

suggest hypotheses for mechanisms of sudden death in man, they do not, of course, deal directly with cases of sudden death.

The Effect of Smoking on Sudden Cardiac Death in Animals

The smoking and health report of 1976 (138) has tabulated in Table A20 (pp. 103-108) papers concerned with the effect of smoke or nicotine on the cardiovascular system of animals. In the presence of myocardial ischemia, exposure to tobacco smoke or nicotine may precipitate conditions of increased cardiac demand, relative ischemia, and, in one experiment, arrhythmias. Bellet and colleagues (20) found that the ventricular fibrillation threshold was reduced in dogs exposed by intubation to cigarette smoke both in the presence and in the absence of acute myocardial infarction.

Malinow and colleagues failed to induce infarction or sudden death in cholesterol-fed cynomolgus monkeys by chronic exposure to CO (80). There are, however, no animal experiments in which animals have been brought chronically to a state of incipient myocardial ischemia by atherogenesis and then exposed to whole smoke by inhalation in a nonstressful setting.

Research Needs

There are fewer data on sudden cardiac death than on myocardial infarction in general. Smoking is clearly a strong risk factor for sudden death, but present indications are that it is not unique among the mix of risk factors for coronary heart disease and that it is not highly predictive. However, there are theoretical reasons to speculate that smoking might have a relationship to sudden death, not only through its effects on the circulation, but also through a myocardial one. It should be considered whether present epidemiological and clinical research data are adequate to exclude in smokers a myocardial element in sudden cardiac death, in relation to either first or multiple heart attacks, or whether additional research is warranted.

The mechanisms of sudden cardiac death, its precursor states, and preventive therapy require further elucidation. These should be clarified where possible in man and in experimental animal models with close analogy to man. The study of smoking or of smoke constituents as variables in such studies may be informative both about sudden death and the role of smoking in its occurrence.

Conclusions

Smoking is a powerful risk factor for sudden cardiac death. It is, however, only one of the general group of risk factors that contribute to coronary heart disease and sudden death. The mechanisms by which smoking might induce sudden death, in addition to an exacerbation of coronary artery arteriosclerosis, can be hypothesized from experiments

that indicate that an exacerbation of regional ischemia may promote electrical instability of the heart, fibrillation, or asystole. Further research will be required if these mechanisms are to be well understood and if they are to be shown to be actual mechanisms in man in relation to smoking and sudden death.

Angina Pectoris

The Nature of Angina Pectoris in Humans

Pain in the thorax may have several different origins and can create a difficult problem of differential diagnosis. Angina pectoris arises typically in the face of exercise and increased demand for work and oxygen on the part of the heart which cannot be met immediately in the presence of ischemia imposed by coronary atherosclerosis. The origin of the pain is thought to be the ischemic myocardium. It can occur in individuals with or free from preexisting myocardial infarction. Since the common use of angiographic diagnostic methods, it has become apparent that angina also occurs occasionally in persons with little or no evidence of coronary arteriosclerosis.

Angina pectoris is associated with an increased death rate from heart attack. Women survive better than men. Among the risk factors associated with a poorer prognosis are hypertension, cardiac hypertrophy, congestive heart failure, and electrocardiographic abnormalities (149). Recent studies employing angiography have shown a close relationship between the extent of coronary arteriosclerosis and prognosis in angina pectoris. Reeves and associates (108) have summarized these reports to indicate that if only one of the three major coronary artery branches is significantly stenosed, an annual mortality rate of about 2 percent results; if two major branches are stenosed, the resulting annual mortality rate is about 7 percent a year; with three-vessel disease, it is about 11 percent a year.

Summary of Epidemiological Data

The major studies on smoking in relation to the incidence of angina pectoris in the United States are not consistent in their conclusions. The 1976 report on smoking and health (138) has tabulated four major reports in Table 5 on page 33. (Table 5 is reproduced below as Table 6.) Doyle and colleagues (38) report no association in a 10-year follow-up of men from the Albany civil servant study, together with men from the Framingham Heart Study. Jenkins, et al. (63) reported a slight positive association, but not a statistically significant one. Similarly, Kannel and Castelli (70) reported on both men and women from the Framingham Heart Study and found a positive risk association among men and a negative one among women. In a large study of 110,000 men and women enrolled in a health insurance medical care plan in New York City and followed for 3 years, Shapiro, et al. (122) reported a

TABLE 6. — Coronary heart disease morbidity as related to smoking — angina pectoris — prospective studies (Risk ratios—actual number of CHD manifestations shown in parentheses).¹ [SM = Smokers NS = Nonsmokers]

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments									
Doyle, et al., 1964, U.S.A.	3,888 males, Framingham, 30-65 years of age and follow-up	Detailed medical examination and follow-up	10	81	NS	1.00(90)			NS include ex-smokers and pipe and cigar smokers								
					All	1.00(51)											
					<20	1.17(15)											
					20	0.88(18)											
					>20	1.18(18)											
Fenkin, et al., 1968, U.S.A.	3,182 males aged 35-60 at entry	Initial medical examination and follow-up by repeat examination	6 1/2	29	NS	1.00(9)			NS include former pipe and cigar smokers								
					All current cigarettes	1.44(16)											
					>14	1.68(14)											
Kazani, et al., U.S.A.	5,127 males and females, years of age 30-60	Medical examination and follow-up	12	107	Males												
					NS	1.00(16)											
					Heavy SM, >20 cigarettes	2.98(17)											
					Females												
					NS	1.00(28)											
Cigarette SM	0.85(14)																
Shapiro, et al., 1969, U.S.A.	110,000 male and female enrollees of New York City HIP 35-64 years of age	Baseline medical interview and examination and regular follow-up	3	Total Unspecified	Males		Males	Males	p<.001								
					NS	1.00				NS	1.00	25-44	45-54	55-64	p<.05		
					Current cigarette	1.91				1.30	SM	1.71	NS	1.00	1.00	1.00	NS include ex-smokers
					<40	1.51				1.30	Current cigarette	2.40	1.57	2.05			
					>40	4.85					<40	2.85	1.40	1.54			
											>40	10.15	2.58	4.15			
					Females												
					NS	1.00				1.00	1.00						
					Current cigarette	1.56				1.97	0.97						
					<40	1.67				1.58	1.04						
					>40						4.12						

¹Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

SOURCE: U. S. Public Health Service (124).

significantly increased incidence rate for smokers among men who were current users of cigarettes. Among females, the trend was positive but not significant. A study of the incidence over 5 years of angina among 10,000 Israeli men found that there was a higher incidence rate among men who smoked over 20 cigarettes a day than in those who smoked less, but the difference did not reach the 0.01 level of significance (91). In addition, a questionnaire survey (45) of about 70,000 persons has found that more smokers than nonsmokers admitted to chest pain. Some nine different kinds of angina-like and nonanginal pains were included as chest pain. Reid and associates have reported a significant association between angina and current cigarette smoking among British civil servants (110).

The Effect of Smoking on Angina Pectoris

As noted above, the predictive risk factor association of smoking with the incidence of angina pectoris is not clear. However, there is evidence among persons with angina that smoking lessens the threshold of exercise for the onset of pain. Aronow (7, 8, 9, 10, 12) has reported clinical studies in which smoking cigarettes with high, low, or no nicotine content aggravated angina. In these studies, high nicotine cigarettes aggravated exercise-induced angina more than low nicotine cigarettes, and low nicotine cigarettes more than cigarettes without nicotine. He has also reported in patients with angina pectoris and coronary artery stenosis documented by angiography that when 50 parts per million of CO were inhaled until the mean COHb level of venous blood was raised to 2.68 percent, it was accompanied by a significant decrease in exercise time before anginal pain. There was also a decrease in the amount of cardiac work represented by the product of systolic blood pressure and heart rate needed before the onset of angina compared to when air was breathed. S-T segment depression of 1.0 mm or greater in the electrocardiogram occurred earlier, after less exercise and at lower cardiac work levels among these patients when they breathed CO rather than air. Although it is uncommon, there are patients in whom the act of smoking a cigarette will itself precipitate an attack of angina (26, 143).

An interpretation of such data is that, in the patient with a compromised regional myocardial blood supply who can provide little or no compensatory increase in circulation to meet an increased cardiac demand, smoking enhances both hypoxia and cardiac demand, resulting in a more severe ischemia and an earlier onset of angina.

Research Needs

Epidemiological data with respect to the predictive or risk factor association of smoking and angina pectoris tend to show an inconsistent positive association. Despite this unsatisfactory state of affairs,

there would seem relatively little reason to attempt to study the issue further at this time.

Conclusions

Studies of the possible role of smoking as a risk factor for the incidence of angina pectoris suggest a positive association, but the findings are inconsistent.

In patients with angina pectoris, smoking lowers the threshold for the onset of angina. Both nicotine and CO aggravate exercise-induced angina.

Cerebrovascular Disease

The Nature of Cerebrovascular Disease in Man

The underlying circumstances of stroke are varied. They include tumors and bleeding dyscrasias leading to intracerebral hemorrhage or infarction, unusual diseases of blood vessels in the brain, aneurysms of intracranial vessels, embolism, thrombosis, vascular rupture, and atherosclerosis of the vessels of the neck and their distributing vessels in the brain.

The great majority of strokes, perhaps more than 90 percent, may be classified either as intracerebral hemorrhage associated primarily with hypertension, or ischemic cerebral infarction associated with atherothrombotic disease of the vessels of the neck and their main distributing branches in the brain. Infarction is more common than hemorrhage. The clinical diagnostic subclassification or separation of hemorrhagic stroke and ischemic stroke contains an appreciable margin for misclassification. It is these conditions that are under consideration here, rather than the rare disorders.

The risk factor data for stroke have been considered recently by two panels (31, 40). They are less clearly defined than those for coronary heart disease. The strongest gradients of risk are associated with age, blood pressure, preexisting cardiovascular disease, and diabetes mellitus. Prospective studies have not found a clear and direct relationship with serum cholesterol concentration. It has been of interest that a Japanese study has recently reported that among a population with a high incidence of stroke but low levels of blood cholesterol by Western standards, there was no evidence that hypercholesterolemia defined as levels above 200 mgm/100 ml increased the incidence of stroke. Cerebral infarct developed in 11 percent of those with hypertension and hypercholesterolemia and 21 percent of those with hypertension alone (101).

Models of cerebrovascular disease in animals have largely been limited to acute occlusive manipulations. Only recently have experimental dietary and hypertensive sclerosis of cerebral vessels with cerebral hemorrhage (58) been reported in nonhuman primates. A

genetic strain of stroke-prone, spontaneously-hypertensive rats has been developed.

Summary of Epidemiological Data

The epidemiological data on cerebrovascular disease (stroke) and smoking were summarized in the 1976 reference edition of the report on *The Health Consequences of Smoking* (138), Table 137 (pp. 64-66). Kannel reviewed the subject for the Third World Conference on Smoking and Health (68).

The results of various studies have not been congruent and no conclusion can be stated with confidence. Kannel has noted that the prospectively collected data have been difficult to interpret because of deficiencies, such as small sample numbers, failure to consider separately cerebral hemorrhage and ischemic infarction, failure to consider separately men and women, and inadequate classification by age.

The 1976 report on *The Health Consequences of Smoking* (138) comments (on page 152 and in light of its data in Table 7 on page 153, reproduced below as Table 7) on the possible role of age dependency in the various studies, noting that cigarette smoking may be a risk factor for stroke at all ages, but that other causes of stroke may be proportionately so important in older ages that the smoking risk is masked by strokes due to other causes in studies that do not involve very large populations. Although two very large studies, involving about 250,000 and 1,000,000 respondents, found relative risks of about 1.52 and 1.41 for cigarette smokers (41), no certain conclusion can be offered at the present time because of apparently conflicting data. A recent study of a large cohort of women has reported that the risk of subarachnoid hemorrhage is significantly associated both with cigarette smoking and with the use of oral contraceptives. The risk to cigarette smokers was 5.7 times that of nonsmokers while it was increased 6.5 times for users of oral contraceptives. The risk was increased 22 times among women who both smoked and used oral contraceptives compared to nonsmokers and nonusers (106).

The Effect of Smoking on Cerebrovascular Disease

It has been noted that risk factor data are inconclusive on the relation of smoking to the incidence of stroke. Carbon dioxide causes cerebrovascular dilatation. Both nicotine and CO increase cerebral blood flow (123). Unlike the case of cardiac metabolism, there is no evidence that nicotine affects cerebral oxidative metabolism in a dose equivalent to smoking. It is uncertain that these effects relate in any way to stroke. It may be speculated that pathogenetic mechanisms could operate through effects on blood platelets, oxygen transfer, emboli from the heart, or through vessel wall toxicity and enhanced atherogenesis of large and small vessels to the brain. There are no data

TABLE 7.—Age-standardized death rates and mortality ratios for cerebral vascular lesions for men and women, by type of smoking (lifetime history) and age at start of study

Type of smoking	Age groups			
	45-54	55-64	65-74	75-84
CVL death rates per 100,000 person-years				
Men				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,168
Total	35	116	391	1,272
Women				
Never smoker regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
CVL mortality ratios				
Men				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	0.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	0.73
Cigarette only	1.50	1.41	1.37	0.86
Women				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

NOTE. - CVL = Cerebral vascular lesions.
SOURCE: U. S. Public Health Service (198).

dealing directly with experimental cerebrovascular disease in animals and smoking that examine such pathogenetic hypotheses.

Research Needs

Clarification of the existing conflicting epidemiological data may be sought. It has been suggested by Kannel (68) that a retrospective study of brain infarctions under the age of 55 years might help to resolve some uncertainties.

Chronic experimental cerebrovascular disease of hypertensive or atherosclerotic types in animals has received little attention. Such disease has recently been produced in nonhuman primates (58). While its characterization is incomplete, it may possibly offer an opportunity to study the effects of smoking or of smoke constituents. The effect of smoke constituents on the stroke-prone rat is also an area for study.

Conclusions

The relationship of smoking to the incidence of stroke is not established. An association with subarachnoid hemorrhage has been reported in women.

Peripheral Vascular Disease

The Nature of Peripheral Vascular Disease in Man

Atherosclerotic peripheral vascular disease (PVD) is primarily a stenosing or occlusive disorder of the arteries of the legs. Other branches of the aorta such as the subclavian, celiac, or renal arteries may be diseased similarly, but we apply the term to the arteries that supply the leg unless noted otherwise. Atherosclerotic involvement resembles that of the coronary arteries or aorta, but the plaques are more fibrous and cellular and contain less fat. Involvement includes not only the large iliac and femoral arteries, but extends to branches in the anastomotic connections around the knee and to the lesser branches of the lower leg and foot. Thrombosis is common, and embolism from ulcerated plaques in the aorta or iliac arteries occurs. The effect is to create distal circulatory ischemia of a chronic nature that can be complicated by acute occlusive events. The circulation to the leg may become inadequate to the needs of the muscles during exercise. Pain in the calf or thigh is precipitated by exercise, relieved by rest, and is designated intermittent claudication. It resembles angina pectoris in these respects and it is often a changeable and unstable symptom. Severe ischemia will result over time, in some individuals, in tissue atrophy and necrosis or ischemic gangrene.

The risk factors for atherosclerotic peripheral vascular disease are generally similar to those for coronary heart disease, but an elevated blood pressure may be only a minor contributor to risk of PVD (68).

Peripheral vascular disease has been reported in experimental dietary atherosclerosis in the nonhuman primate, but the subject has only recently received systematic study (144).

Summary of Epidemiological Data

Kannel has recently reviewed the data pertaining to occlusive peripheral vascular disease (68). Several clinical reports find that about 90 percent of individuals with arteriosclerotic obstructive peripheral vascular disease (PVD) are cigarette smokers. This is a marked excess of smokers compared to the general or age- and sex-matched population. Moreover, clinical experience finds that continuation of smoking worsens prognosis after surgical therapy (157). In one clinical study of 187 consecutive patients who underwent surgical vascular grafting with synthetic grafts for arterial occlusive disease of the lower abdominal aorta and iliac arteries, the patients who continued to smoke more than a pack a day had three times the graft occlusion rate of nonsmokers, both in absolute terms and in month-patency time (113). Koch (75) has reported that cessation of smoking will lead to a reversion of risk to that of nonsmokers over 5 years. Diabetes is a strong risk factor for PVD; it acts synergistically with smoking. A diabetic who smokes is reported to have a 50 percent greater risk of PVD than one who does not (151). Lawton has reported from a small series examined by angiography that smoking is associated with atherosclerotic distortion of the distal aorta and common iliac arteries in a dose-dependent manner, but not with lesions in the external iliac or femoral arteries (77).

Epidemiological studies have also demonstrated an association of PVD with smoking. In one, it was concluded that cigarette smoking was more common than expected for both sexes among those with PVD, that it was an independent risk factor, and that 70 percent of nondiabetic PVD was related to smoking (152). The prospective Framingham Heart Study reports a strong association between smoking and obstructive peripheral vascular disease including intermittent claudication (68). At all ages and in both sexes a higher incidence of claudication was found in smokers. Heavy smokers had a three times greater incidence and the risk tended to relate directly to the number of cigarettes smoked. The effect was independent by multivariate analysis. At any level of other risk factors the smoker is at greater risk than the nonsmoker. Smoking was found to contribute as strongly to PVD in women as in men. Data for pipe and cigar smoking do not appear to be available.

The Effect of Smoking on Peripheral Vascular Disease

The epidemiological and clinical evidence for smoking as a risk factor has been noted above. The Framingham data on multiple risk factors allow the identification of a top decile of risk from which 40 percent of

cases will emerge (68). Wald, et al. (146) have reported a closer association between blood COHb in smokers and myocardial infarction, angina, or intermittent claudication (considered together) than with smoking history in a survey of Copenhagen workers.

An acute effect of CO on intermittent claudication has been noted by Aronow, et al. (11). They have reported that patients manifesting intermittent claudication of the calf or thigh muscles, and angiographic evidence of iliofemoral arteriosclerosis, who breathed CO to increase mean venous COHb levels from 1.08 to 2.77 percent, experienced a decreased exercise threshold to produce leg pain.

Table A30 (pp. 129-130) of the 1976 report on *The Health Consequences of Smoking* (138) lists a number of experiments in man in which the effect of smoking or of nicotine was assessed on some aspect of the peripheral circulation of the arm or leg. The data are not consistent, although the tabulated data in normal individuals tend to show a decrease in skin temperature and a decrease in blood flow. In another study, calf-blood flow was measured plethysmographically in 51 men, aged 59, who were heavy smokers, but who ceased to smoke for about 2 months. They showed an increase in blood flow during reactive hyperemia (62) after the cessation period. No experiments on animal models of chronic peripheral vascular disease and smoking have been found.

Research Needs

In general, epidemiological data are adequate. It is likely that current epidemiological research will provide additional data to furnish more exact figures than are currently available. New studies appear to be unnecessary except to establish levels of risk for different "less hazardous" cigarettes. The possible association of postmenopausal estrogen treatment, smoking, and PVD in older women may warrant attention.

However, it is not clear what roles atherogenesis, nicotine, CO, and perhaps tobacco allergy may play in the development and expression of PVD in smokers or in its responsiveness to smoking withdrawal. Studies of the mechanisms responsible for these aspects of smoking and PVD are warranted and may also have interest for the study of the pathogenesis of atherosclerosis in general.

Animal studies involving chronic or acute smoking, hypertension, atherogenesis, and PVD are possible, particularly in nonhuman primates conditioned to smoke. These may offer a direct, if difficult, experimental approach to understanding the circulatory effects of smoking and smoke components on PVD.

Conclusions

Cigarette smoking is a major risk factor for ischemic peripheral vascular disease of arteriosclerotic type. It increases appreciably the

risk of peripheral vascular disease in diabetes mellitus. Clinical experience and case series studies find that cessation of smoking benefits the prognosis in peripheral vascular disease and is advantageous to its surgical treatment.

Aortic Aneurysm of Atherosclerotic Type

The Nature of Atherosclerotic Aortic Aneurysm

Atherosclerosis involves the abdominal aorta early in life about equally in males and females. Progression of the disease in some individuals is such that large plaques rich in lipid and pultaceous with necrosis become confluent and encroach upon the media of the vessel, causing necrosis of its cells and attenuation of the wall. Dilatation of the vessel and aneurysm formation follows. Thrombosis on the luminal surface is common. Eventually the wall may become so thin that leakage and rupture occur.

Fatal outcome is more common in men than women. The condition usually becomes clinically apparent after the age of 50 and its incidence increases with age. It is not known why some individuals develop this form of progressive disease in the abdominal aorta. An association with smoking is noted below. The morphological features of the process are exaggerated but similar to those of atheroma in other arteries, and it is generally considered that aortic aneurysms of this type are variants of the general process of atherogenesis. There is a high concordance with coronary heart disease.

Equivalent atheromatous lesions have not been produced in experimental animals.

Summary of Epidemiological Data

Atherosclerotic aneurysm of the aorta (nonsyphilitic aneurysm) may cause death by rupture or, occasionally, by thrombotic occlusion. It is an uncommon cause of death, less than 1 percent of cardiovascular deaths being attributed to it. Table 29 (p. 67) of the 1976 report on *The Health Consequences of Smoking (138)* lists four population studies in which a total of 947 such deaths are recorded. The two largest studies—that of Kahn involving more than 248,000 U.S. male veterans, and that of Hammond and Garfinkel involving approximately 358,000 males—find a dose-dependent mortality ratio such that pack-a-day male smokers have a ratio of about 4 or 5, while smokers of more than 39 (Kahn) or 40 (Hammond and Garfinkel) cigarettes per day have a mortality ratio between 7 and 8 when compared with nonsmokers. These are unusually large ratios relative to other atherosclerotic disease. Data permitting multivariate analysis in terms of other conventional risk factors are unavailable.

The Effect of Smoking on Aortic Aneurysm

Aside from the strong risk factor association noted above, nothing more is known about smoking and aneurysm formation in man. It may be speculated that CO exposure enhances the circumstances that promote plaque growth and medial hypoxia, which leads to attenuation and necrosis of the aorta. It may also be speculated that smoking may lead to excessive thrombosis, which leads to excessive plaque development and aneurysm formation. However, there are no data in men with aneurysm formation that allow comment on these speculations.

Spontaneous medial calcific arteriosclerosis occurs in the rabbit, particularly along the thoracic aorta, leading to mild localized aneurysmal dilatations (55). It has generally not been specifically reported in relation to smoking or smoke products, although it may possibly have been observed incidentally in various experiments. Wanstrup and associates (147) reported the enhancement of such change with CO exposure. Schievelbein (120) studied the chronic effect of nicotine in animals (rabbits) liable to develop spontaneous arteriosclerosis in the absence of an atherogenic diet. There was no enhancement of morphological arteriosclerosis by nicotine, but the aortas of the experimentally treated group contained more calcium, more free fatty acids, and more lipoprotein lipase. Aneurysmal differences were not noted.

Research Needs

Atherosclerotic aneurysms of the aorta are uncommon. Study of their pathogenesis is not likely to be promising in the absence of convenient animal model analogues. A study of experimental poststenotic dilatation might illuminate atherogenic processes in relation to smoking. Research initiatives in this area show little promise at present.

Conclusions

Cigarette smoking is a strong risk factor for atherosclerotic aortic aneurysm. The association provides a mortality ratio of about eight among males who smoke more than about 40 cigarettes a day and a dose relationship is evident.

High Blood Pressure

The Nature of Hypertension

Many factors are known to be involved in and affect the control of arterial blood pressure. It is directly dependent on cardiac output and total peripheral resistance. Some of the factors influencing pressure include the renin-angiotensin system, aldosterone, catecholamines, central and peripheral nervous activity, plasma volume, changes in

vessel elasticity, red cell mass and blood viscosity, sodium metabolism, obesity, and genetic predisposition. The manner or means by which most cases of hypertension—essential hypertension—develop is not understood. The effect, however, is to enhance atherogenesis and atherosclerotic diseases, particularly heart disease and stroke, and to shorten life.

Experimental models of hypertension in animals are available for research. There are both genetic models and those induced by hormonal and surgical procedures. However, smoke or smoke constituents have not been assessed in such models.

Summary of Epidemiological Data

Arterial hypertension is a very common disorder constituting a risk factor for atherogenesis, stroke, heart attack, heart failure, renal failure, and retinal damage. Hypertension is a continuous variable and an independent risk factor.

Although smoking can raise blood pressure acutely, there is no evidence that smoking induces hypertension. On the contrary, smokers appear to have, on the average, a slightly lower blood pressure than nonsmokers. Table A8 (pp. 99-100) of the 1976 report on smoking and health (138) tabulates several studies; recent reports repeat such data trends or show little relationship (23, 129).

An exception to these data is the finding of Kahn and associates (67) in their study of 10,000 Israeli male civil servants. In a period of 5 years, they found that the incidence of hypertension adjusted for age was about two times greater in smokers than nonsmokers. However, the conclusion can be considered in additional ways. Since weight gain is associated with an increase in blood pressure and weight loss is associated with a decrease in blood pressure and, moreover, since smokers tend not to gain as much weight as nonsmokers, this complex relationship has attracted attention. Seltzer (121) has offered data in which men who stopped smoking gained about 8 pounds and showed an increase of about 4 mm Hg in systolic blood pressure. In examining the data for weight change, it was found that continuing smokers who lost weight had a decrease in systolic blood pressure of about 3 mm Hg, while quitters who also lost weight had an increase in blood pressure of about 2 mm Hg. The gradient between these two groups was about 5 mm Hg in systolic blood pressure. The reference report of 1976 on *The Health Consequences of Smoking* (138) comments critically on this report (p. 138ff.), and notes a marginal sample size.

Available data indicate that smoking is not a major risk factor for hypertension, and in practice, the association is slightly negative. In this sense, it should be balanced against the other strong positive risk factor associations of smoking for various expressions of heart attack, for PVD, aortic aneurysm, lung disease, and cancers.

Data from several epidemiological studies indicate that, when hypertension is present, its combination with another risk factor, such as elevated blood lipids or smoking, is synergistic.

The Effect of Smoking on Blood Pressure

The chronic epidemiological effects of cigarette smoke on the incidence and level of hypertension and in conjunction with hypertension as an additional risk factor for cardiovascular disease have been noted above.

The acute and transient effect of smoking in man is to increase heart rate and blood pressure to a minor degree. These effects are thought to be due primarily to the action of nicotine releasing catecholamines. In the 1976 report on *The Health Consequences of Smoking* (138), Table A20 (pp. 103-108) and Table A21 (pp. 109-114) summarize a series of acute effects of smoking and nicotine on the blood pressure of animals and humans. Table A22 (p. 115), notes the effects on catecholamines in humans and animals. Beaumont and colleagues (17) have recently reported on a paroxysmal arterial hypertension as a reaction to cigarette smoking in which, under clinical diagnostic testing, a single high nicotine cigarette induced a rise in blood pressure of about 50 mm Hg systolic and 20 mm Hg diastolic over about 20 minutes. The reaction was accompanied by headache, palpitations, and sweating. The reaction was elicited in 13 of 178 persons tested, all of whom were moderate to heavy smokers.

Research Needs

It would be of some interest for an understanding of chronic hypertension to elucidate the pathogenesis of what appears to be a very mild hypotensive chronic effect of smoking. Since genetic and induced animal models of hypertension and hypertensive vasculopathy exist, including stroke-prone spontaneously hypertensive rats, it may be informative to assess the acute and chronic effects of smoke and smoke constituents in them.

Conclusions

Cigarette smoking does not induce chronic hypertension. Indeed, present evidence indicates that it is associated with a mild chronic hypotensive effect. However, in the presence of hypertension as a risk factor for coronary heart disease, smoking acts synergistically to increase the effective risk by joining the risks attributable to hypertension and to smoking alone.

Other Conditions

Among other conditions of interest are arterial and venous thrombosis, the synergism of smoking with oral contraceptives in relation to

myocardial infarction, thromboangiitis obliterans, the effect of smoking on blood lipids and lipoproteins, and tobacco constituents other than CO and nicotine.

Venous Thrombosis

Pathological studies in human autopsies that address the question of a difference in the presence of venous thrombi in relation to smoking habits have not been reported. On the other hand, epidemiological studies have clearly shown that conditions such as myocardial infarction or peripheral vascular disease that are commonly induced or accompanied pathogenetically by arterial thrombosis are more common in smokers than nonsmokers. Vessey and Doll (140) reported in a case control study among 84 women with venous thromboembolism (deep vein thrombosis or pulmonary embolism) that there were no appreciable differences in smoking habits of subjects with or without venous thromboembolism. In the same paper, the authors mention a mortality study conducted among British doctors and report that among 31 male deaths from venous thromboembolism over 15 years of observation, the age-standardized mortality rates per 100,000 were 96 among nonsmokers, 57 among cigarette smokers, and 71 among pipe and cigar smokers. Lawson and coworkers (76) report the absence of an effect of smoking on venous thromboembolism among premenopausal women who were users of oral contraceptives. It has been reported that smokers suffer less thrombosis of the deep veins of the leg after myocardial infarction (39, 83). The failure to confirm such a finding has also been published (57). There have been a number of studies of various aspects of blood coagulation and platelet pathophysiology in relation to smoking. In general, these have been acute experimental investigations. Table A27 (pp. 126-1138) of the 1976 report on smoking and health (138) recorded a number of such studies, including a review by Murphy. The data tend in the direction of phenomena that might be expected to promote thrombosis. However, confounding variables are uncertain and the meaning of *in vitro* tests for *in vivo* phenomena of thrombosis is not established.

From the limited data available, smoking does not appear to enhance venous thrombotic disease.

The interest in venous thrombosis and smoking lies not only in the question of the presence or absence of an association but in its possible meaning for arterial thrombosis. Arterial thrombosis is involved to an important degree in atherogenesis, and in the precipitation and complication of heart attack, ischemic stroke, and peripheral vascular disease. There are research opportunities to learn more about thrombosis in general and, in particular, in relation to possible pathogenetic associations with smoking.

Thromboangiitis Obliterans (Buerger's Disease)

Buerger's disease is a relatively rare vascular disease that severely affects the legs and sometimes affects the arms and other vessels. It is usually present as a painful ischemic disease of progressive and subacute type in young male adults. Pathologically, there is a focal subacute inflammatory phase involving the artery, nerve, and vein coursing in the limb. The vascular inflammation is accompanied by arterial and venous thrombosis and local obstruction to the circulation. A migrating thrombophlebitis is often prominent. Lesions may heal with vascular sclerosis and new lesions may appear at other sites. The ultimate outcome is ischemic loss of the limb(s) and when the lesion extends to other vessels, loss of life. While the disease has been regarded as a fulminant form of atherosclerosis (153), the more common view with stronger evidence is that it is a separate disease (87) and a vasculitis. An infectious etiology (24) has been proposed, as has a hypersensitivity cause (54). Risk factors such as hypercholesterolemia or diabetes are not present and coronary heart disease occurs only very late in the course of the disease.

Smoking has been noted clinically to be strongly associated with Buerger's disease (68). Retrospective studies indicate that its occurrence among nonsmokers must be very rare. The lesions are compatible with an angiitis of hypersensitive or immunologic pathogenesis. Therefore, it has been speculated that hypersensitivity to tobacco components may be the basis of thromboangiitis obliterans (54). The evidence for this theory is suggestive but inadequate at present. Adequate investigations will probably require the use of much purer tobacco antigens than have been available in the past (19). There is conceptual interest for the pathogenesis of atherosclerosis in such investigations that extends beyond thromboangiitis itself since atherosclerotic lesions commonly show evidence of a slight inflammatory component and since a form of coronary atherosclerosis bearing a remarkable resemblance to advanced plaques in man has been produced in fat-fed rabbits by immunologic means (93), and also because a glycoprotein isolated from tobacco leaves has been shown to activate Factor XII in samples of human plasma, resulting in the generation of clotting activity, fibrinolytic activity, and kinin activity (18).

Oral Contraceptives, Smoking, Myocardial Infarction, and Subarachnoid Hemorrhage Among Women

Extensive population studies have determined that the risk of non-fatal myocardial infarction among women during child bearing ages is increased by a factor of about two times by the use of estrogen-containing oral contraceptives, and that it is increased to about 10 times the expected value when users also smoke (61, 81, 82, 102). A recent study reports that oral contraceptive use increases the risk of

subarachnoid hemorrhage about six times and that the additional use of cigarettes increases the risk to about 20 times (106).

The mechanisms that may underlie these phenomena in women are considered elsewhere, but estrogen and estrogen analogue administration to men with cancer of the prostate or with preexisting myocardial infarction have been shown to increase the risk of heart attack (30, 141). These reports did not contain information on smoking, however. While the associations between smoking, oral contraceptive use, and enhanced risk of cardiovascular disease are not in doubt, research opportunities exist in seeking explanations for the effect.

The Effect of Smoking on Blood Lipids

The report, *The Health Consequences of Smoking* of 1976 (138), dealt with the question of a possible effect of smoking on blood or serum cholesterol. Acute effects in man and animals were tabulated in Tables A25 and A25a (pp. 119-124). Case control and population studies are listed in Table A7 (pp. 94-98). The data are not very uniform, but there is a preponderance of results in man in which smokers have a somewhat higher blood cholesterol level than nonsmokers. Paul (103) has recently presented additional data with this same finding. Dawber has analyzed the Framingham Heart Study data in terms of pipe, cigar, and cigarette smoking (33). Since these forms of smoking deliver different amounts of tar, nicotine, and CO to the smoker, such an analysis might reflect specific responses on the part of the serum lipids. No major differences were found. Pipesmokers had average cholesterol levels of about 216.25 mg, cigar smokers of 220.95 mg, and cigarette smokers of 224.34 mg (nonsmokers 223.83 mg). These differences are too small to account for the observed differences in risk associated with type of smoking habit. There may indeed be a minor tendency for cigarette smokers to have slightly elevated blood cholesterol levels for whatever reason, but smoking and cholesterol are clearly established independent risk factors.

Experimental data based on acute manipulation of smoke exposure or nicotine appear to show a consistent elevation of free fatty acids in the blood. Animals exposed to CO and high cholesterol diets have been reported to develop more hypercholesterolemia than expected, but confirmation has not been established with whole smoke (14, 136).

Other recent reports have found HDL levels to be a strong and independent risk factor for coronary heart disease that has an inverse relationship (49, 92, 94); high levels are protective and low levels are associated with increased risk. Both in a subset of the Tromso study (94) and in the Framingham study (49), almost identical HDL cholesterol levels among smokers and nonsmokers were found; there was no significant association between them.

Observations on 10,000 males in Israel show that alpha cholesterol is depressed among smokers of cigarettes compared to nonsmokers and

ex-smokers, with the trend persisting in different age groups. The concentration of alpha cholesterol decreased according to increased amounts smoked daily when the smokers were grouped as never having smoked, and having smoked 0 to 10, 11 to 20, and more than 20 cigarettes smoked per day. Total serum cholesterol, and hence beta cholesterol, were increased in direct relationship to the amount smoked (48). HDL cholesterol has also been measured among approximately 4,000 men and women who are the adult offspring of the original Framingham Heart Study cohort. After control for reported alcohol consumption, subscapular skinfold thickness, and age in multiple regression analysis, cigarette smoking was found to be associated with significantly lower HDL levels in both men and women. There was no evidence of lower HDL cholesterol among former cigarette smokers (47). In an examination of 447 women and 471 men aged 40 or 41 in Holland, it has been found that HDL cholesterol is (as expected) higher in women than in men. Cigarette smoking was associated with a reduced serum HDL-cholesterol in both men and women. Among the women there was also a strong negative association with the use of oral contraceptives that was independent of smoking (4).

Hulley and colleagues (59) have recently reported in a multiple-risk-factor intervention trial group that over a period of a year the change in serum thiocyanate (an indirect measure of smoking activity) showed a univariate regression coefficient, with an HDL cholesterol of $-.12$ that was significant at less than the 0.05 level. The multivariate regression coefficient was $-.15$ and significant at less than 0.01. While more data should be gathered to ascertain the effect of smoking on HDL levels, present indications are that, when other factors that also affect HDL levels are controlled in statistical analysis, cigarette smoking displays an independent inverse relationship with HDL levels. Moreover, since total cholesterol levels appear to be slightly elevated among smokers, lipoprotein cholesterol that is positively atherogenic will also be increased. Consequently, it can be hypothesized that the effect of smoking on CHD morbidity and mortality may be to some degree a reflection of altered lipoprotein metabolism.

Other Constituents of Smoke

Smoke is a remarkably complex mixture of chemical substances and physical chemical states. Our understanding of the relationships of nicotine and CO and of whole smoke to cardiovascular disease have been noted above. Other substances have attracted some investigation also. Those of possible cardiovascular interest include cadmium, zinc, chromium, carbon disulphide, carbon dioxide, hydrogen cyanide, oxides of nitrogen, and polonium-210. McMillan (90) concluded that, while these substances provide interesting grounds for speculation as to their possible role in cardiovascular disease, only nicotine and CO offer both data and rational concepts for a role in smoking and cardiovascular

disease that command serious attention at the present time. As noted very briefly above in the section on thromboangiitis and considered in a separate chapter, hypersensitivity to tobacco protein does offer reasonable concepts in relation to the pathogenesis of arteriosclerosis, thrombosis, and angiitis. Its investigation will require more systematic study and the use of immunologic methods superior to those employed in the past.

Discussion and Conclusions

The present report on cardiovascular disease and smoking is able to summarize and to comment on far more extensive and detailed data than were available 15 years ago. It draws heavily on the 1976 reference report on smoking and health (138) and adds recent references.

Systematic observations on the associations between smoking and cardiovascular diseases have been made on considerably more than a million individuals in the United States alone and have involved many millions of person-years of experience. The majority of these have been gathered on men.

Sample sizes are now extensive in both retrospective and prospective studies. The variables observed in retrospective studies have been relatively limited; in some prospective studies, they have been more numerous and have allowed for complex analyses in which the independence of smoking as a risk factor among other risk factors has been defined.

The data collected from western countries, particularly the United States, but also the United Kingdom, Canada, and others, show that smoking is one of three major independent risk factors for heart attack manifest as fatal and nonfatal myocardial infarction and sudden cardiac death in adult men and women. Moreover, the effect is dose related, synergistic with other risk factors for heart attack, and of stronger association at younger ages. Based on smaller but still extensive samples, smoking cigarettes is strongly associated with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta.

There is no reasonable doubt that cigarette smoking as a risk factor for these cardiovascular diseases has been proven. Its dimensions as a risk factor for them have been established for the American public.

Atherosclerosis, the basic lesion of ischemic disease studied at autopsy, has been observed in restricted samples and limited numbers of cases. Nevertheless, the data establish adequately that cigarette smoking is associated with more severe and extensive atherosclerosis of the aorta and coronary arteries than is found among nonsmokers. The effect is related to the amount smoked. Existing autopsy data have not allowed adequate multivariate analysis, but several prospec-

tive studies have now collected sufficient standard risk factor data, including smoking information and autopsy findings, to report preliminary multivariate analyses. While more data might be desirable in order to establish better the dimensions of effect as seen at autopsy, and more data are needed to extend multivariate analyses, there is no reasonable doubt that cigarette smoking enhances atherogenesis. This knowledge establishes a fundamental rationale for the findings on the incidence of heart attack, including sudden cardiac death, aortic aneurysm, and peripheral vascular disease in relation to smoking. It is somewhat uncertain, but likely, that smoking has an adverse effect on the recurrence of heart attack among survivors of a prior myocardial infarction.

On the other hand, epidemiologic data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive. There are major and unresolved inconsistencies between existing reports. While certain reports on these diseases may have more technical strength than others and thus provide more credible conclusions, a basis for drawing final conclusions is not established in these two conditions. It is of interest that, in acute experiments on atherosclerotic patients with angina pectoris or with the intermittent claudication of peripheral vascular disease, smoking or exposure to carbon monoxide reduces the patients' established threshold for the precipitation of angina or claudication.

There is no apparent relationship between smoking and the incidence of hypertension. Available evidence indicates a neutral or slight hypotensive effect. Nevertheless, in the presence of hypertension, smoking joins with hypertension to affect the patient with the cardiovascular burden of both risk factors.

There are opportunities for further epidemiological research into smoking as a risk factor for cardiovascular disease; these have been detailed in each of the foregoing sections. The need and priority of such research should be debated in specific cases. It can be argued that little public health or medical therapeutic advantage would arise from a clarification of the relationship of smoking to angina or cerebrovascular disease in the face of the existing conclusive evidence of its adverse effect on the incidence of heart attack and lung diseases and the benefits of smoking avoidance or cessation. On the other hand, it could be of some medical value to learn more accurately what the association may be for second heart attacks. It would be of great interest for preventive medicine to know whether smoking affects the severity of atherosclerosis of the aorta and coronary arteries in childhood and adolescence and the premature development of adult forms of lesions in youth. It would also be of great interest to learn whether present-day cigarettes modified to deliver less tar and nicotine are less hazardous for cardiovascular health. Earlier data, which no longer represent current products, found that low tar and nicotine cigarettes

carried less risk than high tar and nicotine ones but that they also bore a considerably greater risk than not smoking.

Relatively little is known about the mechanisms by which smoking enhances atherogenesis or increases the risk of heart attack. This ignorance in no way weakens the force of the information noted above; nevertheless, better insight into the pathogenesis of these effects would be of potential value in designing less hazardous cigarettes or in attempting otherwise to limit the hazard of smoking. Moreover, it is likely that there would be an appreciable gain of information about basic processes of atherogenesis, thrombosis, cardiac metabolism and ischemia, and cardiac rhythmicity and ectopic electrical activity. Some experiments can be done acutely in man; many can be done in animal models with smoke constituents. Chronic or acute experiments in nonhuman primates with natural or modified whole smoke taken by inhalation in a humanlike nonaversive manner of smoking now appear possible. It should be emphasized that a number of strong concepts exist in atherogenesis, thrombosis, and cardiac structure and function within which to mount appropriate experiments.

Data on the epidemiological relationships between smoking and heart attack, peripheral vascular disease, aortic aneurysm, and arteriosclerosis noted above have been assembled in a manner to allow a statistical statement of the nature of the correlations between cigarette smoking and cardiovascular disease. Correlation is not synonymous with causation. It is important for the public to understand the nature or character of the associations that have been found. The characteristics are fully established for heart attack and include the fact that the correlations are strong ones, generally having a relative risk of two or more. They are consistent, reappearing in different population samples over and over, and they are independent of other major risk factors. There is also a graded relationship; smoking is an antecedent event in time and the cessation of smoking is followed by a reduction in risk over time; the association has strong predictive capacity in the same population sample and also when applied to other samples. Within the limits of the research that has been done, the findings of epidemiology, clinical investigation, and pathology are generally congruent. The results from the various disciplines and techniques of study tend to support each other. Although there are reports which do not confirm the statements made above, they constitute a minor part of the data and fail to cast reasonable doubt. Animal experimentation is not yet well developed in smoking research in relation to cardiovascular disease.

Smoking is not a necessary condition for atherosclerosis and heart attack since these occur in nonsmokers. Repeated and very extensive experience has found, however, that it is a sufficient condition to increase the mortality from heart attack among the category of people who smoke and that it does so in a predictable way.

Given the characteristics of its associations with heart attack (such as strength, graded relationship, independence, consistency, antecedence, loss of relationship on withdrawal, predictive capability, and a degree of coherence), it can be concluded that smoking is causally related to coronary heart disease in the common sense of that idea and for the purposes of preventive medicine. It may be argued that the characteristics of the associations noted above would occur if people who were constitutionally liable to heart attack were also constitutionally liable to smoke; that is, that smoking activity and susceptibility to atherosclerotic heart disease were both due to some underlying constitutional condition of the individual. An attempt has been made to study this point by observing large numbers of monozygotic and dizygotic twins. The result has been inconclusive. A discussion of references will be found in the 1976 report on *The Health Consequences of Smoking* (p. 44ff.) (138). It should be noted, however, that the fact that risk in smokers reverts to normal or nonsmokers' levels after they cease to smoke is contrary to the constitutional concept as expressed above, unless further complex assumptions are made and it is assumed that large numbers of individuals underwent a change in their underlying constitutional factor in midlife, acquired low risk, and ceased to smoke because of that new constitution. This is not to say that genetic susceptibility or resistance may not also be a risk factor that plays a role in the individual expression of or resistance to disease along with other risk factors, or that people who stop smoking may not also adopt additional health-oriented behaviors when they stop; but the constitutional hypothesis as expressed above does not provide a credible basis to doubt that cigarette smoking is a cause of coronary heart disease.

From the point of view of cardiovascular disease, research on the mechanisms whereby smoking causes its adverse effects and a more precise quantification of certain risk factors through epidemiological studies are significant topics of medical science. The major goal in smoking and cardiovascular disease research is, however, the development of long-term effective methods of smoking avoidance and cessation.

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