TABLE 8.—Percent of persons 17 years old and older, who perceive their health to be "excellent," by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both Sexes				
17+	42.7	41.5	43.0	42.8
17–44	51.3	47.7	55.4	53.1
45–64	34.0	32.6	36.7	32.0
65+	27.1	24.7	26.5	28.2
Male				
17+	46.8	44.1	44.0	52.0
17–44	56.7	52.9	59.9	60.8
45–64	36.9	32.3	38.0	40.9
65+	25.5	19.2	25.4	30.0
Female				
17+	39.0	38.7	41.2	38.7
17–44	46.3	42.0	49.2	48.7
45–64	31.3	33.0	34.1	28.9
65+	28.3	32.4	29.3	27.7

SOURCE: Wilson, R.W. (*16*).

been analyzed to determine if this increased hospitalization is for diseases usually associated with smoking.[1]

While smokers tended to report more hospitalizations than did persons who had never smoked, there was no tendency for smokers to report more frequent visits to physicians than those who had never smoked, although former cigarette smokers reported the largest proportion with five or more physician visits during the past year (Table 10).

Respondents in the 1974 Health Interview Survey were also asked whether they had ever tried to quit smoking, whether a doctor had advised them to quit, and whether they had been advised to quit because of specific health conditions. Just under a quarter of all persons who had ever smoked reported that they had been advised by a doctor at one time or another to stop smoking (Table 11). Surprisingly, at least from a public health point of view, at those ages at which the effects of smoking often begin to manifest themselves, 45 to 64, less than one-third of the smokers reported that they had been advised by their physicians to stop smoking. This would appear to indicate a need

[1]There are many types of analyses that could be performed on these data that have not been done because of differing priorities and lack of resources. For example, one interesting area of investigation that was begun, but not completed because of the apparent complexities of the issue, is the relationship between cigarette smoking, health variables, and weight. However, NCHS does make available to researchers public-use data tapes from the various surveys, so that they can conduct their own analyses (*12*).

TABLE 9.—Percent of persons 17 years old and older, with one or more hospital episodes in the year prior to interview, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	13.1	13.5	14.4	12.7
17–44	12.3	13.8	11.7	12.0
45–64	12.9	12.3	15.1	12.1
65+	16.5	16.5	19.7	15.3
Male				
17+	10.2	10.5	12.8	8.3
17–44	7.0	8.6	8.0	5.3
45–64	13.1	12.4	14.5	12.5
65+	17.4	19.0	18.5	14.9
Female				
17+	15.7	16.9	17.5	14.7
17–44	17.2	19.5	16.8	15.9
45–64	12.8	12.3	16.2	12.0
65+	15.8	12.9	23.1	15.4

SOURCE: Wilson, R.W. (*16*).

not only for increased public education, but also for increased educational programs among health professionals. About two-thirds of all present smokers had tried to stop smoking at some time (Table 12).

Since detailed smoking history information was not obtained, it is difficult with these data to determine the more precise relationships between illness, physicians' advice to stop smoking, and actual attempts to stop. Some of the studies conducted in the past by the National Clearinghouse for Smoking and Health and reported elsewhere in this report have attempted to investigate these relationships as well as some of the more attitudinal and psychological aspects of smoking.

Respondents to the Health Interview Survey were asked if a doctor had ever told them they had heart trouble. Among persons under 65 years of age, a larger proportion of both present smokers and former smokers had been told that they had heart trouble compared with persons who had never smoked (Table 13). For example, 15 percent of the male former smokers aged 45 to 64 had been told they had heart trouble compared to 10 percent of those who had never smoked. There is some difficulty interpreting the data for persons over 65 years old, where a higher proportion of those who had never smoked report heart

TABLE 10.—Percent of persons 17 years old and older, with five or more physician visits in the year prior to interview, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	24.8	23.7	27.0	26.1
17–44	22.0	23.0	23.4	22.3
45–64	25.5	24.3	26.4	27.2
65+	34.2	27.0	37.1	34.9
Male				
17+	17.9	16.9	22.9	17.3
17–44	13.4	14.1	16.1	13.1
45–64	21.3	20.7	24.1	20.8
65+	30.2	24.8	33.5	30.4
Female				
17+	30.8	31.3	34.5	30.0
17–44	29.9	32.9	33.5	27.6
45–64	29.2	28.3	31.1	29.4
65+	37.0	30.1	46.8	36.3

SOURCE: Wilson, R.W. (*16*).

trouble, since many of the smokers with heart trouble have already died.

Of those smokers who have been advised by a doctor to stop, about 28 percent were advised to stop because of respiratory disease. About 23 percent of the smokers 65 and older were advised to stop because of circulatory problems, but this proportion drops for the younger smokers. Hardly any smokers reported they were advised to stop because of cancer. However, these data on cancer are also misleading; since the survival rate for lung cancer is relatively low, many smokers would not live long enough to report that the doctor had told them to stop smoking.

The first cycle of the Health and Nutrition Examination Survey contained a number of questions that, when combined, formed an Index of General Psychological Well-Being.[2] This measure provides data on another dimension of the relationship between cigarette smoking and health. In general, current cigarette smokers were found

[2] The Index of General Psychological Well-Being is composed of 18 items with a total of 128 response options. The response option for each item that indicates the greatest distress is scored zero. Some of the items and their response options also permit representations of high-level positive well-being. The total index scores range from 0 thru 110, with low scores indicating distress and high scores indicating positive well-being. Generally positive affect is represented by scores above 78 and marginal well-being by scores of 73 to 77. The median score for the population estimates of adults, 25 to 74 years old, was between 83 and 84 (*5*).

TABLE 11.—Percent of persons 17 years old and older who have ever smoked and who were ever advised by a physician to stop smoking, by smoking status, sex, and age: United States 1974

Smoking status and sex	All ages 17+	17–44	45–64	65+
Total ever smoked				
Both sexes	23.9	19.6	29.2	30.1
Male	23.5	17.8	29.2	32.4
Female	24.4	21.8	29.2	25.3
Former smoker				
Both sexes	21.3	14.2	26.3	28.2
Male	22.7	13.5	28.0	29.6
Female	18.9	15.0	22.6	24.2
Present smoker				
Both sexes	25.2	21.5	31.1	32.6
Male	24.0	19.4	30.2	37.0
Female	26.6	23.9	32.1	26.2

SOURCE: Wilson, R.W. (*16*).

TABLE 12.—Percent of present cigarette smokers 17 years old and older who have tried to stop smoking, by sex and age: United States, 1974

Sex	All ages 17	17–44	45–64	65+
Both sexes	64.7	66.0	62.8	61.1
Male	66.0	66.7	65.1	63.3
Female	63.3	65.3	60.2	57.9

SOURCE: Wilson, R.W. (*16*).

to have a slightly lower level of well-being than were nonsmokers. Heavy smokers (more than 1 1/2 packs a day) under 65 years of age report the lowest levels of general well-being and report mean levels of general well-being at marginal levels or lower.

Conclusions

The available evidence in the relationship between cigarette smoking and illness and disability has increased markedly since the first

TABLE 13.—Percent of persons 17 years old and older who have been told by a doctor that they had heart trouble, by cigarette smoking status, sex, and age: United States, 1974

Sex and age	Total	Present smoker	Former smoker	Never smoked
Both sexes				
17+	9.0	7.8	12.9	9.4
17–44	4.2	4.8	4.7	4.1
45–64	11.1	11.6	14.9	9.9
65+	22.9	17.9	28.5	23.3
Male				
17+	8.9	8.2	13.8	8.4
17–44	3.8	4.5	4.7	3.6
45–64	12.0	13.0	15.2	10.0
65+	24.5	18.6	28.5	26.5
Female				
17+	9.0	7.4	11.4	9.9
17–44	4.6	5.1	4.9	4.4
45–64	10.3	10.0	14.3	9.9
65+	21.8	16.8	28.5	22.4

SOURCE: Wilson, R.W. (*16*).

Surgeon General's report was issued, largely as a result of data collected from national probability surveys conducted by NCHS. These data range from the standard health indicators, such as measures of chronic and acute illness and measures of disability days, to less commonly used indicators of lifestyles. The results of analysis performed on these data vary from the more frequently reported findings on disability to data from the Index of General Psychological Well-Being, first reported in this chapter.

The findings tend to be consistent with the large amount of evidence on the relationship between cigarette smoking and mortality, i.e., people who smoke cigarettes report more illness and disability than people who have never smoked cigarettes. While many studies show a reduction in the risk of mortality among former cigarette smokers, data on disability and illness often show continued high risk for former smokers, indicating both a lack of refinement in the current data to distinguish between types of former smokers as well as the fact that once certain diseases occur they do not go away.

The most important aspect of these data collected by NCHS lies not in the substantive analysis prepared by the NCHS staff, but in the

analytic potential of the data to other researchers in the smoking area through the use of NCHS's public-use data tape program.

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4. CARDIOVASCULAR DISEASES.

National Heart, Lung, and Blood Institute

CONTENTS

LIST OF TABLES

Atherosclerosis

Most studies of the pathology of atherosclerosis have been based on autopsies of coroner's or hospital populations in which only a limited fraction of decedents have been examined. They have been valuable for an understanding of the pathogenesis and complications of atherosclerosis. Such studies cannot be taken to represent the prevalence of atherosclerosis in the general population. Studies which attempt to minimize selection bias at autopsy by examining the great majority of decedents in a defined population are rare (*66, 114*).

The most extensive and comprehensive autopsy study that has been conducted is the International Atherosclerosis Project, which collected data from 15 cities in 14 countries and recorded more than 21,000 autopsies according to a standardized protocol and method of evaluation (*85*). The study found a remarkably frequent occurrence of atherosclerotic lesions in the United States; detailed international or geographic differences in the severity of atherosclerosis; raised the issue of whether childhood atherosclerosis evolves into adult forms of atherosclerosis; and documented that, on the average, there are more frequent and extensive coronary plaques in cases with coronary heart disease than in comparison cases regardless of age, sex, geographic location, or race. Approximately the same prevalence and extent of advanced atherosclerosis were seen in coronary heart disease cases regardless of age, sex, and, with few exceptions, of geographic location. While individuals may show considerable variability in the severity of atherosclerosis, the conclusion is that coronary atherosclerosis is of primary importance in the development of coronary heart disease in a population (*133*). Another extensive study in five towns in Europe has been reported by the World Health Organization (WHO) (*66*).

The Nature of Atherosclerosis in Man

Information about atherosclerosis in man derives from pathological studies and from associations observed in clinical or epidemiological studies.

The lesion or plaque is a cellular proliferation in the arterial intima. It contains chiefly smooth muscle cells, but also fibrocytes and cells typical of chronic inflammation. Lipid is commonly present along with cellular products such as collagen, elastic tissue, glycosaminoglycans, and cellular debris from necrosis. Elements of thrombus are common both in and on the plaque. Focal calcification is frequent. Thus, a highly variable and complex range of lesions can be considered under the term atherosclerosis.

The concept of the development of lesions is a synthetic one derived from the observation of many lesions rather than from the actual observation of a single lesion over time. At present, there is

controversy over whether the fatty streaks seen in childhood are the precursors of the more fibrous, raised, and complex adult lesions, or whether some or many adult lesions arise independently of fatty streaks (which also occur in adult life) (*89*). The usual prevalence of atherosclerotic lesions in adult life is such that the aorta and carotid arteries are affected about a decade before the coronary arteries and cerebral arteries, and the latter are affected a decade in advance of the arteries of the leg. However, such relationships are not constant; individual variations are common and, indeed, specific clinical syndromes of localized atherosclerosis are recognized.

Atherosclerotic plaques distort and narrow the calibre of the affected arteries. This reduces the flow of blood through them and creates the condition called ischemia. When ischemia becomes severe, the organs and tissues deprived of blood no longer function properly and clinical disease occurs in the form of coronary heart disease, stroke, or peripheral vascular disease. The occurrence of severe ischemia may arise because of the enlargement of plaques, or it may be precipitated by the development of thrombosis (clot) on plaques, or by other complications that can affect them. The various diseases resulting from ischemia are considered subsequently in this chapter.

Conditions that predispose to the onset of disease in the future, increasing the risk of its occurrence, are spoken of as "risk factors". The concept of risk factors arose from clinical experience with cardiovascular disease, particularly coronary heart disease, rather than with atherosclerosis itself. Prospective population studies such as those considered in the Pooling Project (*107*) further developed the predictive value of selected factors such as cigarette smoking and levels of blood pressure and cholesterol.

Risk factor associations for atherosclerosis as distinct from coronary heart disease are limited in their documentation. The International Atherosclerosis Project (*85*), dealing with autopsy data, concluded that the severity of atherosclerosis is closely associated with the proportion of total calories derived from saturated fat in the diet of the population, with the serum cholesterol levels measured in the population, and with hypertension. The association with smoking was not examined. The WHO (*66*) study documented the association of a number of disease states and conditions with the extent and severity of atherosclerosis. A recent report has described the associations between several variables measured during life and the extent of atherosclerosis of the aorta and coronary arteries seen at autopsy in Japanese-Americans participating in a prospective cardiovascular risk factor study (*112*). Statistically independent associations were found by multivariate analysis between aortic atherosclerosis and age at death, cigarettes smoked per day, serum cholesterol concentration, and blood pressure level. Coronary atherosclerosis was related to relative body

weight, cigarettes smoked per day, and serum cholesterol concentration.

Models of experimental atherosclerosis in species as different as birds, rodents, dogs, swine, and nonhuman primates have been developed. The majority of these models have been induced by feeding saturated fat or cholesterol leading to fat-rich plaques that resemble the fatty streaks of childhood or the very fat-laden plaques occasionally seen in adult life. Other experimental techniques of inducing lesions are: the use of physical injury to arteries leading to acute proliferative plaque development with little or no lipid accumulation; the induction of intimal thrombi with their tissue organization yielding fibro-fatty plaques; immunologic vascular injury with lipid or cholesterol feeding; and, recently (in chickens), viral infection. Among different species of nonhuman primates, the same dietary regimen will produce characteristically a somewhat different distribution of plaques in the arterial tree. Different experimental diets will produce lesions that are characteristically more fatty or more fibrous. Spontaneous fibrous or fibro-fatty plaques occur in many species including birds, rabbits, swine, and nonhuman primates. The enhancement of spontaneous atherogenesis in chickens by polycyclic hydrocarbons has been reported (*1*). A strong genetic control exists in pigeons both for the expression of experimental atherosclerosis and for its localization predominantly either in the aorta or in the coronary arteries. Thus, there is a wide variety of experimental and spontaneous animal models available with which to study atherogenesis.

A huge body of literature deals with the pathogenesis of human and experimental atherosclerosis. Several recent reviews provide a detailed and critical consideration of current concepts (*3,21,22,84,89, 117,119,126,155,156*). The various interrelationships of different pathogenetic processes such as cellular proliferation, lipid accumulation, and thrombotic phenomena are not fully understood. Nevertheless, it is possible to synthesize available data into a frequently explored major working hypothesis of the initial stages of atherogenesis based on extensive experimental data (see particularly *117,155,156*) that support the pathogenetic concept that the arterial endothelium functions normally to separate the intima and media from the blood. The hypothesis holds that local injury results in failure of this barrier function or in loss of endothelial cells and exposure of the subendothelium to whole plasma and to blood platelets. Platelets and plasma contain growth factors capable of inducing smooth muscle cells in the intima and adjacent media to multiply. This loss of barrier function also allows macromolecules such as fibrinogen and very low density (VLDL), intermediate, low density (LDL), and high density (HDL) lipoproteins freer access to the vessel wall. More lipid is internalized by intimal smooth muscle cells and macrophages than their lysosomal digestive systems can catabolize, and they become overloaded with fat

and cholesterol. The amount of sterol externalized metabolically by such cells may exceed the local capacity of HDL to accept and transport it away. Cellular necrosis occurs and both intracellular and structural lipids spill into the extracellular compartment of the intima where they contribute to the lipid burden. The sequence in this hypothesis is endothelial injury, impaired barrier function, and subendothelial exposure to plasma and to platelets, followed by cellular metabolic overload, failed homeostasis, cellular proliferation, and necrosis. In addition, the stigmata of mild chronic inflammation occur promptly, and appearances suggestive of a migration of smooth muscle cells to the lesion are seen. Local cellular production of glycosaminoglycans, collagens, and elastin follows. Progression of the lesions can be through a continuation or cyclical repetitions of the same processes or by thrombosis. Thrombosis, necrosis, calcification, hemorrhage, and ulceration may further complicate the lesion. A large number of agents are suspected to be capable of injuring endothelium and altering its barrier function. It should be noted that the foregoing views are derived from animal experimentation but appear to be congruent with the nature of atherosclerosis in humans.

A novel theory of atherogenesis has been proposed recently that does not necessarily contradict the concepts stated above, but which designates a prior abnormality of the smooth muscle cells that proliferate to form plaques. It has been found that the cells that constitute individual fibrous atherosclerotic plaques in adults are homogenous for an isoenzyme marker. That is, each plaque must either be monoclonal or initially polyclonal with the development of a monotypic character as it has developed (*21*, *22*, *104*, *105*, *135*). If the correct interpretation is that plaques are monoclonal, it is necessary to consider whether this represents a mutation or transformation of vascular cells leading to a local proliferation analogous to benign smooth muscle cell neoplasia. In this view, environmental agents capable of inducing somatic cell mutation, including mutagens derived from tobacco, could be fundamental to the pathogenesis of atherosclerotic plaques, and might cause the primary cellular changes facilitating other conventional risk factors or agents to produce lesions in man. At the present time, data to settle the validity of these interpretations are not available.

The Effect of Smoking on Atherogenesis

Autopsy studies in which smoking behavior has been recorded are not common. Table 19 (pp. 49-51) of the 1976 reference edition of the report, *The Health Consequences of Smoking* (*138*), lists several investigations into this aspect of smoking. This table is reproduced below as Table 1.

These investigations compare, within their particular group of study cases, smokers with nonsmokers and different levels of smoking,

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Severity of aortic sclerosis			Conclusions	Comments
				Above average	Average	Below average		
Wilens and Plair, 1962, U.S.A.	989 consecutive male autopsies at New York City VA hospitals.	Routine clinical records of previous and present admissions.	NS	9.9(161)	60.2	29.8	The authors conclude that in 60 percent of cases, the degree of sclerosis at autopsy was commensurate with age of patient, regardless of smoking habits. In the remaining 40 percent there is evidence that cigarette smoking may be associated with an above-average degree of aortic sclerosis.	Smoking data unavailable for 120 cases. Each aorta specimen given an "atherosclerotic age" by comparison with a standard. If "atherosclerotic age" was found to be 10 years more than real age, the aorta was said to show above-average sclerosis. †$p<0.001$ comparing 9.9 with 25.1 and 29.8 with 13.6.
			<20	19.1(152)	63.2	17.8		
			20–30	26.4(288)	62.5	11.1		
			>30	†25.1(199)	61.3	†13.6		

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Auerbach, et al., 1965, U.S.A.	1,372 autopsies of male patients in Orange, New Jersey, VA hospital for whom smoking habit data were available and who did not have overt CHD at death.	Interview with next of kin.	Degree of coronary artery atherosclerosis (overall age-adjusted results) No atherosclerosis / Slight / Moderate / Advanced NS ..... 5.6(69) / 57.3 / 21.8 / 15.3 Current cigarette <20 ..... 2.6(139) / 30.9 / 37.3 / 29.2 20 39 ..... 0.8(299) / 19.7 / 42.1 / 37.4 >40 ..... 0.6(144) / 18.1 / 35.4 / 45.9	The authors conclude that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers and that the percentage increased with amount of cigarette smoking. This relationship persisted even when cases were matched for age and cause of death.	
Avtandilov, 1965, Russia	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	Comparative size of mean area of atherosclerotic legions in inner coat of coronary arteries. Right coronary artery: SM / NS; Left coronary artery: SM / NS 30–39 ..... †15.5(30) / 1.3(32) / †6.3 / 2.2 40–49 ..... †23.6(34) / 11.5(27) / †15.8 / 4.4 50–59 ..... †36.3(39) / 14.8(39) / †27.9 / 9.9 60–69 ..... †31.9(32) / 23.8(36) / †26.5 / 22.5 70–79 ..... 41.9(18) / 31.7(36) / 26.1 / 35.8	The author concludes that the worst changes were found in the left and right coronary arteries with less severe changes in circumflex artery and aorta.	Causes of death 96-atherosclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at $p<0.05$ level.

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Sackett, et al., 1968, U.S.A.	893 total, including 433 male and 450 female (white) patients autopsied at Roswell Park Memorial Hospital. Represents all deaths 1956–1964 exclusive of 81 male pipe and cigar smokers and 55 incomplete files.	Patient interview on admission.	The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.	The authors conclude that among males, ". . . a large increase in the severity of aortic atherosclerosis occurred in the groups using either cigarettes only or both cigarettes and alcohol as compared with the group using neither cigarettes nor alcohol . . . there was only a small and statistically insignificant difference between the group using cigarettes alone and the group using both cigarettes and alcohol. . . ." The severity of aortic atherosclerosis increased with increasing use of cigarettes, when measured both by intensity and by duration of smoking.	

TABLE 1.—Autopsy studies of atherosclerosis. (Figures in parentheses are number of individuals in that smoking category)[1] [SM = smokers NS = nonsmokers]—Continued

Author, year, country	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
Viel et al., 1968 Chile	1,150 males and 290 females who died violently in 1961-1964. Smoking information available only on 566 males.	Interview with relatives.	The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.	The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible."	
Strong et al., 1969 U.S.A.	747 males 20-64 years of age autopsied between 1963-1966 at Charity Hospital in New Orleans.	Interview with next of kin within 8 weeks of death.	Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).	The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers."	This report concerns only ages 25–64. No data on statistical significance provided.

	25-34	35-44	45-54	55-64
White				
NS	2(5)	19(14)	20(6)	30(11)
1-24 cigarettes/day	9(14)	17(10)	26(16)	39(7)
>25 cigarettes/day	12(9)	31(14)	26(25)	39(20)
Negro				
NS	4(14)	3(8)	16(11)	17(14)
1-24 cigarettes/day	3(39)	11(31)	14(30)	28(22)
>25 cigarettes/day	17(10)	14(17)	29(12)	16(11)

[1] Unless otherwise specified, disparities between the total number of individuals 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 (*1968*).

particularly cigarettes. The trend in such data is that a history of cigarette smoking is associated in a dose-related manner with the severity or extent of aortic or coronary atherosclerosis. In some studies, the differences in atherosclerosis between smokers and nonsmokers are statistically significant. In others, the trend is congruent but not statistically significant. These autopsy studies documenting smoking behavior have generally not permitted analysis for risk factors other than smoking that might affect the severity of atherosclerosis, and have not permitted multivariate analysis common in the large prospective population studies dealing with the morbidity and mortality of heart attack.

A recent report (*132*) has provided additional information by analyzing its data in two categories according to the presence or absence of diseases associated with smoking on the one hand (emphysema, lung cancer) and coronary heart disease on the other (myocardial infarction, hypertension, diabetes, stroke). Atherosclerotic involvement of both the coronary arteries and aorta was greatest in heavy smokers and least in nonsmokers in the total sample of 1,320 men, and in each of the two categories of disease noted above. This study of men aged 25 to 64 years represents the examination at autopsy of residents of the Greater New Orleans area who died in Orleans parish from any cause. Smoking history information, generally, was obtained retrospectively from a respondent with a close knowledge of the decedent (*88*). The WHO study of five towns reported on the association between smoking and atherosclerosis only from Yalta (*79*). The study has less relevance than the New Orleans study for the United States population. It reported a positive association between raised plaques in the aorta and smoking. It failed to find a clear association between coronary artery narrowing or infarction of the heart and smoking. Calcification of plaques in the aorta and coronary arteries was related to coexisting alcohol consumption.

While data from most autopsy series are inadequate for multivariate analysis, several prospective population studies now have sufficient standard risk factor data together with autopsy findings to present preliminary analyses (*131*). A prospective study of cardiovascular risk factors among 8,000 Japanese-Americans living on the island of Oahu has recently published more extensive systematic pathological findings on the vessels in 137 autopsies from the cohort in association with prior risk factor observations. Cigarettes smoked per day were positively and independently associated with the extent of atherosclerosis affecting both the aorta and coronary arteries. The aortic regression coefficient was statistically significant at the 0.05 level and the coronary coefficient at the 0.01 level (*112*).

A recent study of autopsies from a Veterans' Administration hospital (*15*) reported that advanced coronary artery atherosclerosis

was 4.4 times as high in those smoking two packs or more per day as in those who never smoked. This study also examined the coronary arteries microscopically and found that fibrous thickening of the coronary arteries and intramyocardial small arteries was more frequent in smokers. The most marked difference between smokers and nonsmokers was found in the arterioles of the myocardium. Advanced hyaline thickening of arterioles was found in 90.7 percent of those smoking two or more packs per day, in 48.4 percent of those smoking less than one pack per day, and in none of those who never smoked regularly. The study reported on a selected series of 1,056 autopsies from which coronary arterial disease deaths, diabetes, and those with hearts weighing more than 500 g were excluded. A recent report (*98*) reaffirms the occurrence of intramyocardial small-artery sclerosis in smokers. A decrease in arteriolar muscle wall thickness in the myocardium, especially in smokers, was found that was attributed to a lower blood perfusion pressure distal to the small artery lesions noted above.

Overall, there does not appear to be substantial reason to doubt that male cigarette smokers examined at autopsy manifest more coronary and aortic atherosclerosis than nonsmokers. The effect is dose-related. Hyaline thickening of arterioles in the heart apparently is strongly associated with smoking. Specific morphological features of plaques that would be characteristic of smoking have not been delineated.

Experiments in Animals

Table A23 (pp. 116-118) of the 1976 report, *The Health Consequences of Smoking* (*138*), lists seven experiments in which nicotine had inconsistent effects on both spontaneous and diet-induced atherosclerotic lesions in rabbits. In an additional paper, Schievelbein (*120*) has reported no induction of spontaneous arteriosclerotic lesions by nicotine in rabbits, although the aortic content of free fatty acids and of calcium was reported increased in this long-term experiment. Fisher, et al. (*42*) reported no increase in atherogenic effect with small doses of nicotine in animals that were also hypertensive and fed cholesterol.

These experiments have involved the injection or oral administration of nicotine rather than inhalation and generally have employed unusually large doses of nicotine. Equivalent experiments in species such as swine or nonhuman primates that might be preferable to rabbits have apparently not been performed, nor have experiments that simultaneously involve whole smoke or carbon monoxide (CO) administration. The overall impression from available data is that nicotine does not affect atherogenesis in animals. Specific experimental data, however, are unavailable to permit a conclusion about a possible effect on experimental atherogenesis of nicotine inhaled in smoke in doses experienced chronically by smokers.

A small number of experiments involving the effect of CO on atherogenesis have been reported. Initial reports found an enhancement of atherogenesis in the aorta of cholesterol-fed rabbits (*13, 14*) and in the coronary arteries, but not the aorta, of squirrel monkeys (*148*). However, subsequent experiments (*130*) on cholesterol-fed rabbits from the same laboratory, which had earlier concluded that there was a positive effect of CO on atherogenesis, have led to the conclusion that there is no direct enhancement of cholesterol accumulation in the aorta. These more recent short-term experiments controlled dietary hypercholesterolemia by pair feeding and also studied the uptake of radioactive tracer cholesterol from the blood by the aorta. No macroscopically visible atherosclerotic lesions were seen in any animals, although the aortic free cholesterol of the animals fed cholesterol was increased in comparison with the animals receiving no cholesterol. The free cholesterol content of the aortic arch was increased significantly in the animals exposed to CO, but there were no significant differences for the thoracic aorta or for the combined segments. The aortic uptake of labeled cholesterol from the blood was not affected by CO exposure in either hypercholesterolemic or normal animals. The authors suggest that their earlier result may have been due to a relative excess of hypercholesterolemia in CO-exposed animals that had not been pair fed to maintain equal levels of plasma cholesterol. Possible effects of CO diminishing VLDL secretion and chylomicron catabolism have been discussed by Topping (*136*). Other recent studies by Davies and colleagues (*32*) failed to find that exposure of cholesterol-fed rabbits to CO for 4 hours per day yielding carboxyhemoglobin (COHb) levels of 20 percent produced any differences in the aortic content of lipids including cholesterol. The morphological extent of coronary atherosclerosis was greater in the animals exposed to CO. Malinow and associates (*80*) failed to find an enhancing effect of CO in sodium chloride and cholesterol-fed cynomolgus monkeys. In experiments (*2*) with White Carneau pigeons (which develop fibro-fatty spontaneous as well as dietary atherosclerosis), no enhancement of spontaneous aortic atherogenesis was found after exposure to CO. Enhancement of coronary atherogenesis was seen in cholesterol-fed birds exposed to CO and killed after one year of exposure, but not in those sacrificed after about a year and a half. Exposure also enhanced hypercholesteremia. It has been reported that spontaneous arteriosclerotic disease in rabbits is aggravated by exposure to CO (*147*).

It has been reported that, in rabbits, hypoxia increases cholesterol atherogenesis and hyperoxia diminishes it (*72, 74*). Hyperoxia has also been reported to enhance the regression of plaques in rabbits (*139*). Hypoxia and CO have been reported to cause subendothelial edema in rabbits (*13,73*) and smoke inhalation (*46*) to lead acutely to desquamation of aortic endothelial cells and adhesion of platelets in rabbits.

Auerbach and associates have reported on the effect of the chronic inhalation of whole smoke through a tracheostomy apparatus in beagle dogs. A hyaline thickening of myocardial arterioles was found in them, the degree of change being related to the duration and amount smoked (*16*).

At the present time, animal experiments on atherogenesis and CO have provided conflicting data and must be regarded as unsatisfactory. Experiments have variously employed continuous and intermittent exposure, have estimated lesions biochemically and morphologically, and have used diverse short- or long-term dietary loads so that comparisons of results are difficult. Animal experiments remain to be done in which CO or nicotine are varied in a setting of whole smoke administered by inhalation without aversive stress and in a suitable atherogenic context.

Research Needs

While current autopsy data on humans leave no reasonable doubt that smoking promotes atherosclerosis of the aorta and coronary arteries in men, equivalent data do not exist for women or for other major arterial beds. Within practical limits of study, it would be informative for pathogenetic concepts to have better information on multiple-risk factors, including oral contraceptives in conjunction with smoking and with smoking cigarettes of different potential hazard, in autopsy studies. In particular, it would be of great interest to know the influence of smoking on the development of the common fatty streaks and occasional fibrous plaques found at autopsy in adolescents and young adults.

The mechanisms by which smoking enhances atherogenesis require elucidation. Such information might assist in the fabrication of a cigarette less hazardous in terms of atherogenesis and its consequences. Conceptual frameworks and biological systems exist within which to study the mechanisms by which smoking enhances atherogenesis. They include effects on the arterial endothelium, which may alter its permeability to macromolecules; effects on endothelial-platelet interactions which influence thrombogenesis or affect the proliferation of intimal cells; effects on the metabolism of the vessel wall; and systemic and local effects on lipoprotein or sterol metabolism. With respect to the monoclonal hypothesis, research to identify mutagens or promoting agents at the level of the vessel wall is feasible.

A necessary step in such research will be the use of animal models and biological systems that have a high level of analogy with man and that are credible both in terms of experimental atherogenesis and in their exposure to cigarette smoke.

Conclusions

Cigarette smoking has been shown to enhance the prevalence and extent of atherosclerosis of the aorta and coronary arteries in men. Experiments on the effects of nicotine or carbon monoxide on experimental atherogenesis in animals have produced conflicting results and are inconclusive. Chronic inhalation of whole smoke is associated with the development of hyaline thickening of myocardial arterioles in dogs. In man, cigarette smoking is associated with fibrotic and hyaline changes in small arteries and arterioles in the myocardium.

Myocardial Infarction

The Nature of Myocardial Infarction

Heart attack as generally understood can comprise nonfatal or fatal myocardial infarction, cardiac arrest or asystole, and cardiac standstill or ventricular fibrillation. Asystole and fibrillation result in sudden cardiac death. These conditions are generally the result of cardiac ischemia which, in turn, is generally attributable to coronary atherosclerosis, although other conditions may uncommonly precipitate heart attack.

Myocardial infarction is that condition in which a volume of heart muscle fibers in a discrete part of the heart dies because of inadequate circulation. It is generally larger than 5mm in diameter and may be several centimeters in major diameter. It may vary from a small subendocardial portion of the heart to the full thickness of the myocardial wall. It may, particularly when subendocardial in location, impinge on the conducting system of the heart and be conducive to disturbances in conduction. The infarction may affect primarily the pumping capacity of the muscle and lead to acute or chronic circulatory failure. The most common location of infarction involves the left ventricle, but involvement of the right ventricle and atria is common. If the myocardial infarction does not prove to be fatal, it may be subject to local extension during the acute episode of illness. Healing is by scar formation. The patient is at high risk of a second attack.

The association between atherosclerosis of the coronary arteries and myocardial infarction is close. Most cases examined at autopsy show an involvement of about 70 percent or more of the surface of the major vessels, and more than 50 percent stenosis of the lumen with or without recent thrombosis. However, a small minority of cases show less extensive lesions and narrowing, and it has been speculated that these infarctions may have arisen because of vascular spasm, or because of transient vascular occlusion by thrombi that have dissolved after obstructing the coronary circulation.

Ischemia of a local mass of heart muscle initiates a complex chain of biochemical, functional, and structural events at the level of the heart muscle cell that continues to be a subject for intensive research. A