TABLE 2.—*Coronary heart disease mortality*

(Actual number of deaths

[SM = Smokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day		
Hammond and Horn, 1958, U.S.A. (*77, 78*).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	5,297	NS .....1.00 All smokers .1.70 <10 .....1.29 10–20 ....1.89 20–40 .....2.20 >40 .....2.41	(709) (3361) (192) (864) (604) (118)	[2](p<0.001)
Doyle et al., 1964, U.S.A. (*54*).	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 8	93	NS .....1.00 All smokers .2.40 <20 .....2.00 20 .....1.70 >20 .....3.50	(20) (73) (17) (20) (36)	
Doll and Hill, 1964, Great Britain (*50*).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	1,376	NS .....1.00 All smokers .1.35 1–14 ....1.29 15–24 ....1.27 >25 .....1.43		
Strobel and Gsell 1965 Switzerland (*180*).	3,749 male Swiss physicians.	Questionnaire and follow-up of death certificate.	9	162	NS .....1.00 1–20 .....1.48 >20 .....1.76		
Best, 1966 Canada (*24*).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	2,000	NS .....1.00 All smokers .1.60 <10 .....1.55 10–20 .....1.58 >20 .....1.78	(1380) (337) (766) (277)	
Kahn 1966 U.S.A. (*93*).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	10,890	NS .....1.00 All smokers .1.74 1–9 .....1.39 10–20 .....1.78 21–39 .....1.84 >39 .....2.00	(2997) (4150) (439) (2102) (1292) (266)	
Hirayama, 1967, Japan (*84*).	265,118 Japanese adults over age 40.	Trained interviewers and follow-up of death certificate.	1	91	NS .....1.00 1–24 .....1.13 >25 .....1.00	(17) (69) (5)	
Kannel et al., 1968, U.S.A. (*94*).	5,127 males and females age 30–59.	Medical examination and follow-up.	12	52	NS .....1.00 SM>20 ....2.20	(27) (25)	(p<0.05)

[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.

ratios related to smoking—prospective studies

shown in parentheses)[1]

NS = Nonsmokers]

Cigars, pipes	Age variation					Comments
Cigars		*50–54*	*55–59*	*60–64*	*65–69*	
NS..1.00	NS	1.00 (90)	1.00 (142)	1.00 (204)	1.00 (273)	
SM..1.28 (420)	All smokers	1.93 (765)	1.85 (962)	1.66 (921)	1.41 (713)	
Pipes	<10	1.38 (35)	1.38 (50)	1.17 (49)	1.27 (58)	
NS..1.00	10–20	2.00 (213)	2.04 (258)	1.91 (235)	1.58 (158)	
SM..1.03 (312)	>20	2.51 (203)	2.47 (199)	1.92 (129)	1.56 (73)	
						Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
		35–44	*45–64*	*65–84*		
	NS	1.00	1.00	1.00		
	1–14	3.73	1.40	1.71		
	15–24	4.45	1.73	1.27		
	>25	1.36	1.92	1.58		
NS..1.00 SM..1.45						
Cigars		*30–49*	*50–69*	*70 and over*		
NS..1.00	NS	1.00	1.00	1.00		
SM..0.98 (16)	<10	0.97 (18)	1.56 (220)	1.71 (99)		
Pipes	10–20	1.45 (115)	1.67 (557)	1.29 (94)		
NS..1.00	>20	1.85 (65)	1.76 (184)	1.73 (28)		
SM..0.96 (95)						
Cigars NS..1.00 SM..1.04 (623) *Pipes* NS..1.00 SM..1.08 (386)						
						Preliminary report.

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

TABLE 2.—*Coronary heart disease mortality ratios*

(Actual number of deaths

[SM = Smokers

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day			
Hammond and Garfinkel, 1969, U.S.A. (*76*).	358,534 males 445,875 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	
Paffenbarger and Wing 1969 U.S.A. (*146*)	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		($p<0.01$)
					SM	1.50	(385)	
Paffenbarger et al., 1970, U.S.A. (*144*).	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)	($p<0.01$)
					SM >20	2.08	(154)	
Taylor et al., 1970, U.S.A. (*183*).	2,571 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)	
Weir and Dunn, 1970, U.S.A. (*205*).	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		
					All smokers	1.60		
					±10	1.39		
					±20	1.67		
					>30	1.74		
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	239	NS	1.00	(27)	
					<10	1.65	(34)	
					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.

related to smoking—prospective studies (cont.)

shown in parentheses)[1]

NS = Nonsmokers]

Cigars, pipes	Age variation				Comments
		Males			†Based on 5–9 deaths.
	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	1.00	
	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	—	
	30–44	*45–54*	*55–69*		
	NS 1.00	1.00	1.00		
	(p<0.01)				
	SM 1.80 (88)	1.60 (163)	1.20 (134)		
					Data apply only to those free of CHD at entry.
	35–44	*45–54*	*55–64*	*65–69*	NS includes pipes and cigars. SM includes ex-smokers.
	NS 1.00	1.00	1.00	1.00	
	±10 .....4.22	2.05	1.41	1.17	
	±20 .....6.14	3.17	1.64	1.26	
	±30 .....8.57	3.33	1.66	1.36	
	>40 .....7.93	3.15	1.42	1.42	
	All 6.24	2.95	1.56	1.24	
1.00 (27) 1.20 (24)					

TABLE 3.—*Sudden death from coronary*

(Mortality ratios—actual number

Author year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths
Pooling Project, American Heart Association, 1970, U.S.A. (*88*).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	145

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD

[SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Doyle et al., 1964, U.S.A. (*54*).	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 .....1.00 (52) All smokers ....2.36 (191) <20 .....1.98 (44) 20 .....2.05 (64) >20 ..... 3.04 (83)
Stamler et al., 1966, U.S.A. (*177*).	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 .....1.00 (2) <10 cigarettes. < 5 cigars.... < 5 pipes..... } 2.92 (6) 10–19 cigarettes.3.67 (8) >20 cigarettes. > 5 cigars.... > 5 pipes..... } 3.83 (29)
Epstein, 1967, U.S.A. (*61*).	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* NS .....1.00 (1) EX .....6.53 (10) Cigarettes .....5.20 (36) *Females* NS .....1.00 (21) EX .....0.89 (3) Cigarettes 1.02 (14)

[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.

heart disease related to smoking

of deaths shown in parentheses)

Cigarettes/day	Cigars, pipes	Comment
Never smoked 1.00 (15)	1.00 (15)	See table 1 for description of Pooling Project.
10 .....1.90 (23)	1.36 (13)	
20 .....1.90 (50)		
>20 .....3.36 (44)		

morbidity as related to smoking

manifestations shown in parentheses)[1]

EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation	Comments
		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.
		NS includes ex-smokers. Includes all CHD.
Males—Continued *60 and over* 1.00 (7) 1.27 (11) 1.96 (23) *Females*—Continued 1.00 (47) 1.31 (5) 0.42 (2)	*Males* *40–59* SM ....1.80 (2) *60 and over* SM 0.86 (6)	Reexamination of patients was spread over 1½–6-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.

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD
[SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Jenkins, et al., 1968, U.S.A. (*90*).	3,182 males 39–59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4½	104 myocardial infarctions.	NS .....1.00 (21) EX .....2.47 (15) Current .....2.78 (68) 0–15/day .....†1.39 (45) >16 .....3.06 (59)
Kannel, et al., 1968, U.S.A. (*94*).	5,127 males and females 30–59 years of age.	Medical examination and follow-up.	12	228 myocardial infarctions. 380 CHD.	*Myocardial Infarction* *Males* NS .....1.00 (21) All SM .....1.51 (153) Heavy SM ....1.85 (59) *Risk of CHD (overall)* *Males* NS .....1.00 (61) 1–10 .....1.34 (25) 11–20 .....1.80 (90) >20 .....2.41 (76)
Shapiro et al., 1969, U.S.A. (*172*).	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.	*Males* NS .....1.00 All current ....2.14 cigarettes (p<0.01) <20 .....1.50 >20 .....2.33 >40 .....6.36
Keys 1970 Yugoslavia Finland Italy Netherlands Greece (*111*).	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) All current (>20) 1.31 (103)

[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.*

morbidity as related to smoking (cont.)

manifestations shown in parentheses)[1]
EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

	Pipes, cigars	Age variation						Comments
			39–49		*50–59*			†Includes non-smokers and ex-smokers. NS includes former pipe and cigar smokers.
(p<0.001)		NS.	1.00	(4)	1.00	(6)		
(p<0.001) (comparing 0–15 and 16+)		Current	4.23	(35)	2.26	(33)		
Myocardial infarction—Continued								
Females								
1.00 (31)								
1.71 (23)								
Risk of CHD (overall)—Continued								
Females								
1.00 (89)								
0.86 (18)								
1.29 (18)								
0.93 (3)								
Females	*Males only*	*Males*			*Females*			Total myocardial infarction includes those dead within 48 hours.
1.00	NS 1.00	*35–44*	*45–54*	*55–64*	*35–44*	*45–54*	*55–64*	
2.00	SM 1.82	1.00	1.00	1.00	1.00	1.00	1.00	
(p>0.01)	(p<0.01)	2.47	3.06	1.69	2.25	2.87	1.80	
1.77		0.52 / 3.04	2.15 / 3.29	1.32 / 1.81	1.25	2.31	1.65	
5.92		10.09	7.69	5.30	20.25	11.79	4.07	
								NS include ex-smokers.
								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.

TABLE 4.—*Coronary heart disease*

(Risk ratios—actual number of CHD
[SM = Smokers NS = Nonsmokers

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Taylor, et al. 1970 U.S.A. (*183*).	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 ....1.00 (62) All current 1.77 (150)
Dayton et al., 1970, U.S.A. (*48, 49*).	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 .....1.00 (25) 10–20 .....1.04 (22) >20 .....1.17 (13)
Dunn et al., 1970 U.S.A. (*55*).	13,148 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 14	Total unspecified.	
Pooling Project, American Heart Association 1970, U.S.A. (*88*).	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 ..1.00 (53) <10 .....1.65 (72) 20 .....2.08 (205) >20 .....3.28 (154)
Paul et al., 1963, U.S.A. (*148*).	1,989 Western Electric Co. male workers participating in a prospective study for 4½ years.	Screening examination and history.			*Coronary cases (87)* NS ..... 23 1– 7 ..... 2 8–12 ..... 9 13–17 ..... 6 18–22 ..... 47 23–27 ..... 3 >28 9

[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.

morbidity as related to smoking (cont.)

manifestations shown in parentheses)[1]
EX = Ex-smokers]

PROSPECTIVE STUDIES—Continued

	Pipes, cigars	Age variation			Comments
					All CHD including EKG diagnoses.
					No data on NS as a separate group.
		30–39	*40–49*	*50–59*	† Includes NS, EX, and <20 cigarettes/day.
		†Low SM 1.00(25)	1.00(125)	1.00(157)	‡ >20 cigarettes/day.
		‡High SM 2.17(10)	0.90 (31)	1.41 (53)	Includes all CHD but *excludes death*.
					No data available comparing smokers and nonsmokers.
	1.00(53)				
	1.25(54)				
Noncoronary controls (1,786)					88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.
33					
7					
11					
12					
30					
2					
6					
($p<0.005$)					

studies have shown an increased risk of this manifestation among smokers, others have not (see table 5).

From these longitudinal studies, it has become increasingly clear that cigarette smoking is one of several risk factors for CHD and that it exerts both an independent effect and an effect in conjunction with the other risk factors. The basic concept may be expressed as follows: The more risk factors a given individual has, the greater the chance of his developing CHD. The importance of the constellation of coronary risk factors which include cigarette smoking, high blood pressure, and high serum cholesterol in predicting the risk for CHD is illustrated in figures 1 through 3. Other risk factors are included in certain of these figures and are discussed below.

Knowledge of the effects of cigarette smoke on the cardiovascular system has developed concurrently with the knowledge derived from the epidemiological studies. Nicotine, as well as cigarette smoke, has been shown to increase heart rate, stroke volume, and blood pressure, all most probably secondary to the promotion of catecholamine release from the adrenal gland and other chromaffin tissue. This release of catecholamines is also considered to be the cause of the rise in serum free fatty acids observed upon the inhalation of cigarette smoke. Studies concerning the effect of nicotine on cardiac rhythm have also suggested that smoking might contribute to sudden death from ventricular fibrillation.

In addition, research efforts have also been directed toward the effects of smoking on blood clotting and thrombosis; since many cases of sudden death and myocardial infarction are associated with thrombosis in a diseased coronary artery branch. Cigarette smoking may be associated with increased platelet aggregation *in vitro* and thus might play a role in the development of such thrombi or platelet plugs *in vivo*.

Other mechanisms have been investigated. Because cigarette smoking has been shown in some studies to be related to the prevalence of angina pectoris as well as to the incidence of myocardial infarction, it has been suggested that smoking enhances the development of atherosclerotic lesions. Autopsy and experimental studies have shown that cigarette smoking plays a role in atherogenesis. The administration of nicotine has been observed to increase the severity of cholesterol-induced atherosclerotic lesions in experimental animals. Attention is presently being given to carbon monoxide, which is present in cigarette smoke in such concentrations as to cause carboxyhemoglobin concentrations in the blood of smokers as high as 10 percent. Based on research in animals, it is reasonable to conclude that the atherosclerotic process may be enhanced, in part, by the relative arterial hypoxemia in cigarette

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments
Doyle et al., 1964, U.S.A. (*54*).	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 8	81	NS .....1.00 (30) All .....1.09 (51) <20 .....1.17 (15) 20 .....0.99 (18) >20 .....1.15 (18)			NS include ex-smokers and pipe and cigar smokers.
Jenkins et al., 1968, U.S.A. (*90*).	3,182 males aged 39–59 at entry.	Initial medical examination and follow-up by repeat examination.	4½	29	NS .....1.00 (9) All current cigarettes .....1.44 (16) >16 .....1.63 (14)			NS include *former* pipe and cigar smokers.
Kannel et al., U.S.A. (*94*).	5,127 males and females years of age 30–59	Medical examination and follow-up.	12	107	*Males* NS .....1.00 (16) Heavy SM, >20 cigarettes .....2.04 (17) *Females* NS .....1.00 (58) Cigarette SM 0.65 (16)			
Shapiro et al., 1969, U.S.A. (*172*).	110,000 male and female enrollees of New York City HIP 35–64 years of age.	Baseline medical interview and examination and regular follow-up.	3	Total Unspecified	*Males* *Females* NS .....*1.00* 1.00 Current cigarettes †1.91 1.20 <40 .....1.51 } 1.20 >40 .....4.85 }	*Males* NS...1.00 SM..‡1.71	*Males* *35–44* *45–54* *55–64* NS .....1.00 1.00 1.00 Current cigarettes ..3.40 1.57 2.06 <40 .....2.35 1.40 1.54 >40 .....10.15 2.58 6.15 *Females* NS .....1.00 1.00 1.00 Current cigarettes ..1.56 1.67 0.97 <40 .....1.67 1.53 1.04 >40 ..... — 4.12 —	†(p<0.01) ‡(p<0.05) NS include ex-smokers.

[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.

smokers caused by the increased carboxyhemoglobin level.

With respect to the acute event of myocardial infarction, attention has been focused on the role of nicotine. Nicotine stimulates the myocardium, increasing its oxygen demand. Other experiments have demonstrated that in the face of diminished coronary flow (due to partial occlusion from severe atherosclerosis in man or to partial mechanical obstruction in the animal), nicotine does not lead to an increase in coronary blood flow as seen in the normal individual. These effects exaggerate the oxygen deficit when the supply of oxygen has already been decreased by the presence of carboxyhemoglobin. Thus, a marked imbalance between oxygen demand (which has been increased) and oxygen supply (which has been decreased) is created by the inhalation of CO and nicotine. This imbalance may contribute to acute coronary insufficiency and myocardial infarction.

EPIDEMIOLOGICAL STUDIES

Numerous epidemiological studies, both retrospective and prospective, have been carried out in various countries in order to identify the risk factors associated with the development of coronary heart disease (CHD). Many of these studies have included smoking as one of the variables investigated. Tables 2 to 4 present the major findings.

Coronary Heart Disease Mortality

Table 2 lists the various prospective studies concerning the relation of CHD mortality and smoking. These studies demonstrate the dose-related effect of cigarette smoking on the risk of developing CHD. For example, the Dorn Study of U.S. Veterans as reported by Kahn (*93*) reveals progressively increasing mortality ratios, from 1.39 for those smoking 1 to 9 cigarettes per day to 2.00 for those smoking more than 39 cigarettes per day. Although the data are not detailed in the accompanying tables, several of these studies have also shown that increased rates of CHD mortality are associated with increased cigarette dosage, as measured by the degree of inhalation and the age at which smoking began. Although not as striking, the data for females reveal the same trends.

In most studies, the smokers' increased risk of dying from CHD appears to be limited mainly to those who smoke cigarettes. Some studies that have investigated other forms of smoking have shown much smaller increases in risk for pipe and cigar smokers when compared to nonsmokers. However, the recent study by Shapiro, et al. (*172*) of a large population enrolled in the Health Insurance Plan (HIP) of New York City showed a significantly increased

risk for the development of myocardial infarction and rapidly fatal myocardial infarction for a group consisting of both pipe and cigar smokers.

Table 3 details the findings of the American Heart Association Pooling Project on sudden death. The Pooling Project, a national cooperative project of the AHA Council on Epidemiology, is described in table 1 (*88*). Cigarette smokers in the 30 to 59 year age group incurred a risk of sudden death from CHD substantially greater than that of nonsmokers. Pipe and cigar smokers were observed to show a risk slightly greater than that of nonsmokers (table 3).

The relative risk of CHD mortality is greatest among cigarette smokers (as well as among those with other risk factors) in the younger age groups and decreases among the elderly. In table 2, Hammond and Horn found that for those smoking more than one pack per day, the risk is 2.51 in the 50 to 54 year age group and 1.56 in the 65 to 69 year age group. Although the relative risk for CHD among smokers decreases in the older age groups, the actual number of excess deaths among smokers continues to climb since the differences in death rates between smokers and nonsmokers continue to rise.

Coronary Heart Disease Morbidity

Tables 4 and 5 list the prospective studies carried on in a number of countries to identify the risk of CHD morbidity incurred by smoking. Here, CHD morbidity includes myocardial infarction as well as angina pectoris. Certain studies, notably those of Doyle, et al. (*54*), Keys, et al. (*111*), and Taylor, et al. (*183*) include a number of CHD deaths in their data that could not be separated out using the information provided in their respective reports. As noted in the discussion on CHD mortality, the CHD risk ratio increases significantly as the number of cigarettes smoked per day increases. Similarly, the HIP data of Shapiro, et al. (*172*) show that the elevated morbidity ratios declined with increasing age as has been shown for mortality ratios.

A recent monograph edited by Keys (*111*) dealt with the 5-year CHD incidence in males age 40 to 59 from seven countries. As summarized in table 4, cigarette smoking was found to be associated with an increased incidence of CHD in the U.S. railroad worker population, 2,571 individuals (*183*). None of the differences in ratio between smokers and nonsmokers was statistically significant for the 13 other population samples which varied in size from 505 to 982 individuals, from the five other countries. (Smoking was not considered in the two Japanese populations.) When more cases

become available to provide greater statistical stability to the rates, this intercultural comparison should prove illuminating.

The results of those studies which have separated out angina pectoris as a manifestation of CHD are presented in table 5. Doyle, et al. (*54*) found no relationship between this manifestation of CHD and cigarette smoking. Both Jenkins, et al. (*90*) and Kannel, et al. (*94*) observed increased risk ratios among male cigarette smokers although these differences were not statistically significant. More recently, Shapiro, et al. (*172*) found a significantly increased risk for angina among their male cigarette smokers as well as increasing risk ratios with increasing dosage among both males and females, particularly in the younger age groups. A variety of hypothetical explanations have been advanced to account for this seeming contradiction. Among these are the relatively small number of cases, the difficulties associated with the definitive diagnosis of the syndrome, and differences in the methods of classifying those cases of angina pectoris which are followed by myocardial infarction.

Retrospective Studies

Table A6 presents data from the various retrospective studies of CHD prevalence. Most of these are case-control studies and show an increased percentage of smokers among those with clinical CHD when compared with a selected control population, usually without apparent CHD. Two of these studies include data on mortality.

The Interaction of Cigarette Smoking and Other CHD Risk Factors

The preceding section has reviewed the epidemiologic evidence which supports the judgment that cigarette smoking is a significant risk factor in the development of CHD. Many of the studies discussed above have identified a number of biochemical, physiological, and environmental factors, other than cigarette smoking, which also increase the risk of developing CHD. These risk factors include elevated serum lipids (particularly serum cholesterol) and hypertension, which, with cigarette smoking, are considered to be of greatest importance. Other factors are obesity, physical inactivity, elevated resting heart rate, diabetes (as well as asymptomatic hyperglycemia), electrocardiographic abnormalities, and a positive family history of premature CHD (*88*).

A number of these studies have also found that these factors, when present in the same individual, exert a combined effect on the risk of developing CHD. Figures 1 through 3 depict this interaction of risk factors. As may be noted in Figures 1 and 2, the

additional factor of smoking greatly increases the risk of developing CHD among those people already at high risk because of other factors.

Furthermore, these studies have shown that the effect of smoking on the risk of developing CHD is statistically independent of the other risk factors. That is, when the effect of the other factors is statistically controlled, smoking continues to exert a significant effect on increasing the risk of developing and dying from CHD.

Smoking and Serum Lipids

The interaction of smoking and serum lipid levels in the development of CHD should be considered in the light of information concerning the relationship of smoking to serum lipid levels. Table A7 presents studies which deal with the association between smoking and lipids, notably cholesterol, triglycerides, and lipoproteins (concerned with lipid transport). While some of the studies have indicated that smokers show increased serum levels of these lipid constituents, others have not. The populations investigated and the methods of the various studies show significant variation. This lack of comparability makes interpretation of the findings difficult.

It is clear, however, that in the presence of high serum cholesterol, cigarette smoking increases the risk of CHD. Figure 4 depicts the data from the Chicago Peoples Gas, Light and Coke Company study which show that smoking greatly increases the risk of CHD in each of the cholesterol groups.

Smoking and Hypertension

Some epidemiological studies have indicated that smokers tend to have lower mean systolic and/or diastolic blood pressures than nonsmokers, while other studies have not found this to be the case (table A8). Reid, et al. (*155*), in a study of 1,300 British and American postal workers, found that the blood pressure difference between the smoking and nonsmoking groups was eliminated after controlling for body weight.

Tables 9 through 11, derived from the study by Borhani, et al. (*27*), demonstrate the following associations: That for both smokers and nonsmokers, the risk of dying from CHD increases with increasing diastolic or systolic pressure, and that the risk of mortality from CHD is higher among smokers than among nonsmokers in each blood pressure group. Cigarette smoking, therefore, has been shown to elevate CHD mortality independently both of its effect on blood pressure and of the effect of hypertension on CHD.

Smoking and Physical Inactivity

The recent study by Shapiro, et al. (*172*) of more than 110,000

TABLE 9.—*Death rates from coronary heart disease, by systolic blood pressure: ILWU mortality study 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Systolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–54	<130	1,877	27	2,413	8
	130–149	2,066	34	2,912	17
	150–169	740	95	1,177	26
	>170	369	109	672	45
55–64	<130	1,067	84	1,550	[2]6
	130–149	1,380	94	2,401	[3]25
	150–169	647	93	1,558	45
	>170	524	210	1,117	125

[1] Rate per 10,000 person-years of observation.

[2] $p<0.025$.

[3] $p<0.01$

SOURCE: Borhani, N. O., et al. (27).

TABLE 10.—*Death rates from coronary heart disease, by diastolic blood pressure: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Diastolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–54	<80	1,527	26	1,700	6
	80– 89	2,115	47	2,947	17
	90– 99	961	52	1,507	33
	>100	448	89	1,020	20
55–64	<80	1,059	104	1,447	[2]21
	80– 89	1,521	59	2,704	15
	90– 99	669	194	1,521	[3]46
	>100	369	163	954	147

[1] Rate per 10,000 person-years of observation.

[2] $p<0.05$.

[3] $p<0.01$.

SOURCE: Borhani, N. O., et al. (27).

TABLE 11.—*Death rates from coronary heart disease, among hypertensives and nonhypertensives: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Blood pressure status [1]	Smokers: Person-years of observation	Smokers: Death rate [2]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate [2]
45–54	Hypertensives	883	125	1,871	[3]32
	Nonhypertensives	4,169	29	5,303	13
55–64	Hypertensives	931	150	2,219	95
	Nonhypertensives	2,687	93	4,407	[3]16

[1] According to the WHO recommendation, the following cut-off points are recommended for the definition of hypertension:

(1) Normotension—below 140/90 mm. Hg.

(2) Hypertension—systolic blood pressure 160 mm. Hg. or over, or diastolic 95 mm. Hg. or over, or both.

(3) Borderline—the residual category. In this analysis, Normotensives and Borderlines were combined and the population was grouped into 'Nonhypertensives' (1 and 3) and 'Hypertensives' (2).

[2] Rate per 10,000 person-years of observation.

[3] $p<0.01$.

SOURCE: Borhani, N. O., et al. (27).

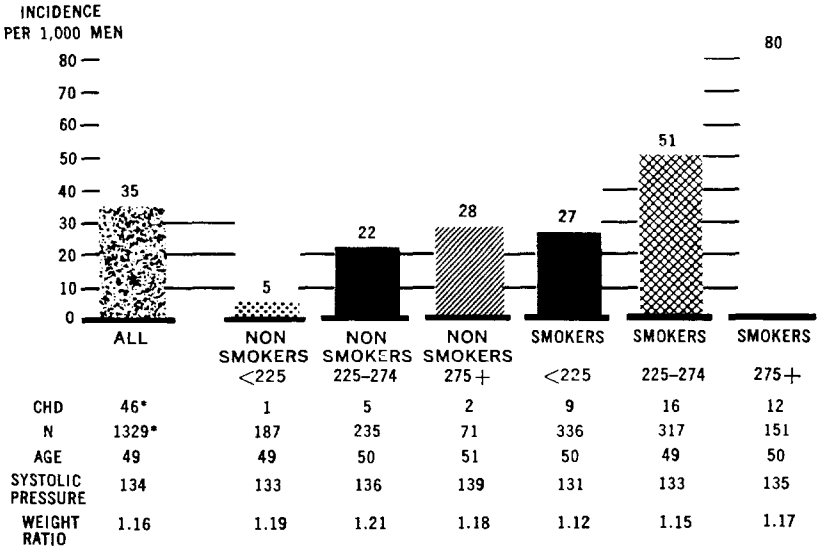


FIGURE 4—Relationship between smoking status and serum cholesterol level at initial examination, and incidence of clinical coronary heart disease in men originally age 40–59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958–1962. *For 34 men, no information on smoking status was available; one of these men had a coronary episode.

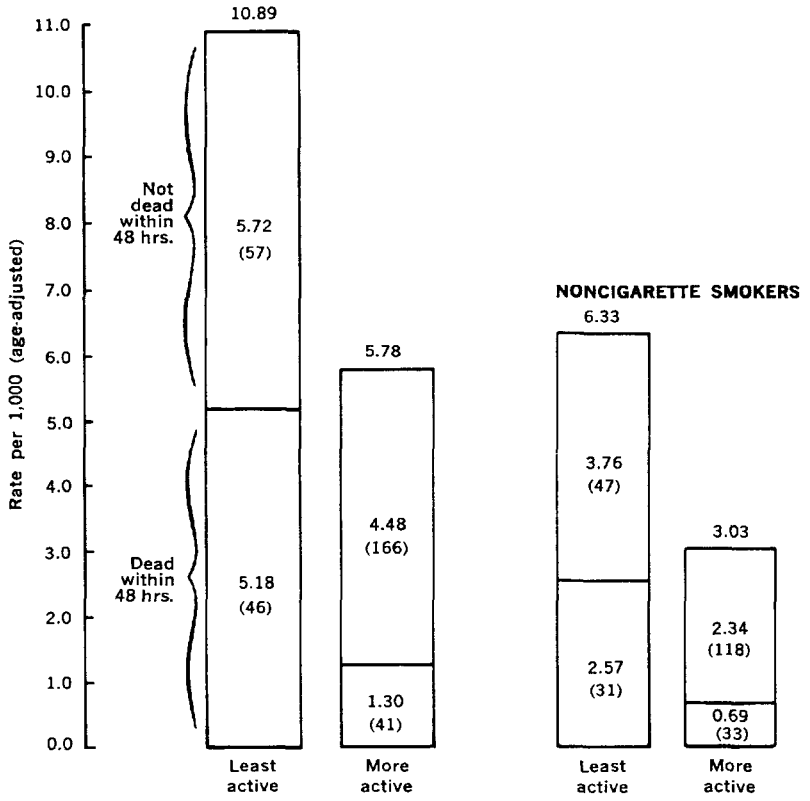
SOURCE: Stamler, J., et al. (*177*).

persons participating in the Health Insurance Plan of New York City has further identified and elaborated upon the interaction of the various risk factors. Physical inactivity, both in employment and during leisure time, was found to be a potent risk factor for the development of CHD, particularly for rapidly fatal myocardial infarction.

Figure 5 depicts the effect which smoking exerts on CHD in combination with physical inactivity. Of note, also, is the observation that within each activity grouping, smoking greatly increases the risk of myocardial infarction, thus exerting an independent effect.

Smoking and Obesity

The analysis by Truett, et al. (*190*) of the risk factor data from the Framingham study revealed that weight, while a significant risk factor, had a considerably smaller effect on CHD incidence than serum cholesterol, cigarette smoking, or elevated blood pressure. The results concerning the interaction of smoking and obesity from the San Francisco longshoremen study are shown in table 12.



Note: Both for cigarette smokers and noncigarette smokers differences between rates among the least and more active men are statistically significant for total MI and rapidly fatal MIs at the 0.99 confidence level. For other MIs the difference is statistically significant only for the nonsmokers (confidence level 0.95).

FIGURE 5—Average annual incidence of first myocardial infarction among men in relation to overall physical activity class and smoking habits (age-adjusted rates per 1,000)

(Actual number of deaths or myocardial infarctions are represented by figures in parentheses)

SOURCE: Shapiro, S., et al. (*172*).

This table shows that cigarette smokers in the 55 to 64 year age group were observed to have higher CHD death rates than nonsmokers in all weight categories. Similar findings, although not in all weight groups, were observed for the 45 to 54 year age group. Cigarette smoking is thus shown to be a CHD risk factor independent of body weight.

TABLE 12.—*Death rates from coronary heart disease among men without abnormalities related to cardiopulmonary diseases by weight classification in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Weight classification [1]	Smokers: Person-years of observation	Smokers: Death rate [2]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate [2]
45–54	Not overweight	388	21	279	7
	Slightly overweight	962	28	1,096	0
	Moderately overweight	1,383	28	1,574	28
	Markedly overweight	1,055	22	1,797	0
55–64	Not overweight	222	43	247	0
	Slightly overweight	536	75	605	36
	Moderately overweight	855	109	1,320	[3]11
	Markedly overweight	735	88	1,653	[3]12

[1] The four classes are defined in the text.
[2] Rate per 10,000 person-years of observation.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (*27*).

TABLE 13.—*Death rates from coronary heart disease, by electrocardiographic findings in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Electrocardiographic findings in 1951	Smokers: Person-years of observation	Smokers: Death rate [1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate [1]
45–54	Abnormal	586	102	1,020	39
	Normal	4,454	38	6,134	15
55–64	Abnormal	583	223	1,149	96
	Normal	3,031	86	5,479	[2]31

[1] Rate per 10,000 person-years of observation.
[2] $p<0.005$.
SOURCE: Borhani, N. O., et al. (*27*).

TABLE 14.—*1958 status with respect to heart rate, blood pressure, cigarette smoking, and 10-year mortality rates, by cause (1,329 men originally age 40–59 and free of definite coronary heart disease) Peoples Gas Co. Study, 1958–68*

1958 risk factor status				Ten-year mortality, 1958-68			
				All causes		CHD	
Heart rate	Cigarette smoking	Diastolic pressure	Number of men	Number	Rate	Number	Rate
NH	NH	NH	378	20	[1]48.3	5	[1]12.0
H	NH	NH	45	6	114.9	3	70.3
NH	NH	H	107	14	118.3	6	51.8
H	NH	H	30	8	221.6	3	52.0
NH	H	NH	491	57	115.8	19	38.9
H	H	NH	127	22	171.1	8	62.3
NH	H	H	103	22	190.4	6	55.0
H	H	H	44	13	265.4	5	94.9
All			[2]1,325	162	113.2	55	39.4

[1] Rate per thousand. All rates are age-adjusted by 5-year age groups to U.S. male population, 1960. High (H): Heart rate ≧80; ≧10 cigarettes per day; diastolic blood pressure ≧90 mm. Hg. NH is not high, i.e., below specified cutting points.
[2] No smoking data available on 4 of the 1,329 men.
SOURCE: Berkson, D. M., et al. (*23*).

TABLE 15.—*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, reference	Results			Comments
		All CHD events	*All myocardial infarction*	
Jenkins et al., 1968 U.S.A. (*90*).	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. (*76*).	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 (263)	1.28 (564)	
		Total definite myocardial infarction		
Shapiro et al., 1969, U.S.A. (*172*).	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. (*88*).	Never smoked	1.00 (27)	1.00 (53)	See table 4 for description of Pooling Project.
	>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)	

TABLE 16.—*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: Current smokers	Age started smoking 15–19: Discontinued for five or more years	Age started smoking 20–24: Current smokers	Age started smoking 20–24: Discontinued for five or more years
		(Probability $\times 10^5$)			
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: Cornfield, J., Mitchell, S. (*45*).

Based on data derived from Kahn, H. A. (*93*).

Smoking and Electrocardiographic Abnormalities

Electrocardiographic (ECG) abnormalities such as T-wave and ST-segment changes as well as a number of arrhythmias are useful indicators of CHD and may, therefore, be predictive of the development of clinically overt CHD manifestations. The results summarized in table 13, from the prospective study by Borhani, et al. (*27*), reflect the joint predictive value of smoking and ECG abnormalities on the death rate from CHD.

Smoking and Heart Rate

Recent analysis by Berkson, et al. (*23*) of the data derived from the Chicago Peoples Gas, Light and Coke Company study of middle-aged men revealed that resting heart rates of 80 or greater were associated with an increase in the risk of death from CHD. These authors found that this association was independent of the other major coronary risk factors.

Table 14 presents the interaction between smoking, blood pressure, and elevated heart rate in increasing the risk of CHD mortality. This study shows that cigarette smoking increases CHD risk in the presence of elevated heart rate as well as in its absence.

THE EFFECT OF CESSATION OF CIGARETTE SMOKING ON CORONARY HEART DISEASE

A number of epidemiological studies have been concerned with the CHD incidence and mortality among ex-cigarette smokers as compared with current smokers (*51, 76, 88, 90, 93, 172*). These studies are listed in table 15. Table 16 presents the data derived by Cornfield and Mitchell (*45*) from the Dorn Study of U.S. Veterans (*93*).

Ex-cigarette smokers show a reduced risk of both myocardial infarction and death from CHD relative to that of continuing cigarette smokers. The Pooling Project (*88*) and the Western Collaborative Study Group (*192*) which adjusted for the other risk factors of elevated serum cholesterol and blood pressure observed this relationship. Hammond and Garfinkel (*76*) noted that cessation of smoking is accompanied by a relative decrease in risk of death from CHD within 1 year after stopping.

This decreased risk of CHD among ex-smokers further strengthens the relationship between smoking and CHD. It must be noted, however, that the group of ex-smokers is composed of individuals who have stopped smoking for a variety of reasons. Those who stop because of ill health and the presence of symptoms are generally at high risk and can bias the group results in one direction;

those healthy persons who stop as part of a general concern about their health and may adopt a number of self-protective health practices are generally at low risk and can bias the group results in the other direction. Therefore, ex-smokers as a group are not fully representative of the entire population of smokers and may have limited value in predicting what would happen if large numbers of cigarette smokers stopped smoking purely for self-protection. Certain incidence studies, such as the Pooling Project (*88*), were initiated with only clinically healthy individuals. The data from such studies, as well as those from the British physicians study, contain ex-smoker data less influenced by these biases.

Fletcher and Horn (*63*) have recently presented data derived from the British physicians study of Doll and Hill. Over the past 10-15 years, cigarette smoking rates among British physicians have declined significantly in comparison with those of the general British population. The information presented by these authors concerning all cardiovascular diseases showed that for individuals between the ages of 35 and 64, the age-adjusted death rate for CHD declined by 6 percent among physicians and rose by 10 percent among the male population of England and Wales during the period from 1953–57 to 1961–65.

THE CONSTITUTIONAL HYPOTHESIS

The effect of smoking on the incidence of CHD has been found to be independent of the influence of the other CHD risk factors. When such risk factors as high serum cholesterol (*177*), increased blood pressure (*27*), elevated resting heart rate (*23*), physical inactivity (*172*), obesity (*27*), and electrocardiographic abnormalities (*27*) have been controlled, cigarette smokers still show higher rates of CHD than nonsmokers.

It has been suggested by some (*39*, *170*) that the relationship between cigarette smoking and CHD has a constitutional basis. That is people with certain constitutional make-ups are more likely to develop CHD, and the same people are more likely to smoke cigarettes. This hypothesis maintains that the relationship between cigarette smoking and CHD is thus largely fortuitous and that the significant relationships are between the genetic make-up of the individual and CHD and between the genetic make-up of the individual and his becoming a cigarette smoker. Two sets of epidemiologic data bear on this hypothesis.

It has been maintained that people with a certain temperament are more likely to smoke and also more likely to develop CHD. These characteristics have been demonstrated for those with the

Type A behavior pattern of Rosenmann, et al. (*159*) which is characterized by competitiveness, excessive drive, and an enhanced sense of time urgency. The prospective study organized by the Western Collaborative Group indicates that individuals who exhibit this type of personality are more likely to have or develop CHD than those without it (Type B), whether or not they smoke. When the incidence rates of CHD are analyzed with respect to smoking and personality types (tables A17, A18), it is noted that in both Type A and Type B individuals the incidence of CHD is greater among cigarette smokers than among nonsmokers. This research indicates that both personality type, as measured in these studies, and cigarette smoking contribute independently as risk factors to the development of CHD. To what extent such behavior patterns are determined constitutionally or represent acquired characteristics is still open to question.

The other type of research designed to study the genetic hypothesis has made use of data from registries of twins. Cederlof, et al. (*37, 38, 39, 40*) have utilized the Twin Registries of Sweden and the Veterans Follow-Up Agency of the U.S. National Academy of Sciences–National Research Council to investigate the relative contributions of heredity and smoking to cardiovascular and bronchopulmonary symptom prevalence. Data obtained by mailed questionnaires were analyzed for the following characteristics: zygosity of the same-sex twin pair, urban-rural residence differences, smoking concordance, and history of various symptoms. Comparisons were made between smoking discordant monozygotic (identical) pairs and smoking discordant dizygotic (fraternal) pairs, and between unmatched twin pairs and matched twin pairs. Smoking discordance has been defined somewhat differently in various reports but, in general, describes twin pairs in which the smoking habits differ between the two members of the same twin pair.

Analyzing the data obtained from 9,319 Swedish twin pairs (72.3 percent of the possible respondents), Cederlof, et al. (*39*) found that respiratory symptoms were more common among smokers in both the unmatched and matched smoking discordant twin pair groups. The authors analyzed the data in two distinct manners. Group A analysis, which did not control for genetic factors utilized two groups; the first composed of all the firstborn, and the second of those listed second on the birth certificates. Group B analysis utilized MZ and DZ twin pairs which were discordant for smoking, thereby controlling genetic factors. "Angina pectoris," as defined by a certain pattern of responses to the questionnaire, was found to be more prevalent among smokers in Group A, but this difference was not present when the data from Group B were analyzed. Males in the first group exhibited a "hypermorbidity ratio"

of 1.6, while those in the second group were found to have one of approximately 1.1. The authors concluded that this difference between the two groups provides better support for the importance of constitutional factors as against the importance of cigarette smoking in the development of angina pectoris.

A similar study was done using the responses of 4,379 U.S. Veteran twin pairs (approximately 60 percent of estimated available total) who completed the mailed questionnaires (*38*). Cederlof, et al. found a significantly increased prevalence of chest pain and "angina pectoris" among smokers when Group A was analyzed. Analysis of the smoking-discordant matched twin pairs (Group B) revealed no association between smoking and cardiovascular symptoms among the monozygotic pairs. The dizygotic pair data did show a slight association. The authors concluded that this lack of association among the monozygotes and its presence among the dizygotes and unmatched pairs strengthens the case for a constitutional hypothesis.

A major problem in these studies is the small number of cases available and, therefore, the statistical instability of the results. In the Swedish study, among the 274 monozygotes, only 19 smokers and 16 nonsmokers were classified as having angina pectoris while among the 733 dizygotes, 25 smokers and 25 nonsmokers were so classified. In neither group was the difference between the prevalence ratios found in the Group A analysis and that in the Group B analysis of statistical significance. Analysis of the data on women shows a similar lack of significance.

Similar criticisms may be made of the study which utilized the U.S. Veteran Twin Registry. In that study, the authors observed that the difference in the prevalence of angina pectoris between the low-cigarette-exposure and high-cigarette-exposure dizygotic groups was not present among the monozygotes. The authors questioned whether the excess morbidity associated with cigarette smoking found in the dizygotic group was causal as it was not possible to reproduce the association when studying monozygotic smoking-discordant twin pairs. As noted above, the numbers in this study are also small so that the differences in rates do not approach statistical significance.

Tibblin (*188*) has questioned the value of a mailed questionnaire to diagnose heart disease. The questionnaire as originally constructed was used and validated by interview technique alone (*157, 158*). Cederlof, et al. (*40*) conducted a study to determine the validity of this questionnaire as a mailed instrument by personally interviewing and examining 170 of the twin pairs who had replied. Of the eight males who were diagnosed as having "angina pectoris" by the questionnaire, four were found to be free of symptoms on