CHD, nonfatal myocardial infarction, and angina pectoris. Thus, the cases classified as angina pectoris are those remaining who have not experienced a more serious CHD event, and as noted above, this diagnosis may lack sensitivity and specificity for coronary atherosclerotic disease. Variation in the strength of association between smoking and angina pectoris may be influenced by these methodological considerations (*48, 49, 121, 135, 229*).

A number of well-documented, clinical series of patients with angina pectoris and severe CHD confirmed by coronary angiography, surgery, or post-mortem examination have been reported (*4, 11, 32, 42, 97, 98, 118, 171, 201, 253, 268, 272*). These studies provide important information for clinical management and add insights into relationships with risk factors. However, causal inferences must be made with caution when measurements of risk factors have been made after the onset of clinical disease and data from appropriate comparison groups are not available.

Epidemic CHD and the Application of Epidemiologic Methodology

CHD was thought to be uncommon in the early part of this century when most deaths were caused by infectious disease. Before the mid-century, however, CHD had become the leading cause of death, and year to year increases were large (*101, 159*). Neither the cause of CHD nor the reasons for the rising epidemic could be explained. Nevertheless, pioneering efforts in cardiovascular epidemiology revealed that certain characteristics were observed more often in CHD cases, and epidemiologic investigations were begun to obtain data with which to make causal inferences (*40, 86, 143*).

Prospective Cohort Studies: Intensive Population Studies of Risk Factors and CHD

In several early investigations, cigarette smoking and several other characteristics were observed to be strongly associated with CHD (*60, 136, 276*). To clarify the nature of these relationships, defined population samples were examined for personal characteristics that could be related to CHD. Intensive observation for subsequent incidence of CHD through reexamination and surveillance activities in members of population samples that were free of disease at the baseline examination provided a substantial part of the data from which causal inferences relating to smoking and CHD were made. A number of these are briefly described in the following pages. In each study, smokers were found more likely to develop CHD than nonsmokers.

Studies in U.S. Whites

Within the U.S. population, CHD mortality has been highest in white men, and they were investigated most intensively in the early prospective studies. To provide a sufficiently large number of cases for detailed analyses of the relationship of CHD to cigarette smoking and other risk factors, several of the long-term epidemiologic studies agreed to pool their data in the National Cooperative Pooling Project

sponsored by the Council on Epidemiology of the American Heart Association and supported by the American Heart Association and the National Heart Institute, now designated the National Heart, Lung, and Blood Institute (*168, 214*). Five of the studies participating in this effort had used comparable methodology in data collection so that the data from each of these five cohorts could be pooled for analysis. In Table 1, analyses for the pooled data are referred to as "Pool 5." The five cohort studies contributing to the pooled data will be characterized briefly individually, and then analysis of the pooled data will be summarized.

Framingham Heart Disease Epidemiology Study

The Framingham study was initiated by the Public Health Service in 1948. The members of the prospective cohort were 2,282 men and 2,845 women who were aged 29 through 62 and free of CHD at initial examination (*40, 86, 133*). The cohort was based on a random subsample of the residents of Framingham, Massachusetts; the response rate was 69 percent. The respondents were supplemented by volunteers who had similar characteristics. A standardized cardiovascular examination at entry included information on habits, physical characteristics, and blood chemistries. Reexamination has been carried out biennially for ascertainment of cardiovascular disease and changes in characteristics. Cardiovascular disease case ascertainment has included community and mortality surveillance activities (*86, 136*). Analyses through 24 years of followup have shown that cigarette smoking is strongly related to MI and death from CHD (*40, 133, 135*). In Table 1, Framingham data analysis is shown with that of the other cohorts participating in the National Cooperative Pooling Project. The excess risk of MI and death from CHD was found to increase progressively with the number of cigarettes smoked (Table 1).

The relationship to angina pectoris has been less clear. In the 12-year and the 24-year followup data analyses, however, male cigarette smokers were observed to experience a higher incidence of angina pectoris than were nonsmokers (*40, 135*). The effect was stronger at younger ages; after 24 years of followup, the incidence of angina pectoris in those 30 to 39 years old at entry to the study was twice as high in smokers as in nonsmokers (Figure 1).

Albany Cardiovascular Health Center Study

In 1952 the New York State Health Department established at the Albany Medical College a prospective study of male civil servants working in Albany. Participation was obtained from 87 percent of eligible men aged 40 through 54, of whom 1,823 were free of CHD at initial examination. After 6 years, the incidence of MI and death from CHD was significantly higher in cigarette smokers in compari-

TABLE 1.—National Cooperative Pooling Project. Analysis of the incidence of CHD by smoking behavior in five participating cohorts individually and in the data pooled for the five cohorts with comparable methodology (Pool 5). Standardized incidence ratio, risk ratios, number of men, person-years of experience, and number of first events

Smoking behavior	Standardized incidence ratio by study group					
	Pool 5	ALB	CH-GAS	CH-WE	FRAM	TECUM
All	100	100	100	100	100	100
Nonsmokers	58	55	48	59	67	(53)
Never smoked	54	45	(53)	44	77	(60)
Past smoker	63	67	56	89	(46)	(50)
<1/2 pack/day	55	(67)		(43)	78	(43)
Cigar and pipe only	71	78	(58)	98	57	(61)
Cigarette smokers						
About 1/2 pack/day	104	(52)	(64)	139	106	(151)
About 1 pack/day	120	108	125	128	119	117
>1 pack/day	183	200	190	162	174	151
Risk ratio ≥1 pack/day Nonsmokers	2.5	2.7	3.3	2.4	2.2	( )
95% confidence interval						
Low	2.1	1.8	2.1	1.6	1.5	( )
High	3.1	4.3	6.2	3.7	3.4	( )
Risk ratio >1 pack/day Nonsmokers	3.2	3.7	4.0	2.8	2.6	( )
95% confidence interval						
Low	2.6	2.4	2.5	1.2	1.8	( )
High	4.2	6.1	8.4	5.5	4.5	( )
Number of men at risk	8,282	1,796	1,258	1,926	2,162	1,140
Person-years of experience	70,970	17,240	11,017	16,072	19,756	6,885
Number of first events	644	154	123	140	178	49

NOTE: ALB: Albany Cardiovascular Health Center Study
CH-GAS: Chicago Peoples Gas Company Study
CH-WE: Chicago Western Electric Company Study
FRAM: Framingham Heart Disease Epidemiology Study
TECUM: Tecumseh Health Study
NOTE: ( ): based on fewer than 10 first events.
SOURCE: Pooling Project Research Group (*214*).

son with nonsmokers (*48*). Subsequent analysis after 10 years of followup confirmed these findings (Table 1).

Chicago Peoples Gas Company Study

Beginning in 1958, the Chicago Peoples Gas Company medical department examined 1,264 white men aged 40 to 59 (92 percent of

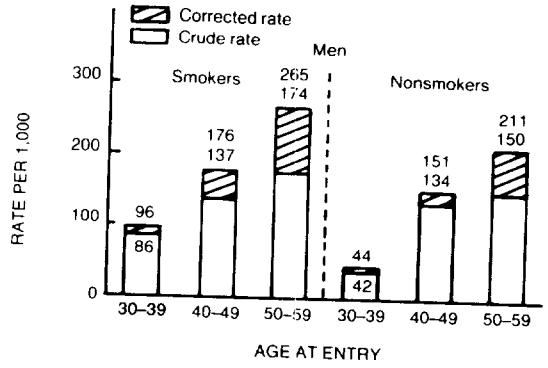

FIGURE 1.—Twenty-four-year incidence of angina pectoris in men, by cigarette smoking status

NOTE: The crude rates have been corrected to take into account those members of the population who are no longer at risk by reason of having developed the disorder in question or having been lost to observation by death.
SOURCE: Dawber (*40*).

those eligible) who were free of CHD (*161, 214*). Analysis of the data obtained during an average of 8.8 years of followup revealed a higher incidence of MI and death from CHD in cigarette smokers than in nonsmokers (Table 1).

Chicago Western Electric Company Study

Beginning in 1957, 67 percent of male Western Electric Company, Chicago, employees aged 40 to 55 were examined; 1,981 were free of CHD (*161, 206, 214*). After an average followup of 8.3 years, the incidence of MI and death from CHD was higher in cigarette smokers than in nonsmokers (Table 1).

Tecumseh Health Study

The Tecumseh health study began examination of the entire community of Tecumseh, Michigan, in 1959; participation was obtained from 90 percent (*61, 214*). Included was a cohort of 1,240 white men aged 40 to 59 who were free of CHD at initial examination. During an average followup of 8.05 years, the incidence of MI and death from CHD was higher in cigarette smokers than in nonsmokers (Table 1).

Minnesota Business and Professional Men Study

Selected Minnesota business and professional men were first examined in 1948; 284 men aged 40 to 59 years were free of CHD (*144, 214*). During an average followup of 14.1 years, those who

smoked cigarettes experienced a higher incidence of MI and death from CHD than did nonsmokers.

Minnesota-Based Railroad Worker Study

Among eligible railroad men working in the northwest sector of the United States, 65 percent participated in the Minnesota-based railroad worker study examinations beginning in 1958 (*143, 214*). Of these men, who were white, aged 40 to 59 years, and free of CHD at first examination, 2,571 were followed for an average of 4.9 years. Those who smoked cigarettes experienced a higher incidence of MI and death from CHD than did nonsmokers.

National Cooperative Pooling Project

As indicated above, the data from five of the cohorts participating in the National Cooperative Pooling Project were pooled for those white men who were aged 40 to 59 years, were free of CHD at initial exam, had comparable baseline examinations, and were followed for up to 10 years with comparable case ascertainment (Table 1). The demographic and other characteristics of these cohorts were similar to the characteristics of middle-aged white men in general living in the United States during the same period (*190–196*).

Subjects contributing to the pooled data numbered 8,422; during an average followup of 8.5 years (72,011 person-years), 688 cases of major CHD were observed (*214*). Major CHD was defined as nonfatal or fatal MI or sudden death from CHD (death in less than 3 hours from the onset of illness).

Risk of CHD With Smoking

According to the pooled data for men aged 40 to 59, those who smoked a pack or more of cigarettes per day at initial examination experienced a risk for a first major coronary event that was 2.5 times as great as the risk of nonsmokers (Table 1). In these analyses, nonsmokers included those who never smoked, cigar and pipe only smokers, past smokers, and those who smoked less than half a pack per day. Those smoking less than half a pack per day consisted largely of those who smoked occasionally or only two or three cigarettes per day. For each of the five cohorts separately, the relative risks varied from 2.2 to 3.3.

The risk was greatest in those with the heaviest smoking habits in all age groups (Table 2), and excess incidence attributable to smoking more than one pack of cigarettes per day tended to increase with increasing age up to age 60; however, with increasing age, relative risk declined. This apparent paradox is due to the rapid rise of CHD incidence with age. The excess incidence in heavy smokers (more than one pack per day) was large and statistically significant for