reduction in arterial blood flow such that cellular oxygen demand is not met by oxygen supply causes myocardial cells to shift their metabolism to anaerobic glycolysis and to accumulate lactate and other acidic metabolites. Such acidosis depresses cellular contractility. For reasons that remain to be clarified, cell membranes are damaged by ischemia. Moreover, the mitochondria are sensitive to ischemia and rapidly lose their ability to synthesize adenosine triphosphate, and are unable to maintain the energy requirements of the cell to live and function. Cell death ensues (*65*, *137*). The organized contraction of the heart is integrated by the sequential spread of an electrical stimulus. Ischemia, with or without overt infarction, can disrupt this integration and alter rhythmic stimulation, causing bradycardia or asystole or, more commonly, aberrant foci of electrical activity and fibrillation.

Hypoxia is not identical with ischemia since hypoxia can occur while the circulation maintains the local concentrations of other ions and substrates. However, the lack of adequate cellular oxygen is so important a part of the events summarized above that the addition of hypoxia to a marginally tolerated ischemia may initiate critical changes.

Since the major risk factors can be shown to enhance atherogenesis, it is usually implied that their association with heart attack is through the ischemia resulting from coronary atherosclerosis. However, direct effects upon cardiac function may also play a role. Hypertension increases the work and mass of the heart and creates a larger nutritional demand and relative ischemia. Nicotine releases catecholamines and transiently increases cardiac rate and work. Carbon monoxide decreases oxygen availability to the heart.

Animal models of acute myocardial infarction include embolism of the coronary arteries, slow or rapid constriction of arteries, intimal sclerosis and narrowing by various techniques and, by dietary cholesterol, atherosclerosis leading to acute or subacute myocardial ischemia and infarction. These different models can serve different experimental purposes. Each has limited analogy to myocardial infarction in man because infarction in man is itself a pathologically variable phenomenon and because of anatomical differences in size and circulation between animal and human hearts. Perhaps the model creating events most like those in man is the nonhuman primate (particularly M. fascicularis) with advanced dietary atherosclerosis. It is however, a variable one (*58*).

Summary of Epidemiological Data

The epidemiological concept of risk factors for myocardial infarction is based on data gathered prospectively or retrospectively about myocardial infarction rather than about atherosclerosis per se. As noted in the section on atherosclerosis, the data that associate risk factors with human atherosclerosis seen at post mortem are limited. On the other

hand, there is a very large body of data, suitable for treatment by sophisticated analytical methods, that associates risk factors with myocardial infarction. Usually, the data are treated in terms of fatal infarcts including both sudden and nonsudden (acute) death. However, analyses have dealt with sudden death alone, morbidity, and congestive heart failure in individuals free of detectible heart disease on initial study, individuals with some evidence of disease when first seen, and those experiencing second heart attacks.

Prospective studies of risk factor associations with myocardial infarction or coronary heart disease (CHD) have identified a number of clinical descriptors strongly associated with liability to future infarction. These descriptors include age, male sex relative to female sex before age 65, blood cholesterol level, arterial blood pressure, and cigarette smoking. Other associations have also been documented, including the "Type A personality," diabetes mellitus, obesity, blood uric acid, the use of oral contraceptives, hematocrit reading, evidence of coronary heart disease or other atherosclerotic disease, vital capacity, family history, and physical inactivity. Recently high density lipoprotein (HDL) has been shown to be apparently protective against myocardial infarction (*49, 92*).

Reports dealing with risk factors, particularly smoking, but in many studies with other risk factors as well, have been extensively tabulated in the 1976 reference edition of *The Health Consequences of Smoking.* (*138*) (Tables 1-4, pp. 19-31; Tables 9-14, pp. 38-41; Table A6, pp. 89-93; Tables A17-A18, pp. 101-102). The tables of the prospective studies of CHD mortality (Table 2, pp. 22-25) and morbidity (Table 4, pp. 26-31) are reproduced below as Tables 2 and 3. The major risk factors of blood cholesterol level, blood pressure, and cigarette smoking are independent and strong predictors of susceptibility to CHD. Each is dose-related to the liability to CHD, and each of about the same importance when considered independently. Cessation of smoking and reduction of high blood pressure will reduce the risks of cardiovascular disease. As summarized in Tables 15 and 16 on page 42 of the 1976 report (*138*) (and reproduced below as Tables 4 and 5), it has been found that ex-smokers suffer fewer myocaridal infarctions than continuing smokers. With reduced blood pressure it has been shown that less cerebrovascular disease and congestive heart failure occur. The effect of reducing blood cholesterol on liability to CHD remains under study.

Identified risk factors account for a major part but not all of the variance in CHD among a population. Cigarette smoking is an important risk factor, but it is not essential, nor is it, in those parts of the world in which people have levels of cholesterol in the range of about 160 mg percent, as strong a risk factor as in the United States. It has been reported from a follow-up study of about 265,000 adults over 40 years old in Japan (*99*) that smokers compared with nonsmokers have a relative mortality ratio of 1.22 for death from all causes and

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		Cigars, pipes		Age variation				Comments
Hammond and Horn, 1958, U.S.A.	187,783 white males in 9 states 50–69 years of age	Questionnaire and follow-up of death certificate	3 1/2	5,297	NS	1.00 (709)	$^2(p<0.001)$	Cigars		50–54	55–59	60–64	65–69	
					All smokers	1.70 (3361)	NS	1.00	NS	1.00 (90)	1.00 (142)	1.00 (204)	1.00 (273)	
					<10	1.29 (192)	SM	1.28 (420)	All smokers	1.93 (765)	1.85 (962)	1.66 (921)	1.41 (713)	
					10–20	1.89 (864)		Pipes	<10	1.38 (35)	1.38 (50)	1.17 (49)	1.27 (58)	
					20–40	2.20 (604)	NS	1.00	10–20	2.00 (213)	2.04 (258)	1.91 (235)	1.58 (158)	
					>40	2.41 (118)	SM	1.03 (312)	>20	2.51 (203)	2.47 (199)	1.92 (129)	1.56 (73)	
Doyle et al., 1964, U.S.A.	2,282 males, Framingham, 30–62 years of age. 1,913 males, Albany, 39–55 years of age.	Detailed medical examination and follow-up	10	93	NS	1.00 (20)								Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
			8		All smokers	2.40 (73)								
					<20	2.00 (17)								
					20	1.70 (20)								
					>20	3.50 (36)								
Doll and Hill, 1964, Great Britain	Approximately 41,000 male British physicians	Questionnaire and follow-up of death certificate	10	1,376	NS	1.00				35–44	45–64	65–84		
					All smokers	1.35	NS			1.00	1.00	1.00		
					1–14	1.29	1–14			3.73	1.40	1.71		
					15–24	1.27	15–24			4.45	1.73	1.27		
					>25	1.43	>25			1.36	1.92	1.58		

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Strobel and Gsell 1965 Switzerland	3,749 male Swiss physicians	Questionnaire and follow-up of death certificate	9	162	NS ..... 1.00 1-20 ..... 1.48 >20 ..... 1.76	NS ..... 1.00 SM 1.45		
Best, 1966 Canada	Approximately 78,000 male Canadian veterans	Questionnaire and follow-up of death certificate	6	2,000	NS ..... 1.00 All smokers 1.60 (1380) <10 ..... 1.55 (337) 10-20 ..... 1.58 (766) >20 ..... 1.78 (277)	Cigars NS .. 1.00 SM .. 0.98 (16) Pipes NS .. 1.00 SM .. 0.96 (95)	30-49 50-69 70 and over NS ..... 1.00 1.00 1.00 <10 ..... 0.97 (18) 1.56 (220) 1.71 (99) 10-20 ..... 1.45 (115) 1.67 (557) 1.29 (94) >20 ..... 1.85 (65) 1.76 (184) 1.73 (28)	
Kahn 1966 U.S.A.	U.S. male veterans 2,265,674 person years	Questionnaire and follow-up of death certificate	8 1/2	10,890	NS ..... 1.00 (2997) All smokers 1.74 (4150) 1-9 ..... 1.39 (439) 10-20 ..... 1.78 (2102) 21-39 ..... 1.84 (1292) >39 ..... 2.00 (266)	Cigars NS .. 1.00 SM .. 1.04 (623) Pipes NS .. 1.00 SM .. 1.08 (386)		

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Hirayama, 1967, Japan	265,118 Japanese adults over age 40	Trained interviewers and follow-up of death certificate	1	91	NS 1.00 (17) 1-24 1.13 (69) 25 1.00 (5)			Preliminary report
Kannel et al., 1968, U.S.A.	5,127 males and females age 30-59	Medical examination and follow-up	12	52	NS 1.00 (27) SM 20 2.20 (25)	(p= 0.05)		
Hammond and Garfinkel, 1969, U.S.A.	358,384 males 445,855 females age 40-79 at entry	Questionnaire and follow-up of death certificate	6	14,819	Males / Females NS 1.00 / 1.00 1-9 1.27 / 0.84 10-19 1.60 / 1.22 20-30 1.73 / 1.52 >40 1.77 / 0.61		Males 40-49 / 50-59 / 60-69 / 70-79 NS 1.00 / 1.00 / 1.00 / 1.00 1-9 1.60 / 1.59 / 1.48 / 1.14 10-19 2.59 / 2.13 / 1.82 / 1.41 20-30 3.76 / 2.40 / 1.91 / 1.49 >40 5.51 / 2.79 / 1.79 / 1.47 Females NS 1.00 / 1.00 / 1.00 1-9 1.31 / 1.15 / 1.04 / 0.76 10-19 2.08 / 2.37 / 1.79 / 0.98 20-30 3.62 / 2.68 / 2.08 / 1.27 >40 †3.31 / 3.73 / †2.02	†Based on 5-9 deaths.

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Paffenbarger and Wang 1969 U.S.A.	50,000 male former students	Baseline interview and examination and follow-up by death certificate	17.51	1,146 matched with 2,292 controls	NS ..... 1.00 SM ..... 1.50 (385) (p< 0.01)	NS ..... 1.00 (p< 0.01) SM 1.80 (88)	30-44 45-54 55-69 1.00 1.00 1.60 (160) 1.20 (134)	
Paffenbarger et al., 1970, U.S.A.	3,263 male longshoremen 35-64 years of age.	Initial multiphasic screening and follow-up of death certificate.	16	291	NS and ≤20 1.00 (137) SM >20 2.08 (154) (p< 0.01)			
Taylor et al., 1970, U.S.A.	2,371 male railroad employees 40-59 years of age at entry	Interviews and regular follow-up examination.	5	46	NS 1.00 (4) ≤20 ..... 1.97 (20) >20 ..... 3.60 (22)			Data apply only to those free of CHD at entry

TABLE 2.—Coronary heart disease mortality ratios related to smoking—prospective studies. (Actual number of deaths shown in parentheses)[1] [SM = Smokers NS = Nonsmokers]—Continued

Author, year, country	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		Cigars, pipes	Age variation				Comments
									35–44	45–54	55–64	65–69	
Weir and Dunn, 1970, U.S.A.	68,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	1,718	NS	1.00		NS	1.00	1.00	1.00	1.00	NS includes pipes and cigars.
					All smokers	1.60		±10	4.22	2.06	1.41	1.17	SM includes ex-smokers.
					±10	1.39		±20	6.14	3.17	1.64	1.26	
					±20	1.67		±30	8.57	3.33	1.66	1.36	
					>30	1.74		>40	7.93	3.15	1.42	1.42	
								All	6.24	2.95	1.56	1.24	
Pooling Project, American Heart Association, 1970, U.S.A.	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	239	NS	1.00 (27)	1.00 (27)						
					<10	1.65 (34)	1.20 (24)						
					20	1.70 (86)							
					>20	3.00 (68)							

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

[2]"p" values specified only for those provided by authors.

SOURCE: U.S. Public Health Service (*138*).

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day		Pipes, cigars	Age variation	Comments
Doyle et al., 1964, U.S.A.	2,282 males Framingham, 30-62 years of age. 1,913 males Albany, 39-55 years of age.	Detailed medical examination and follow-up.	10	243 myocardial infarctions and CHD deaths.	NS All smokers <20 20 >20	1.00(52) 2.36(191) 1.98(44) 2.05(64) 3.04(83)			Data include CHD deaths, only on males 40-49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
Stamler et al., 1966, U.S.A.	1,329 CHD-free male employees of Peoples Gas Company 40-59 years of age.	Interview and examination with clinic follow-up.	4	46 CHD	NS <10 cigarettes <5 cigars <5 pipes 10-19 cigarettes >20 cigarettes >5 cigars >5 pipes	1.00(2) 2.92(6) 3.67(8) 3.83(29) 			NS includes ex-smokers. Includes all CHD.

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars	Age variation			Comments
Jenkins, et al., 1968, U.S.A.	3,182 males 39-59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4 1/2	104 myocardial infarctions.	NS	1.00(21)				39-49	50-59	†Includes nonsmokers and ex-smokers. NS includes former pipe and cigar smokers.
					EX	2.47(15)	($p<0.001$)		NS	1.00(4)	1.00(6)	
					Current	2.78(68)			Current	4.23(35)	2.26(33)	
					0-15/day	†1.39(45)	($p<0.001$)					
					>16	3.06(59)	(comparing 0-15 and 16+)					
Kannel, et al., 1968, U.S.A.	5,127 males and females 30-59 years of age.	Medical examination and follow-up.	12	228 myocardial infarctions. 380 CHD.	Myocardial Infarction							
					Males		Females					
					NS	1.00(21)	1.00(31)					
					All SM	*1.51(153)*	*1.71(23)*					
					Heavy SM	1.85(59)						
					Risk of CHD (overall)							
						Males	Females					
					NS	1.00(61)	1.00(89)					
					1-10	1.34(25)	0.86(18)					
					11-20	1.80(90)	1.29(18)					
					>20	2.41(76)	0.93(3)					

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars		Age variation	Comments
Epstein, 1967, U.S.A.	6,565 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions.		Males 40-59	60 and over		Males 40-59		Reexamination of patients was spread over 1 1/2 6-year period, but data are reported in terms of 4-year incidence rates. Actual number of CHD incidents derived from data on incidence and total in smoking class.
					NS	1.00(1)	1.00(7)	SM	1.80(2)		
					EX	6.53(10)	1.27(11)		60 and over		
					Cigarettes	5.20(36)	1.96(23)	SM	0.86(6)		
						Females					
					NS	1.00(21)	1.00(47)				
					EX	0.89(3)	1.31(5)				
					Cigarettes	1.02(14)	0.42(2)				

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars		Age variation						Comments
						Males	Females	Males only			Males			Females		
Shapiro et al., 1969, U.S.A.	110,000 male and female enrollees of Health Insurance Plan of Greater New York (HIP) 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	3	Total unspecified.	NS	1.00	1.00	NS	1.00	35-44	45-54	55-64	35-44	45-54	55-64	Total myocardial infarction includes those dead within 48 hours
					All current cigarettes	2.14 (p<0.01)	2.00 (p>0.01)	SM (p<0.01)	1.82	1.00	1.00	1.00	1.00	1.00	1.00	
					<20	1.50				2.47	3.06	1.69	2.25	2.87	1.80	
					>20	2.33	1.77			0.52	2.15	1.32	1.25	2.31	1.65	
					>40	6.36	5.92			3.04	3.29	1.81				
										10.09	7.69	5.30	20.25	11.79	4.07	NS include ex-smokers.
Keys 1970 Yugoslavia Finland Italy Netherlands Greece	9,186 males in 5 countries 40-59 years of age at entry.	Interviews and regular follow-up examination by local physicians.	5	65 deaths. 80 *myocardial* infarctions. 128 angina pectoris. 155 other †428 total.	NS, EX (SM <20)	1.00(305)										Includes all CHD incidence including EKG diagnoses. Covers all countries investigated except U.S.A. †Difference between total CHD and the sum of smoking groups is due to difference in figures presented by authors.
					All current (>20)	1.31(103)										

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day		Pipes, cigars	Age variation	Comments
Taylor, et al. 1970 U.S.A.	2,571 male railroad employees 40-59 years of age at entry.	Interviews and regular follow-up examination.	5	46 deaths. 33 myocardial-infarctions. 78 angina pectoris. 55 other CHD. 212 total.	NS and EX ..... All current	1.00(62) 1.77(150)			All CHD including EKG diagnoses.
Dayton et al., 1970, U.S.A.	422 male U.S. veterans participating as controls in a clinical trial of a diet high in unsaturated fat.	Interviews and routine follow-up examinations.	up to 8	27 sudden deaths. 44 definite myocardial infarctions.	<10 ..... 10-20 ..... >20	1.00(25) 1.04(22) 1.17(13)			No data on NS as a separate group.

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Pipes, cigars	Age variation	Comments
Dunn et al., 1970 U.S.A.	13,148 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 14	Total unspecified.			30-39 40-49 50-59 †Low SM 1.00(25) 1.00(125) 1.00(157) ‡High SM 2.17(10) 0.90(31) 1.41(53)	†Includes NS, EX, and <20 cigarettes/day. ‡ >20 cigarettes/day. Includes all CHD but excludes death. No data available comparing smokers and nonsmokers.
Pooling Project, American Heart Association 1970, U.S.A.	7,427 white males 30-59 years of age at entry.	Medical examination and follow-up.	10	538 Includes fatal and nonfatal myocardial infarction and sudden death.	Never smoked ..... <10 ..... 20 ..... >20	1.00(53) 1.65(72) 2.08(206) 3.28(154)	1.00(53) 1.25(54)	

TABLE 3.—Coronary heart disease morbidity as related to smoking. (Risk ratios—actual number of CHD manifestations shown in parentheses)[1] [SM = Smokers NS = Nonsmokers EX = Ex-smokers]—Continued

PROSPECTIVE STUDIES									
Author, year, country	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day			Pipes, cigars	Age variation	Comments
						Coronary cases (87)	Noncoronary controls (1,786)			
Paul et al., 1963, U.S.A.	1,989 Western Electric Co. male workers participating in a prospective study for 4 1/2 years.	Screening examination and history.			NS	23	33			88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.
					1-7	2	7			
					8-12	9	11			
					13-17	6	12			
					18-22	47	30			
					23-27	3	2			
					>28	9	6			
							($p<0.005$)			

[1]Unless 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 (*158*).

TABLE 4.—The effect of the cessation of cigarette smoking on the incidence of CHD. (Incidence ratios—actual number of cases or events are shown in parentheses)

Author, year, country	Results			Comments
		All CHD events	All myocardial infarction	
Jenkins, et al., 1968 U.S.A.	Never smoked	1.00(30)	1.00(21)	
	Current cigarette smokers	2.36(84)	2.78(68)	
	Former cigarette smokers	2.15(19)	2.47(15)	
		Death from CHD		
		Smoked 1–19 cigarettes/day	Smoked >20 cigarettes/day	
Hammond and Garfinkel, 1969, U.S.A.	Never smoked regularly	1.00(1,841)	1.00(1,841)	Male data only
	Current cigarette smokers	1.90(1,063)	2.55(2,822)	
	Stopped <1 year	1.62(29)	1.61(62)	
	1–4	1.22(57)	1.51(154)	
	5–9	1.26(55)	1.16(135)	
	10–19	0.96(52)	1.25(133)	
	>20	1.08(70)	1.05(80)	
	All ex-cigarette smokers	1.16(253)	1.28(564)	
		Total definite myocardial infarction		
Shapiro, et al., 1969, U.S.A.	Never smoked	1.00		
	Current cigarette smokers	1.87		
	Stopped ≤5 years	0.76		
		All CHD deaths	First major coronary event	
Pooling Project, American Heart Association 1970, U.S.A.	Never smoked	1.00(27)	1.00(53)	
	>½ pack/day	1.65(34)	1.65(72)	
	1 pack/day	1.70(86)	2.08(205)	
	>1 pack/day	3.00(68)	3.28(154)	
	Ex-smokers	0.80(19)	1.25(51)	

SOURCE: U. S. Public Health Service (*158*).

1.16 for all cardiovascular diseases in males. The reported ratios were 1.64 among men and 1.57 among women for ischemic heart disease. This effect on ischemic heart disease was related directly to the

TABLE 5.—Annual probability of death from coronary heart disease, in current and discontinued smokers, by age, maximum amount smoked, and age started smoking

Age	Maximum daily number of cigarettes smoked	Age started smoking 15–19		Age started smoking 20–24	
		Current smokers	Discontinued for five or more years	Current smokers	Discontinued for five or more years
		(Probability x 10^5)			
55–64	0	501	—	501	—
	10–20	798	568	811	551
	21–39	969	766	872	698
65–74[1]	0	1,015	—	1,015	—
	10–20	1,501	1,169	1,478	1,213
	21–39	1,710	1,334	1,573	1,098

[1]For age group 65–74, probabilities for discontinued smokers are for 10 or more years of discontinuance since data for the 5–9 year discontinuance group are not given.

SOURCE: U. S. Public Health Service (*138*).

amount smoked and to the age at which smoking began, in a study of a small subset of the population.

In industrial societies which share about the same general nutritional and metabolic circumstances as the United States, it has been shown repeatedly that cigarette smoking is associated with a considerable increase in risk of myocardial infarction and death following infarction when compared to the risk among nonsmokers. The effect is dose-related in terms of years of smoking, number of cigarettes smoked per day, and the habit of inhaling. The association is generally consistent, reproducible, and predictive. It is independent in the sense that its effect is found when other risk factors for heart disease are controlled in statistical analysis. The effect is seen chiefly in cigarette smokers. Pipe and cigar smokers are apparently at only minor increased risk. The effect is greatest in young middle life and decreases with age to become a minor risk beyond age 65. Cessation of smoking reduces, over time, the increased risk attributable to smoking toward the risk of nonsmokers. While most of the data have been gathered on men, there are sufficient data to provide similar general conclusions that cigarette smoking is also a risk factor for myocardial infarction in women. The studies of Hammond and Garfinkle, listed in Table 2, and of Shapiro and colleagues, in Table 3, record positive associations between smoking and mortality and morbidity from CHD in large populations of women. It has been observed that women who use oral contraceptive pills are at higher risk of infarction if they also smoke (*102*). Recently, a case-control study has reported that, among 55 women who had suffered myocardial infarction below the age of 50 years, the proportion of smokers was 89 percent compared to 55 percent among

the case controls ($p < 0.001$). A dose relationship was present. Compared to nonsmokers, heavy smokers using 35 or more cigarettes a day had an infarction rate estimated to be increased 20 times. The women did not use oral contraceptives (*124*).

The final report of the Pooling Project considers data from the Albany civil servant study, the Chicago Peoples Gas Co. study, the Chicago Western Electric Co. study, the Framingham community heart study, and the Tecumseh community study. It presents typical findings from prospective studies and ones that are particularly important for the United States because the data are derived from several locations in the country. In this report (*107*), fatal and nonfatal myocardial infarction and sudden coronary heart disease death have been designated as major coronary events.

Cholesterol values, blood pressure readings, and smoking history observed just once in men at the beginning of a 10-year follow-up period showed a high predictibility of risk of CHD. Multiple logistic analysis showed these three characteristics to be independent. Combinations of these risks were not additive but compounded. The highest combined quintile of risk characteristics compared to the lowest quintile had a relative risk of CHD events of about 6 to 1. About 40 percent of cases emerged from the 20 percent at highest risk, while 86 percent emerged from the upper 60 percent of risk traits, and 96 percent derived from the upper 80 percent. Not only is risk of CHD events associated with the more deviant levels of these traits, but appreciable risk may attach to combinations of mild deviations of risk factors.

Smoking habit was classified as more than a pack of cigarettes a day, about a pack a day, about half a pack a day, less than half a pack, cigar and pipe only, never smoked, and past smokers. For most analyses, the report groups past smokers, never smoked, and smokers of less than half a pack a day into a single group labeled nonsmokers, noting that the majority of the less than a half pack per day smokers were only occasional users. This group of nonsmokers was then compared with those who smoked more. It was found that men who smoked a pack or more a day had a standardized incidence or risk ratio[1] of a first major coronary event 2.5 times that of the nonsmoker (confidence interval 2.1 to 3.1). Those who reported smoking more than a pack a day were found to have 3.2 times the risk of nonsmokers in terms of standardized incidence ratio (confidence limits 2.6 to 4.2). The risk of pipe and cigar smokers was intermediate between that of the nonsmokers and the half a pack a day smokers, but was not statistically different from either group in this study. Risk was found

[1]This calculation removes that portion of any difference attributable to age differentials. The average rate for the total group is assigned the value of 100. The rates for subgroups are proportional to the average for the entire group after removing the effects of age.

to rise rapidly above half a pack a day and to be almost twice as high in the pack a day group of cigarette smokers.

Among additional recent papers, the Framingham Heart Study reports that smoking 20 cigarettes a day is associated with an annual incidence of coronary events per 1,000 in the fifth, sixth, and seventh decades of life of 11.9, 19.3, and 19 per 1000 of population. The corresponding rates for nonsmokers were 3.6, 5.7, and 15.3 (*69*). The Western Collaborative Group Study (*116*) in California has detailed a dose relationship of relative risk analysed for the fifth and sixth decades of life among men smoking either less than a pack per day, a pack, and more than a pack in comparison with nonsmokers. The reported relative risks were 1.05, 1.53, and 1.93 in the fifth decade, and 0.098, 1.63, and 2.32 in the sixth. Reid and colleagues (*110*) have reported on more than 18,000 male civil servants in Great Britain between the ages of 40 and 64 who were followed over 5 years of prospective study. The risk of death from coronary heart disease was lowest among nonsmokers or ex-smokers. Current smokers had a significantly higher risk of death from CHD. Moreover, when classified by inhalation habit, inhalers were found to have higher risk of CHD death than those who do not inhale. In yet another study from Great Britain, more than 34,000 physicians have been followed for 20 years. It is reported that annual death rates (per 100,000, standardized for age) among light, medium, and heavy smokers for ischemic heart disease are 501, 598, and 677 respectively (*35*).

There have been inconsistent reports on the effect of smoking on the occurrence of a second or subsequent heart attack. Studies in New York (*150*) failed to find a relationship between smoking and second heart attacks, while the Newcastle and Scottish studies (*43, 111*) did find an adverse trend. A recent contribution to this issue has been the findings of the Coronary Drug Project Research Group (*29*) who reported on 2,789 male survivors of myocardial infarction in the New York Heart Association cardiac functional classes I or II. These men had been randomized to placebo treatment and usual care. They were followed for 5 years and provide a natural history study under usual current therapy conditions. Smokers at the time of entry into the study were at somewhat higher risk than nonsmokers. The relative risk of smoking after myocardial infarction was appreciable, but less than for men with no prior history of heart attack as, for example, those documented in the Pooling Project (*107*). The absolute risk of death is much higher for men who have already experienced a myocardial infarction, however, so that the difference in mortality rates for them between smokers and nonsmokers becomes correspondingly important. In this study, the hospitalization rate was 36 percent higher for cardiovascular events among smokers than nonsmokers.

Other recent papers include the Western Collaborative Group Study (*64*), which has reported that the number of cigarettes smoked daily

correlates significantly with the occurrence of new myocardial infarction among men who have had a prior attack. Mulcahy and colleagues (*97*) have reported that over a 5-year period, subsequent smoking after an infarction did not affect morbidity, but there was an increased mortality among those who continued to smoke. In the British civil servant study (*115*), it was found that among those with existing evidence of ischemic heart disease, the mortality rates over 5 years were 4.7 and 4.0 percent among those who smoked relative to nonsmokers. Again, in a Swedish study (*154*), those who ceased to smoke after a heart attack had only half the rate of nonfatal recurrences, and half the rate of cardiovascular mortality of those who continued to smoke over a 2-year follow-up period.

There is persuasive evidence from population studies in the United States and in the United Kingdom (*35*) that ex-smokers adopt a lesser risk after ceasing to smoke, which in time is little different from the nonsmoker who never smoked. The 1976 reference report on *The Health Consequences of Smoking* (*138*) tabulated several important studies in Tables 15 and 16 on page 42 (reproduced above as Tables 4 and 5). The Framingham Heart Study (*50*) also reports a beneficial effect below the age of 65. Men who stopped smoking had coronary attack rates only one-half those who continue to smoke 10 or more cigarettes per day. In a paper that may be germane, although it relates to differences in exposure rather than cessation, Hammond and associates (*53*) find that smokers of low tar and nicotine delivery cigarettes had lower death rates from coronary heart disease than those who smoked the same number of high tar-nicotine cigarettes. Both groups of smokers, however, had higher rates than nonsmokers.

It is of interest in discussing other risk factors that physical activity markedly shortens the half life of carboxyhemoglobin in the blood and that active people attain lower equilibrium levels than sedentary ones when smoking (*27, 56, 145*). Physical activity, particularly when heavy, has been shown in several studies to reduce the incidence of heart attack, and it can be speculated that at least some of this effect may arise from a reduced burden of COHb among physically active smokers (*145*). Morris and colleagues obtained evidence in a study of British civil servants that, among men who did not exercise vigorously during their leisure time, smokers had 2.5 times the risk of nonsmokers. Among the physically active group, however, the relative risk of smokers was 1.5. The amount of tobacco used daily was the same in the two groups (*95*).

The Effect of Smoking on Myocardial Infarction in Man

The epidemiological data that associate cigarette smoking and myocardial infarction are summarized in the preceeding section. The effect is major and adverse for the incidence of first events; it is

apparently also adverse for second attacks, but this is not yet well defined.

The mechanism of effect is usually attributed to an enhancement of coronary atherosclerosis in smokers and the consequent occurrence of cardiac ischemia and ischemic necrosis of heart muscle. Other phenomena have been offered as supplementary mechanisms. Aronow has recently discussed these in the context of relative ischemia and cardiac effects (*5*, *6*). In patients with exercise-inducible angina, smoking various nicotine or non-nicotine-containing cigarettes was found to aggravate angina and in a manner related to the nicotine content. Nicotine-containing cigarettes increase heart rate and blood pressure transiently, non-nicotine cigarettes do not. The nicotine effect is mediated through catecholamine discharge. Both nicotine and non-nicotine cigarettes increase blood CO. There is a decreased availability of oxygen for the heart. Aronow reports a rise in left ventricular end-diastolic pressure and a decrease in stroke volume due to a negative inotropic effect of CO on the myocardium. Jain and associates (*60*) have found that, in normal subjects, smoking decreases the preejection/left ventricular ejection time ratio and external isovolumetric contraction time, whereas in patients with coronary heart disease these measurements increased on smoking. They concluded that left-ventricular performance is diminished after cigarette smoking in the presence of significant coronary artery disease.

In the individual with ischemic heart disease, it is hypothesized that nicotine may aggravate ischemia: by increasing cardiac oxygen demand but not supply; by increasing platelet adhesiveness (*78*) and causing circulatory obstruction at the microvascular or macrovascular level; by lowering the cardiac threshold to ventricular fibrillation (*20*); and by depressing conduction and enhancing automaticity (*52*) favoring the development of arrhythmias. CO might aggravate ischemia by exaggerating hypoxia, producing a negative inotropic effect, reducing the fibrillation threshold (*6*), or increasing platelet adhesiveness (*25*). Regardless of which of these several mechanisms might operate in individual cases, it can be hypothesized that patients on the border of myocardial ischemia may be pushed into impending or actual infarction by the effects of nicotine and CO. Moreover, it may be speculated that, in the presence of coronary atherosclerosis of a degree insufficient to cause ischemia, the actions of smoking on platelet pathophysiology may precipitate occlusive thrombosis and infarction.

These possible mechanisms for the conversion of marginal ischemia into overt infarction may be thought to require that the attack follow immediately in time or coincide with the act of smoking. In fact, experience with myocardial infarction or sudden death does not seem to support the idea that the majority of habitual smokers suffer myocardial infarction or sudden death in such close temporal relationship to the act of smoking. However, the exact timing of the onset of

heart attack by clinical criteria is not possible. A considerable number of infarcts are clinically unrecognized. It is also possible that the initiation of ischemia or of platelet aggregation begun at one time might culminate in heart attack only hours later. At present, it is not possible to clarify these temporal uncertainties.

The Effect of Smoking on Myocardial Infarction in Animals

There are limited data on the effect of smoke constituents on experimental myocardial infarction in animals. Table A20 (pp. 103-108) of the 1976 reference edition of *The Health Consequences of Smoking* (*137*) lists 18 separate publications involving the effect of smoke and nicotine on cardiovascular function. Three studies used animals with coronary artery narrowing or ligation. In one there was an increase in the frequency of nicotine-induced arrhythmias. This was less evident as the time interval (up to 45 days) increased between artery ligation and nicotine challenge. In another study, nicotine increased coronary blood flow less in the presence of coronary narrowing than in normal animals. One paper reported that animals with damaged myocardium due to isoproterenol lesions or ligation of the coronary artery responded to a nicotine challenge with an increased expression of arrhythmias. It was found that it required more nicotine to increase coronary flow and heart rate in rabbits with dietary-induced atherosclerosis than in normal animals. It was also reported that in dogs with acute coronary occlusion that nicotine caused coronary vasodilation in the normal heart, but in ischemic myocardium, flow increased only proportional to aortic pressure. Dogs with coronary occlusion manifest excessive left atrial pressure and ventricular arrhythmias on exposure to nicotine (*36*).

The effect of CO inhalation on monkeys with experimental myocardial infarction produced electrocardiographic evidence of greater myocardial ischemia and increased liability to induced-ventricular fibrillation (*34*).

Research Needs

The epidemiological data relating smoking to myocardial infarction leave no doubt that smoking is a major risk factor for both fatal and nonfatal CHD. Data in certain situations need strengthening or verification. There is much less information concerning women than men. Data are few on the effect of smoking on myocardial infarction in old age. The published reports on the adverse effect of smoking on the incidence of second heart attacks are probably adequate, but are inconsistent and not well-defined. Studies to investigate the separate relationships of nicotine and CO in whole smoke to the incidence of myocardial infarction would be particularly useful. Detailed data on the effect of "less hazardous" cigarettes compared with ordinary cigarettes in relation to myocardial infarction are not available,

although, as noted above, it has been shown that there is a rising gradient of risk of cardiovascular death for smokers of the same number of low, medium, and high tar and nicotine cigarettes (*53*). If such studies are feasible, they could provide for the public and for cigarette production important information about the risks to be attributed to different smoke deliveries of tar, nicotine, CO, and perhaps other substances.

A major need is to understand better the mechanisms by which smoking can induce or affect the evolution of myocardical infarction. Animal experiments using several different models of myocardial ischemia or infarction in conjunction with exposure to smoke constituents alone, and in combination, should provide some clarification. They could be conducted under precise if somewhat artificial circumstances. Nonhuman primates susceptible to experimental atherosclerosis have been trained to smoke in a humanlike manner without overt stress or aversion (*86*), and studies of whole smoke of different characteristics in a more natural setting of acute and chronic inhalation exposure can be done.

Conclusions

Cigarette smoking is a major independent risk factor for the development of fatal and nonfatal myocardial infarction in men and women in the United States. It also appears to be a risk factor for second heart attacks among those who have experienced one, and diminishes survival after a heart attack among those who continue to smoke. It acts synergistically with high blood pressure and elevated blood cholesterol. The effect is directly related to the amount smoked. Ceasing to smoke reduces the risk towards that of nonsmokers. Smokers of low tar and nicotine cigarettes have a higher risk than nonsmokers, but they have a lesser risk than those who smoke high tar and nicotine cigarettes.

Sudden Cardiac Death

The Nature of Sudden Cardiac Death in Man

A recent symposium (*28*) on sudden cardiac death has delineated the nature of the problem and the many definitions that are used to classify it. The data gained from hospital practice and from coroner's experience differ quantitatively from the findings of prospective epidemiological studies, but the nature of the disorder is probably the same in all the samples. Coronary heart disease (CHD) accounts for 90 percent of examples of sudden cardiac death, but there are other cardiac causes for sudden death (*28*).

In a prospective epidemiological study, Kannel and associates (*71*) reported that individuals with overt CHD are four times as liable to sudden death as those without CHD. They report that about 55 percent

of cases occur in individuals with no prior clinical evidence of CHD. The standard CHD risk factors have been confirmed also to be predictors of sudden cardiac death in both a case control study (*44*) and in a prospective cohort investigation (*38*). Whether death from CHD is sudden does not appear to depend upon the mix of risk factors, and no combination of standard risk factors (including smoking) appears to designate those destined to die suddenly in contrast with those who will experience a more protracted death. The proportion of sudden cardiac deaths to more protracted deaths is about the same whether or not prior overt CHD has been recognized (*38, 71*). Evidence has been accumulated in several studies that, in the presence of recognizable heart disease, ventricular premature beats are associated with an excess liability to sudden cardiac death (*142*). A recent study by Ruberman and associates (*118*) followed 1,739 men in the New York City area who had a myocardial infarction at least 3 months before entering the study. They were examined for ventricular premature beats by means of a continuous 1-hour record of the electrocardiogram. The follow-up period was from 6 months to 4 years, averaging 24.4 months. During this period there were 208 deaths, of which 85 were classified as sudden cardiac deaths (defined here as occurring within minutes and in the absence of signs or symptoms suggesting acute myocardial infarction). Much higher mortality was experienced in those subjects manifesting complex beats (runs, early beats, bigeminal, and multiform beats) than in those without. The authors report that by the 3-year observation point the risk of sudden cardiac death, adjusted for age, was four times above the comparison experience, and the risk of death from any cause was 2.6 times greater than expected. Moreover, although such complex beats were often associated in this study with other findings that relate to severe heart damage, they were shown to be independent risk factors.

Autopsy studies on persons dying sudden cardiac deaths have produced somewhat variable findings. In general there is a close association with extensive and severe coronary atherosclerosis, and an appreciable number of patients show evidence of old or recent myocardial infarction. Reichenbach and coauthors (*109*) have tabulated data from several studies. Their own experience in the Seattle, Washington area was that 97 percent of decedents had a prior history of heart disease (much higher than other studies); 55 percent had pathological evidence of old myocardial infarction; 8 percent had less than 75 percent luminal stenosis in any major coronary artery with the remainder showing 75 percent or greater stenosis in one or more vessels; and 57 percent had occlusion of one or more vessels. Recently formed thrombi were found in 10 percent of hearts, which was, generally, appreciably less than other studies; acute myocardial infarction was found in only 5 percent of hearts, which also was, generally, appreciably less than in other studies. Other reports that

consider a history of smoking in relation to autopsy examinations and sudden death are those of Spain and coworkers (*127, 128*) and Friedman and associates (*44*).

Two major mechanisms for sudden cardiac death may be postulated. One is asystole or arrest, generally arising in response to severe ischemia and impending or spreading acute myocardial infarction. The other is ventricular fibrillation arising from regional myocardial ischemia and ventricular ectopy and modulated by a number of circumstances that may contribute to electrical instability of the heart.

Sudden Cardiac Death in Animals

Sudden death has been reported in nonhuman primates that were fed cholesterol to induce atherosclerosis (*58*), and it has been induced in many experiments by acute coronary ligation or obstruction. The latter experiments have produced a large body of data on the ability of regional ischemia to initiate ventricular fibrillation and sudden cardiac death, and have helped to elucidate local tissue metabolism, electrical behavior, and the relation of neural and pharmacologic agents to the precipitation or control of arrythmias and fibrillation.

Summary of Epidemiological Data

Sudden cardiac death is the first manifestation of coronary heart disease (CHD) in about 20 percent of CHD deaths. Of all CHD deaths about 50 to 60 percent are sudden (*71*).

The 1976 reference report on smoking and health (*138*) noted in Table 3 (p. 26) data on sudden cardiac death from the Pooling Project that found an increased mortality ratio of 1.9 for men who smoked either 10-or-less or 20 cigarettes a day, and a ratio of 3.36 for those smoking more than 20 a day, in comparison with nonsmokers (1.00). A more recent report combines data from Framingham and the Albany Civil Servant Study (*38, 71*). These data relate to men only, and are derived from 1,838 subjects from Albany, New York, and 2,282 from Framingham, Massachusetts, aged 45 to 74, and were collected prospectively over 16 years. Sudden death was defined as demise within one hour of onset. Deaths within 30 days of a known heart attack were excluded as were those of subjects found dead in bed. Data are presented on the associations between sudden cardiac death and a number of factors such as age, a prior history of CHD, blood pressure, serum cholesterol, and other items. Smoking was found to be a risk factor, with smokers having a threefold higher rate than nonsmokers. In a multivariate analysis of systolic blood pressure, electrocardiographic evidence of left ventricular cardiac hypertrophy, relative body weight, cigarettes smoked per day, and serum cholesterol as contributors to risk among men ages 45 to 54 and 55 to 64 at their biennial examination antecedent to death, it was judged that, of these factors, the use of cigarettes was the most potent contributor to sudden death.

A case control study based on the Kaiser-Permanente health insurance system in California (*44*) has reported on 197 sudden cardiac deaths among men. The case to control findings with reference to percentage of smokers among 40- to 54-year-old decedents were 67.9 and 39.3. It was found that smoking had a somewhat stronger relationship to deaths occurring 1 hour after onset of symptoms than to instantaneous deaths or those within 1 hour. Talbott, et al. (*134*) have reported on sudden death among white women and find an excess use of tobacco and alcohol among those dying suddenly.

The relationship of smoking to sudden death among those with existing recognized CHD has had little attention. In a prospective study, Graham and associates (*51*) found no association between smoking and mode of death in patients known to have had a prior infarction. Oberman and co-workers found no relationship between the major risk factors including smoking and sudden death in patients evaluated earlier for ischemic heart disease (*100*). It was found that the best five variable models to predict sudden death in this group of patients included the number of coronary arteries obstructed 70 percent or more, the use of digitalis or diuretics, premature beats and ventricular conduction defects. The Coronary Drug Project (*29*), which was also a prospective study, reported a 5-year age and race adjusted sudden death-rate ratio of smokers to nonsmokers of 1.28 (t value 1.98) in the placebo or customary therapy group.

The Effect of Smoking on Sudden Cardiac Death in Man

The epidemiological associations have been noted above. The act of cigarette smoking does not appear to be immediately related in time to sudden death. In relation to second heart attacks, Moss and colleagues (*96*) report a prospective follow-up study of patients discharged from hospital after myocardial infarction. They reported on 42 deaths (sudden and nonsudden) of cardiac nature in the following 6 months. Information on smoking prior to death was available on 28 patients; of these, only 5 were said to have smoked in the week before death.

The mechanisms postulated to explain the association of sudden cardiac death with smoking have been described under atherogenesis and under myocardial infarction as possible mechanisms for effects of smoke, nicotine, and CO. They include accelerated atherogenesis, enhancement of ischemia through inotropic effects, increased platelet adhesiveness obstructing coronary flow, or, through increased cardiac work caused by nicotine, and simultaneously reduced oxygen delivery to the heart due to CO. Any of these mechanisms can be evoked as possible initiators of critical ischemia and of sudden death due to asystole or to ventricular fibrillation. The smoking and health report of 1976 (*138*) tabulates in Table A21 (pp. 109-114) the effects of smoking and nicotine on the cardiovascular system in man. While these data