

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results																																															
				Distribution by percentage of degree of atherosclerosis by smoking habits standardized for age (macroscopic study)																																															
				<table border="1"> <thead> <tr> <th rowspan="2">Degree of atherosclerosis</th> <th colspan="5">Current cigarette smokers</th> <th rowspan="2">Ex-cigarette smoker</th> </tr> <tr> <th>Never smoked regularly</th> <th>< pack per day</th> <th>1-2 packs per day</th> <th>2+ packs per day</th> <th>Cigar/pipe</th> </tr> </thead> <tbody> <tr> <td>None or minimal</td> <td>59.8</td> <td>45.2</td> <td>36.6</td> <td>32.6</td> <td>36.3</td> <td>50.9</td> </tr> <tr> <td>Slight</td> <td>24.7</td> <td>26.9</td> <td>27.9</td> <td>27.5</td> <td>28.4</td> <td>25.5</td> </tr> <tr> <td>Moderate</td> <td>10.2</td> <td>16.2</td> <td>16.0</td> <td>16.5</td> <td>21.0</td> <td>12.6</td> </tr> <tr> <td>Advanced</td> <td>5.3</td> <td>11.7</td> <td>19.5</td> <td>23.4</td> <td>14.3</td> <td>11.0</td> </tr> <tr> <td>Total</td> <td>100.0</td> <td>100.0</td> <td>100.0</td> <td>100.0</td> <td>100.0</td> <td>100.0</td> </tr> </tbody> </table>	Degree of atherosclerosis	Current cigarette smokers					Ex-cigarette smoker	Never smoked regularly	< pack per day	1-2 packs per day	2+ packs per day	Cigar/pipe	None or minimal	59.8	45.2	36.6	32.6	36.3	50.9	Slight	24.7	26.9	27.9	27.5	28.4	25.5	Moderate	10.2	16.2	16.0	16.5	21.0	12.6	Advanced	5.3	11.7	19.5	23.4	14.3	11.0	Total	100.0	100.0	100.0	100.0	100.0	100.0
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Lifšic (37)	894 autopsies of males 20-79 at death in Yalta	Interview with relatives	Visual grading	Ratio of the extent of atherosclerotic lesions in the average coronary artery between nonsmokers and smokers																																															
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TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results			
Schettler et al. (63)	Autopsies of 89 males aged 60-94 at death in Tokyo	Interview with relatives	Visual grading	Stenosis			
				Smoking	No	Yes	Total
				No	6	8	14
				Yes, daily	8	67	75
Total	14	75	89				
Rhoads et al. (56)	109 autopsies of Japanese American males born 1900-1919 who participated in Honolulu heart study	Interview with subject	AHA panel	Mean coronary atherosclerosis grade versus selected attributes			
				Regression coefficients			
				Examination variables	Simple	Multiple ¹	
				Relative weight (%)	0.031 ³	0.025 ²	
				Cigarettes/day	0.022 ²	0.024 ³	
				Cholesterol(mg/dl)	0.011 ³	0.009 ³	
				Triglycerides(mg/dl)	0.002 ²	NS ⁴	
				Glucose(mg/dl)	0.004 ²	NS ⁴	
				Hematocrit (%)	0.069 ²	NS ⁴	
				¹ Multiple regression was done by a step-wise elimination procedure beginning with the set of variables shown; coefficients are for the final step. Multiple correlation (final step)=0.46 (N=108). ² Significant at 0.05 level. ³ Significant at 0.01 level. ⁴ NS, variable included in first step; deleted as not significant at 0.05 level.			

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results	O-E																	
					O-E			FaF			ATL			N								
					0	1-24	25+	0	1-24	25+	0	1-24	25+	0	1-24	25+						
Tracy et al. (77)	Autopsies of 1,320 white and black males, age 25-64 at death	Interview with next of kin	Visual grading	Means of observed minus expected raised-among-lesions(O-E), fatty streaks among flat surfaces (FaF), all types lesion (ATL), and number of cases (N) by age, race, and cause of death according to smoking category. ¹ Coronary arteries combined.																		
					Age (yr)																	
					White basal																	
					25-34	5.9	5.1	18.3	4.4	9.3	5.9	7.3	15.7	13.4	12	25	14					
					35-44	-2.2	13.4	11.8	13.9	7.3	16.9	24.9	21.1	38.1	20	22	25					
					45-54	4.5	0.2	11.7	16.4	18.7	14.5	30.6	37.0	36.9	10	28	41					
					55-64	2.8	3.4	5.8	17.1	17.3	19.5	40.5	49.0	49.8	21	19	32					
					White CHD																	
					25-34	X	X	X	X	X	X	X	X	X	X	X	X	X	0	0	1	
					35-44	17.9	8.5	16.0	16.9	29.1	20.4	37.3	69.6	60.9	6	9	15					
					45-54	0.8	7.5	6.3	23.2	23.9	25.7	68.8	64.9	70.0	5	24	33					
					55-64	3.9	5.4	30.0	24.5	15.7	66.7	70.7	64.7	9	21	32						
Black basal																						
25-34	-3.9	-2.6	3.6	8.4	9.0	12.7	11.4	11.3	19.6	24	76	18										
35-44	-7.4	-8.2	-9.4	11.2	17.3	19.6	13.8	25.5	30.6	15	70	31										
45-54	-14.9	-15.5	-3.7	19.4	20.6	21.7	28.0	32.0	37.5	19	51	26										
55-64	-19.6	-2.8	-1.1	28.1	19.9	21.9	41.9	39.5	33.8	27	41	15										
Black CHD																						
25-34	X	-9.7	X	X	17.3	X	X	27.8	X	0	5	0										

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results												
				35-44	X	4.4	-0.4	X	32.2	32.1	X	60.3	62.1	2	8	12
				45-54	X	5.5	0.4	X	25.7	31.4	X	65.7	70.4	2	25	12
				55-64	-0.1	-4.7	7.2	31.4	31.1	20.8	80.3	57.4	62.4	11	15	9
¹ ATL as percent surface fatty streaks (F) plus raised lesions (R); FaF=F ÷ (100 - R);O-E in percentage units explained in the text; X indicates subgroups having fewer than five members.																
Holme et al. (29)	129 autopsies from 16,2000 males aged 40-49 in Oslo prospective CHD study	Interview with subject	Visual grading	Correlation coefficient between number of cigarettes and raised lesions in the coronary arteries = .039, not significant.												
Sternby (77)	60 autopsies of 703 males in CHD study in Malmo, Sweden	Interview with subject	Visual grading	Smoking and stenosis or atherosclerosis in the left anterior descending coronary artery												
				Smoking category		Number		LAD raised lesions			Coronary artery stenosis					
				Non		3		68			33					
				Ex		8		52			38					
				Light		18		45			39					
				Heavy		17		54			59					

TABLE 1.—Continued.

Study	Population	Data collection method	Measure of atherosclerosis	Results			
				Correlation coefficients			
				Total (139)	Rural (36)	Urban (103)	
Sorlie et al. (70)	139 autopsies of 9,824 Puerto Rican males aged 35-79 in a prospective study	Interview with subject	Visual grading	Association of atherosclerosis in coronary arteries with antemortem characteristics: simple correlation coefficients (Puerto Rico heart health program)			
				Characteristics measured at exam 1			
				Systolic blood pressure	0.22	0.07	0.30
				Diastolic blood pressure	0.26	0.09	0.30
				Serum cholesterol	0.42	0.59	0.38
				Age, exam 1	0.01	0.32	-0.08
				Relative weight	0.21	-0.15	0.25
				Physical activity	-0.18	0.06	-0.22
				Blood glucose	0.20	-0.04	0.21
				Hematocrit	0.14	0.38	0.12
				Education level	0.14	-0.40	0.24
				Income	0.16	-0.17	0.18
				Cigarettes smoked	-0.16	-0.05	-0.22
				Calories (24-hour recall)	-0.14	-0.43	-0.07
				Starch (24-hour recall)	-0.17	-0.29	-0.09
				Alcohol (24-hour recall)	-0.10	-0.10	-0.13
				Total fats (24-hour recall)	-0.04	-0.53	0.03
				Triglycerides (fasting)	0.23	0.49	0.19
				Ventricular rate	0.13	0.20	0.08
				Vital capacity	-0.19	-0.13	-0.16

lesions were not identical, the findings from both of these large studies of autopsied men in the United States were remarkably similar. Both studies reported more extensive coronary atherosclerosis among the cigarette smokers than among the nonsmokers, and for the major comparisons, with only rare exceptions, there was an orderly progression of least extensive lesions in nonsmokers, intermediate extent of lesions in light or moderate smokers, and most extensive lesions in heavy smokers.

In the New Orleans study (74), lesions were measured not only by visual evaluation, but also by optical electronic scanning of radiographic images of the flattened arteries. The measurements of lesions from radiographs—relative mean coronary wall thickness and percentage of the coronary artery intima involved with calcification—were consistently greater for the heavy smokers than for the nonsmokers. A variety of statistical analyses on smoking measures and atherosclerotic lesions were performed to determine the significance of the various differences and trends. These analyses confirmed that the major differences between the heavy smokers and the nonsmokers in extent of raised atherosclerotic lesions (the sum of fibrous plaques, complicated lesions, and calcified lesions) were significant. A one-way multivariate analysis of nine atherosclerotic variables clearly indicated that there were statistically significant differences among the three categories of smokers (heavy, light to moderate, and nonsmokers) for mean coronary wall thickness, raised lesions in the coronary arteries, percentage of cases positive for fibrous plaques, percentage of cases positive for complicated lesions, and percentage of cases positive for calcified lesions, with lower values in nonsmokers and higher values in the heavy smokers.

Patel et al. (53) evaluated this same data on smoking and atherosclerotic lesions to examine further the interrelationships with measures of obesity. The confounding effects of diseases such as hypertension and diabetes mellitus were controlled by excluding such cases from the analysis. The confounding effects of age and measures of smoking habits on the association between atherosclerosis and obesity were controlled by multivariate regression analysis. This analysis disclosed an inverse relationship between smoking habits and obesity. There was also a weak positive association—when age and smoking were controlled for—between measures of obesity and mean coronary wall thickness and raised lesions in the coronary arteries among whites, but not among blacks. In the black men, again with age and smoking controlled in the analysis, a weak association between fatty streaks in the coronary arteries and obesity was found. This analysis confirmed the previously reported relationships between smoking habits and atherosclerosis, as measured by mean coronary wall thickness, coronary calcifications, and raised lesions in the coronary arteries.

Since their first report in 1965, Auerbach and his associates have investigated the relationship of cigarette smoking to microscopic findings in the coronary arteries (4). This study indicated that lesions were most extensive in cigarette smokers and confirmed earlier studies by Auerbach et al. (6) and Strong and Richards (74). The microscopic portion of the Auerbach et al. study (4) showed that fibrous thickening, atheroma, and calcifications of the coronary arteries all increased with increasing number of cigarettes smoked per day. They also found that the fibrous thickening of arteries increased in relation to the number of cigarettes smoked per day as the size of the artery decreased; i.e., it was least in the coronary arteries and greatest in the myocardial arteries.

Lifšic (37) reported on the relationship of cigarette smoking to coronary atherosclerotic lesions based on the Yalta sample from the World Health Organization (87) autopsy study of five cities in Europe. Information on cigarette smoking was obtained by means of interviews with the subjects' near relatives. The prevalence and extent of atherosclerotic lesions were evaluated in autopsies of 865 men, aged 20 to 79 years, out of the 1,220 deaths occurring in Yalta residents of this age and sex group during the period of study. There was a positive association of smoking with the extent of coronary calcification; however, the author explained this association as being related to coexisting alcohol consumption and stated that smoking alone tended to be negatively associated with coronary calcification. The following paragraph from Lifšic's discussion provides additional information from this report.

There was little significant difference between smokers and nonsmokers in the prevalence and extent of atherosclerotic lesions in the coronary arteries. Thus, of the total of 210 comparisons of different indices of the prevalence and extent of atherosclerotic lesions between subgroups X and W, significant differences positively correlated with smoking were found in only 20. The tendency toward a positive correlation of coronary atherosclerosis with smoking was found mainly in subjects up to the age of 50, but after 60 the opposite tendency prevailed. These age peculiarities agreed with data from other studies showing that differences in the degree of atherosclerosis between smokers and nonsmokers . . . are more distinct below age 60.

The author also mentioned a positive association between smoking and coronary calcification in "strenuous workers." A note added in proof to Lifšic's article states, "Additional study of this material by individually matched case-control analyses revealed a marked trend toward a positive association between smoking and atherosclerotic raised lesions in the coronary arteries" (82). Thus, while the author's abstract does not indicate an important relationship of smoking and coronary atherosclerosis, there are findings in the study that do

indicate significant relationships between smoking and coronary atherosclerosis, especially in the younger subjects.

A subsequent study by Vikhert et al. (83) on material from five cities in the U.S.S.R. evaluated the effect of nutritional status and tobacco smoking on atherosclerotic changes in the coronary arteries as measured by a visual planimetric method. This material was also utilized for a WHO-sponsored epidemiological study of atherosclerosis (87). The vessels examined were from 430 men 40 to 69 years of age. The major analyses concerning tobacco smoking were made from 313 male heavy smokers and 82 nonsmokers. The investigators studied both manual workers and white-collar workers and found that tobacco smoking in combination with overnourishment had a much more positive effect on the development of coronary atherosclerosis in white-collar workers than in the manual workers.

Prospective epidemiologic studies of cardiovascular disease with autopsy followup provide additional information concerning the relationship of smoking to atherosclerotic lesions in the artery wall. The epidemiological studies in Oslo, Puerto Rico, and Honolulu are characterized by careful documentation of selected major risk factors, including cigarette smoking habits during life, and by standardized evaluation of atherosclerotic lesions at autopsy (29, 56, 70). Each of these three studies reported findings on the relationship of CHD risk factors to atherosclerotic lesions in more than 100 autopsies of deceased men who had been part of larger cohorts that had been examined and followed during life. In addition, a smaller study from Malmö, Sweden, had some of the same features as these larger studies (71). The Oslo, Malmö, and Puerto Rico studies used identical methods for grading the extent of atherosclerotic lesions. These prospective epidemiologic studies with autopsy followup are in general agreement concerning the relationship of serum cholesterol levels and blood pressure to the extent of atherosclerotic lesions in the coronary vasculature. The findings concerning the relationship of cigarette smoking to the extent of coronary atherosclerosis are not uniform. The Honolulu study (56) showed a significant relationship between smoking habits and extent of coronary atherosclerosis. The Oslo study (29) did not show a significant relationship between cigarette smoking and coronary atherosclerosis. The Puerto Rico study (70) also did not show a significant relationship between smoking and the extent of coronary atherosclerosis. A somewhat similar study from Japan by Hatano and Matsuzaki (26) indicated a significant relationship between cigarette smoking and coronary artery stenosis. Thus, there is some inconsistency concerning the association between cigarette smoking habits and coronary atherosclerosis in the prospective epidemiologic studies with autopsy followup.

In considering this entire body of evidence, however, the preponderance of evidence suggests that cigarette smoking has an effect on the development of atherosclerotic lesions in the coronary artery wall in the U.S. population, and that its effect is not limited to those events immediately surrounding the occlusive episode.

Small Arteries in the Myocardium

Table 2 reviews those studies that have examined the relationship between cigarette smoking and lesions of the arterioles within the myocardium. Auerbach et al. (7) found a relationship between smoking habits and thickening of the walls of the arterioles and small arteries of the myocardium. Auerbach et al. (4) also performed a microscopic study of coronary artery lesions in autopsied men in relation to previous smoking histories. In the microscopic portion of this study, fibrous thickening, atheroma, and calcification increased with an increased number of cigarettes smoked per day. Moderate to advanced hyaline thickening of the arterioles in the myocardium was strongly related to smoking. It was found in 98.6 percent of the autopsied subjects with a two pack per day smoking habit and not found in the group of subjects who never smoked regularly. Naeye and Truong (51) reported essentially similar alterations in the intramyocardial arteries, which developed more rapidly in cigarette smokers than in nonsmokers.

The Aorta

Those studies that provide autopsy and other evidence for the relationship between cigarette smoking and atherosclerosis of the aorta are summarized in Table 3.

Wilens and Plair (85) found significantly more severe sclerosis of the aorta in cigarette smokers than in nonsmokers. Sackett and Winkelstein (61) reported that elderly cigarette smokers had significantly higher rates of aortic calcification, detected on chest X-ray, than did nonsmokers. Sackett et al. (60), in an autopsy study, found a significant relationship between the use of cigarettes and the severity of aortic atherosclerosis. An interim report by Strong et al. (75) concluded that atherosclerotic involvement of aortas was greatest in heavy smokers and least in nonsmokers among autopsied men in New Orleans.

Most of these studies, reviewed in the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (80), indicate that differences between heavy cigarette smokers and nonsmokers are particularly great in young individuals, and that heavy smokers have increased surface involvement with fibrous plaques or more advanced atherosclerotic lesions.

Since the 1971 review, a study of smoking and atherosclerosis in deceased men in New Orleans has been completed. Several reports

TABLE 2.—Autopsy studies of atherosclerosis involving small arteries in the myocardium

Study	Population	Smoking data source	Measure of atherosclerosis	Results								
				Grade of thickness of walls of arterioles ¹								
				Number of men			Percentage of men					
				Grade 0	Grade 1	Grade 2, 3	Total	Grade 0	Grade 1	Grade 2, 3		
Age	Smoking	Total										
< 45	None	22	2	19	1	100.0	9.1	86.4	4.5			
	Cigar-pipe	4	—	1	3	100.0	—	25.0 ²	75.0 ²			
	Ctte ³ 1-19	50	1	31	18	100.0	2.0	62.0	36.0			
	Ctte 20-39	85	4	35	46	100.0	4.7	41.2	54.1			
	Ctte 40+	29	—	10	19	100.0	—	34.5	65.5			
45-59	None	15	1	12	2	100.0	6.7	80.0	13.3			
	Cigar-pipe	13	—	8	5	100.0	—	61.5	38.5			
	Ctte 1-19	33	—	17	16	100.0	—	51.5	48.5			
	Ctte 20-39	99	—	35	64	100.0	—	35.4	64.6			
	Ctte 40+	50	—	11	39	100.0	—	22.0	78.0			
60-69	None	56	4	36	16	100.0	7.1	64.3	28.6			
	Cigar-pipe	35	—	22	13	100.0	—	62.9	37.1			
	Ctte 1-19	92	—	44	48	100.0	—	47.8	52.2			
	Ctte 20-39	193	—	58	135	100.0	—	30.1	69.9			
	Ctte 40+	87	—	21	66	100.0	—	24.1	75.9			
70+	None	32	2	18	12	100.0	6.3	56.2	37.5			
	Cigar-pipe	40	—	19	21	100.0	—	47.5	52.5			
	Ctte 1-19	30	—	12	18	100.0	—	40.0	60.0			
	Ctte 20-39	46	—	12	34	100.0	—	26.1	73.9			
	Ctte 40+	9	—	3	6	100.0	—	33.3 ²	66.7 ²			

¹In the right ventricular wall of 1,020 men by age and smoking habits.

²Percentages based on less than 10 cases.

³Ctte indicates cigarettes.

TABLE 3.—Autopsy studies of atherosclerosis involving the aorta

Study	Population	Smoking data source	Measure of atherosclerosis	Results							
Wilens and Plair (85)	989 consecutive necropses at NY VA hospital	Patient chart	Visual grading	Percent of subjects by smoking status and atherosclerosis							
				Severity of sclerosis	Non-smoker	Heavy	Moderate	Light	Pipe/cigar	Other	
				Number	161	199	288	152	70	119	
				Percent above average	9.9	25.1	26.4	19.1	10	10.9	
				Percent average	60.2	61.3	62.5	63.2	60	63.0	
	Percent below average	29.8	13.6	11.1	17.8	30	26.1				
Strong and Richards (74)	1,320 autopsies of males aged 25-64 at death	Interview with relatives	Visual grading	Mean percent of intimal surface of abdominal aorta involved with raised lesions							
				Average number of cigarettes smoked per day							
				Age and race	0		1-24		25+		
				White males							
				25-34	1		7		7		
				35-44	14		33		44		
				45-54	33		52		56		
				55-64	46		63		71		
				Black males							
				25-34	4		7		9		
35-44	6		20		28						
45-54	14		37		45						
55-64	26		51		56						

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results			
				Nonsmokers		Smokers	
The relationship between smoking and calcification of the thoracic aorta							
Age group	Number	Percent with calcification	Number	Percent with calcification			
Sackett and Winkelstein (61)	590 white male admissions to Roswell Park Memorial Institute in 1955	Patient questionnaire	Chest X-ray for calcification in thoracic aorta				
50-59	61	13	131	11	0.4	192	
60-69	90	18	124	26	0.2	214	
70 and over	116	37	63	54	0.02	184	
Totals	267	25	323	26	—	590	
Age-adjusted percent	—	22	—	30	—	—	
¹ Chi-square of independence, two-tailed.							
The relationship between amount smoked and calcification of the thoracic aorta							
Age group	Nonsmokers		Light smokers		Heavy smokers		Totals
	Number	Percent with calcification	Number	Percent with calcification	Number	Percent with calcification	
50-59	61	13	104	9	27	22	192
60-69	90	18	107	24	17	35	214
70 and over	116	37	63	56	5	40	184
Totals	267	26	274	29	49	27	590
Age-adjusted percent	—	22	—	29	—	32	—

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results			
Sackett et al. (60)	1,019 consecutive autopsies of white patients	Standardized interview with patient on admission	Visual grading on a numerical scale	<u>Mean age-adjusted atherosclerosis ridits versus graded use of cigarettes and alcohol</u>			
				<u>Alcohol</u>		<u>Cigarettes</u>	
				Oz/day	None	1/2 pack	1/2 pack +
				None	.351	.468	.498
				0.5-1.5	.424	.570	.568
1.6+	.428	.528	.589				
Strong et al. (75)	Autopsies of 741 males 20-64 years at death	Interview with relatives	Visual grading and optical scanning	<u>Mean percentage of intimal surface of aorta involved with raised lesions by age, race, and average rate of cigarette smoking in the last 10 years of life</u>			
				<u>Cigarettes per day</u>			
				Age and race	0	1-24	25+
				<u>White males</u>			
				35-44	16	35	49
				45-54	29	52	54
				55-64	48	66	70
				<u>Black males</u>			
				35-44	3	22	24
				45-54	12	38	50
55-64	21	50	49				

TABLE 3 --Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results				
Lifšic (37)	865 autopsies of males aged 20-79 at death in Yalta	Relatives and records	Visual grading	<u>Prevalence of atherosclerotic lesions in the abdominal aorta in different subgroups (percentage)</u>				
				<u>Smoking group</u>	<u>Fatty streak</u>	<u>Fibrous plaque</u>	<u>Complicated lesion</u>	<u>Calcified lesion</u>
				Never	96.5	96.0	43.0	25.0
				Light	92.8	96.5	53.4	42.3
				Heavy	90.7	97.5	60.9	57.3
				<u>Extent of atherosclerotic lesions (percentage of surface) in the abdominal aorta</u>				
				<u>Smoking group</u>	<u>Fatty streak</u>	<u>Fibrous plaque</u>	<u>Complicated lesion</u>	<u>Calcified lesion</u>
				Never	7.0	28.1	2.0	1.2
				Light	6.1	31.8	5.1	2.2
				Heavy	5.8	29.5	4.1	3.4

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results
Rhoads et al. (56)	124 Japanese American males autopsied as part of the Honolulu heart study	Interview with subject	Visual by AHA panel method	<p>Correlation coefficients among selected autopsy and examination variables¹</p> <hr/> <p style="text-align: right;">Aorta (N = 124), atherosclerosis grade</p> <hr/> <p>Age at death 0.30³</p> <p>Examination variables</p> <p>Height (cm) -0.12</p> <p>Relative wt. (%) -0.10</p> <p>Cigarettes/day 0.14</p> <p>Cholesterol (mg/dl) 0.24³</p> <p>Triglycerides (mg/dl) 0.14</p> <p>Uric acid (mg/dl) -0.05²</p> <p>Glucose (mg/dl) 0.15</p> <p>Hematocrit (%) -0.03</p> <p>Vital capacity (liters) -0.23³</p> <p>Alcohol (gm) -0.08²</p> <p>Systolic pressure (mm Hg) 0.29²</p> <p>Diastolic pressure (mm Hg) 0.05</p> <p>Mean coronary grade 0.50² (96)⁴</p> <p>Aorta grade</p> <hr/> <p>¹ N = number of specimens.</p> <p>² Significant at 0.05 level.</p> <p>³ Significant at 0.01 level.</p> <p>⁴ When a correlation coefficient is based on less than 95 percent of the specimens available (because of missing data), the number of observations is indicated in parentheses. There were 96 autopsies with both aorta and coronary vessel grades available, 13 with coronary only, and 28 with aorta only.</p>

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results																																																																													
Auerbach and Garfinkel (5)	1,412 males autopsied at VA hospital	Family	Visual grading	<p>Percentage of selected findings by smoking habits</p> <hr/> <p>Percentage of cases¹</p> <hr/> <p>"Current" cigarette smokers</p> <hr/> <table border="1"> <thead> <tr> <th>Findings</th> <th>Never smoked regularly</th> <th>1 pack per day</th> <th>1-2 packs per day</th> <th>2+ packs per day</th> <th>Cigar or pipe</th> <th>Ex-cigarette smoker</th> </tr> </thead> <tbody> <tr> <td colspan="7">Thoracic aorta</td> </tr> <tr> <td>Many or diffuse distribution of plaques</td> <td>16</td> <td>26</td> <td>41</td> <td>37</td> <td>27</td> <td>29</td> </tr> <tr> <td>Moderate or advanced ulceration</td> <td>4</td> <td>6</td> <td>14</td> <td>12</td> <td>10</td> <td>8</td> </tr> <tr> <td>Moderate or advanced calcification</td> <td>56</td> <td>63</td> <td>74</td> <td>74</td> <td>53</td> <td>67</td> </tr> <tr> <td>Thrombus present</td> <td>4</td> <td>7</td> <td>14</td> <td>11</td> <td>11</td> <td>9</td> </tr> <tr> <td colspan="7">Abdominal aorta</td> </tr> <tr> <td>Many or diffuse distribution of plaques</td> <td>28</td> <td>54</td> <td>68</td> <td>79</td> <td>46</td> <td>53</td> </tr> <tr> <td>Moderate or advanced ulceration</td> <td>7</td> <td>19</td> <td>27</td> <td>27</td> <td>13</td> <td>22</td> </tr> <tr> <td>Moderate or advanced calcification</td> <td>63</td> <td>76</td> <td>84</td> <td>88</td> <td>74</td> <td>81</td> </tr> <tr> <td>Thrombus present</td> <td>7</td> <td>23</td> <td>23</td> <td>31</td> <td>14</td> <td>23</td> </tr> </tbody> </table>	Findings	Never smoked regularly	1 pack per day	1-2 packs per day	2+ packs per day	Cigar or pipe	Ex-cigarette smoker	Thoracic aorta							Many or diffuse distribution of plaques	16	26	41	37	27	29	Moderate or advanced ulceration	4	6	14	12	10	8	Moderate or advanced calcification	56	63	74	74	53	67	Thrombus present	4	7	14	11	11	9	Abdominal aorta							Many or diffuse distribution of plaques	28	54	68	79	46	53	Moderate or advanced ulceration	7	19	27	27	13	22	Moderate or advanced calcification	63	76	84	88	74	81	Thrombus present	7	23	23	31	14	23
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¹ Percentages are adjusted to distribution by age group of all men in study.

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results						
Sternby (71)	60 autopsies from 703 males enrolled in a CHD study in Malmo, Sweden	Interview with subject	Visual grading	Smoking and atherosclerosis of the aorta						
				Smoking category	Number	Raised lesions in the abdominal aorta				
				Non	3	26				
				Ex	8	43				
				Light	18	53				
				Heavy	7	83				
				Smoking and atherosclerosis in peripheral arteries						
				Smoking category	N	iliac artery Raised lesions	Femoral artery Raised lesions	Stenosis (%)	Lower leg artery Raised lesions	Stenosis (%)
				Non	3	17	20	0	2	0
				Ex	8	18	43	33	18	22
Light	18	29	23	6	3	11				
Heavy	17	50	50	35	12	47				

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results								
				O-E			FaF			ATL		
				0	1-24	25+	0	1-24	25+	0	1-24	25+
Tracy et al. (77)	Autopsies of 1,380 white and black males aged 25-64 at death	Interview with relatives	Visual exam	Means of observed minus expected raised-among-lesions (O-E), fatty streaks among flat surfaces (FaF), all types of lesions (ATL), and number of cases (N) by age, race, and cause of death according to smoking category ¹ , abdominal aorta								
Age				0	1-24	25+	0	1-24	25+	0	1-24	25+
White basal												
25-34				-3.7	3.9	0.6	25.3	32.1	36.6	26.4	36.6	34.7
35-44				-7.3	5.0	12.7	22.8	30.8	35.5	27.9	48.1	64.7
45-54				7.7	6.1	3.6	21.3	28.9	31.4	47.3	57.3	65.8
55-64				-0.6	3.0	6.7	33.7	33.1	35.5	56.5	68.6	76.2
White CHD												
25-34				X	X	X	X	X	X	X	X	X
35-44				-18.7	15.3	6.8	43.2	28.2	39.2	55.3	67.9	68.0
45-54				8.0	3.6	7.3	25.7	40.8	33.1	50.0	81.4	73.4
55-64				4.5	5.4	2.2	44.3	37.7	40.1	77.7	82.8	83.7
Black basal												
25-34				-5.3	-3.5	-3.8	28.6	32.8	36.8	30.7	34.9	38.6
35-44				-16.9	-3.1	-3.9	26.5	31.8	33.0	27.8	43.9	45.6
45-54				-15.7	-7.3	-5.4	25.0	32.7	37.4	33.8	47.2	60.0
55-64				-9.5	-0.3	-2.8	29.7	31.6	32.1	43.9	61.6	55.5
Black CHD												
24-34				X	6.3	X	X	39.7	X	X	44.6	X
35-44				X	-2.7	9.3	X	28.0	29.9	X	55.1	61.8
45-54				X	4.6	4.8	X	34.2	38.6	X	72.4	73.0
55-64				-14.4	-2.8	2.5	41.9	35.8	40.7	62.5	66.2	81.4

¹ ATL as % fatty streaks (F) plus raised lesions (R); FaF = $F \div (100 - R)$; O-E in percentage units explained in

TABLE 3.—Continued.

Study	Population	Smoking data source	Measure of atherosclerosis	Results			
the text; X indicates subgroups having fewer than five members.							
Sorlie et al. (70)	139 autopsies of 9,824 Puerto Rican males aged 35-79	Interview with subject	Visual evaluation	Association of atherosclerosis in aorta with antemortem characteristics, simple correlation coefficients (Puerto Rican heart health program)			
				Correlation coefficients			
				Characteristics measured at exam 1	Total (120)	Rural (31)	Urban (89)
				Systolic blood pressure	0.25	0.27	0.24
				Diastolic blood pressure	0.19	0.29	0.16
				Serum cholesterol	0.29	0.38	0.28
				Age, exam 1	0.31	0.39	0.29
				Relative weight	-0.08	-0.22	-0.06
				Physical activity	-0.18	-0.21	-0.14
				Blood glucose	0.14	0.05	0.17
				Hematocrit	0.23	0.33	0.21
				Education	-0.08	-0.23	-0.03
				Income	0.01	-0.01	-0.01
				Cigarettes smoked	0.32	0.37	0.31
				Calories (24-hour recall)	-0.24	-0.55	-0.12
Starch (24-hour recall)	-0.19	-0.45	-0.07				
Alcohol (24-hour recall)	-0.18	-0.39	-0.18				
Total fats (24-hour recall)	-0.19	-0.49	-0.11				
Triglycerides (fasting)	0.11	0.53	0.04				
Ventricular rate	0.07	0.11	0.05				
Vital capacity	-0.29	-0.28	-0.29				

based on the findings in that study, as well as various interpretations of those findings, have been published. Strong and Richards (74) reported the basic findings on the association of cigarette smoking and aortic atherosclerosis in 1,320 autopsied men in New Orleans, 25 to 64 years of age. Aortic lesions were evaluated visually in coded specimens and objectively by analysis of radiographs. Interviewers obtained estimates of cigarette smoking habits of the deceased men from surviving relatives. Data were compared for black men and white men, and also were analyzed in groups according to the presence or absence of diseases thought to be associated with smoking or with coronary heart disease (emphysema, lung cancer, myocardial infarction, hypertension, diabetes mellitus, stroke, etc.). Atherosclerotic involvement of the aorta was greatest in heavy smokers and least in nonsmokers for both races in the total sample, as well as in the basal group (those cases least influenced by the bias of autopsy selection). The lesions were measured not only by visual evaluation, but also by optical electronic scanning of radiographic images of flattened arteries. Atherosclerotic lesions in the abdominal aorta were more extensive in the heavy smokers than in the nonsmokers, and there was an orderly trend of increased lesions with increased smoking. In general, the magnitude of difference in extent of lesions between nonsmokers and heavy smokers was greater in the abdominal aorta than in the coronary arteries. A variety of statistical analyses of smoking measures and atherosclerotic lesions was applied to determine the significance of the various differences and trends. All of the analyses confirmed that the differences between the heavy smokers and the nonsmokers in extent of raised atherosclerotic lesions were significant. A one-way multivariate analysis of nine atherosclerotic variables indicated that there were statistically significant differences among the three categories of smokers (heavy, light to moderate, and nonsmokers) for lesions in the abdominal aorta.

Following the initial report of Strong and Richards (74), there were three additional publications from this study. Two of these were directed toward interpretation of findings in regard to the effect of cigarette smoking on fatty streaks (the earliest grossly visible lesions of atherosclerosis) and raised atherosclerotic lesions (the more advanced stage of the atherosclerotic process). The other study was directed toward the interrelations of obesity, smoking, and atherosclerotic lesions in these same cases.

The original report by Strong and Richards (74) indicated that raised lesions, the more advanced lesions, were greater in heavy smokers than in nonsmokers. They also reported statistically significant differences for fatty streaks in the abdominal aorta and for fatty streaks in the coronary arteries, with the highest values in the nonsmokers and lowest values in the heavy smokers. The well-

recognized problem of evaluating fatty streaks when more advanced lesions of atherosclerosis are present made it difficult to interpret the findings on fatty streaks. Patel et al. (54) approached this problem by using a simple two-parameter model of fatty streaks arising from a normal intimal surface at a constant rate and with subsequent conversion to raised lesions at a constant rate. They concluded that in the abdominal aorta, smoking enhances the formation of fatty streaks as well as the subsequent conversions to more advanced lesions, and in the coronary arteries, smoking seems only to enhance the conversion of fatty streaks to fibrous plaques. Tracy et al. (77) evaluated the same data from the New Orleans study on smoking and atherosclerotic lesions. They approached the problem using a different model: $N \rightleftharpoons F \rightarrow R$, where N denotes normal intima, F denotes fatty streaks, and R denotes raised lesions. In this model, class A causes are viewed as promoting the process from beginning to end, while class B agents act at the first or the second step, but not at both. Their analysis and interpretation suggest that cigarette smoking has a large class B effect. They concluded that the target tissue of smoking is the fatty streak, and the slowly progressing or regressing fatty streak (formed alike in smokers and nonsmokers) is caused to progress more rapidly or to cease to regress by smoking. Both of these studies, Patel et al. (54) and Tracy et al. (77), agree that smoking has a role in the progression of fatty streaks to a more advanced stage of the atherosclerotic process.

Auerbach and Garfinkel in 1980 (5) published findings on smoking habits and atherosclerotic lesions in over 1,400 aortas collected at autopsy from male patients. The extent of atherosclerotic lesions (plaques, ulcerations, and calcification) increased with number of cigarettes smoked, and was also greater in ex-cigarette smokers and pipe smokers than in nonsmokers. The findings were more striking in the abdominal aorta than in the thoracic aorta. Aortic aneurysms were found eight times more frequently among those who smoked one to two packs of cigarettes per day than in nonsmokers.

Lifšic (37) reported on the relationship of cigarette smoking to aortic lesions based on the Yalta sample from the World Health Organization (WHO) autopsy study of five cities in Europe (87). Information on cigarette smoking was obtained by means of interviews with the subjects' near relatives. The prevalence and extent of atherosclerotic lesions were evaluated in autopsies of 865 men, aged 20 to 79 years, out of 1,220 deaths occurring in Yalta residents of this age and sex group during the period of study. There were significant positive relationships between smoking and the extent of fibrous plaques, complicated lesions, and calcified lesions in the abdominal aorta.

Aortic atherosclerosis has also been evaluated using autopsy followup of prospective epidemiologic studies of cardiovascular disease. Epidemiological studies in Puerto Rico and Honolulu documented selected risk factors, including cigarette smoking habits, during life and had standardized evaluation of atherosclerotic lesions at autopsy (56, 70). Each of these studies reported findings on the relationship of risk factors and aortic atherosclerotic lesions in more than 100 deceased men from large cohorts that had been examined and followed during life. A smaller study from Malmö, Sweden, had some of the same features as these larger studies (71). All of these studies found a significant positive relationship between cigarette smoking and aortic atherosclerosis.

The prospective epidemiologic studies with autopsy followup confirmed the relationship between smoking and atherosclerotic aortic lesions found in earlier autopsy studies. The preponderance of evidence suggests that cigarette smoking aggravates or accelerates aortic atherosclerosis, and this effect on atherosclerosis may be more pronounced in the aorta than in the coronary arteries.

Cerebral Vasculature

The relationship between cigarette smoking and atherosclerosis in the cerebral vasculature has not been extensively evaluated. Two studies that have examined this question are summarized in Table 4. Sternby (71) reported that cigarette smokers had more extensive raised lesions in the basilar artery than had nonsmokers. This study was based on 60 autopsy subjects from 703 men born in 1914 who participated in a study of cardiovascular disease in Malmö, Sweden. Holme et al. (29) reported a positive correlation coefficient between raised lesions in the cerebral vessels and the number of cigarettes smoked; this relationship was not statistically significant, however.

The limited amount of information available on the relationship between cigarette smoking and atherosclerosis in the cerebral vasculature does not allow a clear conclusion to be drawn at this time.

Pathophysiologic Mechanisms of Tobacco Smoke

Studies of Components of Tobacco Smoke

The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking were reviewed in the 1971 Report of the Surgeon General *The Health Consequences of Smoking* (80). The major components of cigarette smoke considered in that review were nicotine and carbon monoxide. Numerous investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon experimentally induced changes in the aorta and coronary arteries of animals. When administered alone, nicotine

TABLE 4.—Autopsy studies of atherosclerosis involving cerebral vasulation

Study	Population	Smoking data source	Measure of atherosclerosis	Results															
Sternby (71)	60 autopsied subjects from 703 males in CHD study in Malmo, Sweden	Interview with subject	Visual inspection	<p data-bbox="1144 235 1575 267"><u>Smoking and atherosclerosis in the basilar arteries</u></p> <table border="1" data-bbox="1144 284 1627 462"> <thead> <tr> <th data-bbox="1144 292 1228 341">Smoking category</th> <th data-bbox="1270 316 1344 337">Number</th> <th data-bbox="1396 308 1627 337">Basilar artery raised lesions</th> </tr> </thead> <tbody> <tr> <td data-bbox="1144 365 1197 386">Non</td> <td data-bbox="1291 365 1312 386">3</td> <td data-bbox="1501 365 1522 386">1</td> </tr> <tr> <td data-bbox="1144 389 1176 410">Ex</td> <td data-bbox="1291 389 1312 410">8</td> <td data-bbox="1501 389 1522 410">6</td> </tr> <tr> <td data-bbox="1144 414 1197 435">Light</td> <td data-bbox="1291 414 1323 435">18</td> <td data-bbox="1501 414 1522 435">3</td> </tr> <tr> <td data-bbox="1144 438 1207 459">Heavy</td> <td data-bbox="1291 438 1323 459">17</td> <td data-bbox="1501 438 1522 459">7</td> </tr> </tbody> </table>	Smoking category	Number	Basilar artery raised lesions	Non	3	1	Ex	8	6	Light	18	3	Heavy	17	7
Smoking category	Number	Basilar artery raised lesions																	
Non	3	1																	
Ex	8	6																	
Light	18	3																	
Heavy	17	7																	
Holme et al. (29)	129 autopsies out of 16,200 men aged 40-49 in Oslo CHD study	Interview with subject	Visual grading	Correlation coefficient between raised lesions in the cerebral vessels and number of cigarettes smoked per day is 0.090 (not statistically significant).															

induces certain degenerative or necrotic changes in the arterial wall, but these are characteristically medial changes rather than the intimal changes that characterize atherosclerosis. When nicotine is administered in combination with a high cholesterol diet, it seems to aggravate arterial damage, according to a preponderance of studies. Some studies, however, do not report this synergism between cholesterol feeding and nicotine (16, 84).

Schievelbein and associates (66) reported the effect of long-term nicotine exposure on the development of arteriosclerosis in rabbits. They administered nicotine to rabbits not being fed an atherogenic diet. All animals had arteriosclerotic lesions in the aorta and coronary arteries at the end of the experiment, but there was no difference between the control group and the experimental animals administered nicotine. They reviewed the experiments of several authors who studied nicotine and their own animal experiments and concluded that the evidence did not establish a causative role for nicotine in the etiology of arteriosclerosis.

A recent report by Liu et al. (38) on experimental arterial lesions in rhesus monkeys with various combinations of dietary hypercholesterolemia, hypervitaminosis D(2), and nicotine indicated that the combination of these three factors produced high scores for various measures of arteriosclerotic changes in aorta, coronary, and limb arteries of the monkeys. When the factors were administered singly, however, very little arterial disease was demonstrated over the period of the experiment. The group with all three factors was the only group with significant coronary arteriosclerosis as well as complicated lesions of the arteries of extremities.

Booyse et al. (15) reported the effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. They found that fasting serum levels of glucose, triglyceride, total cholesterol, and LDL cholesterol were elevated in nicotine-treated rabbits as compared with controls. They found no significant differences between the experimental group and the controls for leukocyte, erythrocyte, and platelet counts, or for hematocrit and hemoglobin. Endothelial cells from the aortic arch of the nicotine-treated animals showed extensive changes, such as increased cytoplasmic silver deposition, increased formation of microvilli, and numerous focal areas of "ruffled" endothelium. The authors concluded that nicotine administered orally to rabbits has a demonstrable morphologic effect on endothelial cells in the aortic arch.

While the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive, nicotine is certainly one of the components of tobacco smoke for which there are both some supporting data and a rational conceptualization for a role in the pathogenesis of atherosclerotic lesions. There is little doubt that nicotine alone or in combination with other