hypercholesterolemia (elevation of the blood cholesterol level) is a health problem because it predisposes to diseases that cause significant morbidity and mortality.

Diseases Associated With hypercholesterolemia

Stroke

Stroke refers to brain injury that results from inadequate blood flow to the brain. Common causes include congenital abnormalities of cerebral arteries and hypertensive damage to cerebral blood vessels. In addition, atherosclerosis can cause stroke in three ways: atherosclerotic deposits can block arteries carrying blood to the brain; fragments of the deposits in the major arteries to the brain or elsewhere can dislodge and block smaller arteries; or atherosclerotic deposits can develop in small vessels in the brain causing hemorrhage and stroke. The role of atherosclerosis in the sequence of events leading to a stroke has led many to suspect that hypercholesterolemia might be a risk factor for this syndrome.

Stroke is important because it is a common cause of death and because nonfatal stroke can lead to severe disability and institutionalization. More than 2.6 percent of all men and 2.2 percent of all women aged 65 and over were admitted to hospitals in 1984 with a diagnosis of cerebrovascular disease. The number of stroke deaths per 100,000 men and women aged 65 and over was 447.7 and 495.1, respectively, in 1984 (121). Stroke is the second most common cause of death in Americans aged 85 and over, and the third most common cause in 65 to 84 year-olds.

Peripheral Vascular Disease

Peripheral vascular disease (PVD) refers to obstructive disease of blood vessels of the extremities. Although some authors include disease of the veins and lymphatic vessels in the definition of PVD, this paper will discuss only disease of the arteries, which is more likely than venous or lymphatic disease to be related to hypercholesterolemia. Most PVD is thought to be due to atherosclerotic occlusion of the arteries supplying blood to the lower extremities.

PVD can affect any large artery of the extremities. The most common syndromes are intermittent claudication, a severe exercise-related pain in the calves or buttocks; coldness and numbness in an extremity; impotence; and loss of strength in an affected leg. Severe PVD can lead to skin ulceration, gangrene, and loss of the extremity.

The prevalence of symptomatic PVD is uncertain. Since many individuals with severe PVD have concomitant diabetes and/or coronary heart disease (CHD), it has been difficult to discern the independent effect of PVD on mortality. However, it can produce severe disability since even minimal walking may precipitate severe claudication pain.

Coronary Heart Disease

Ischemic or coronary heart disease refers to the clinical syndromes that result from impaired blood flow to the myocardium (heart muscle), Ischemia, or inadequate blood flow, reflects an imbalance between blood supply and demand and is usually associated with obstructive deposits of cholesterol- rich material in the coronary arteries (coronary atherosclerosis). CHD includes angina pectoris, a characteristic chest pain syndrome; myocardial infarction (heart attack); sudden death, or death occurring within an hour of the onset of symptoms and in the absence of a known cause;[1] and coronary insufficiency, or unstable angina, a syndrome of prolonged chest pain associated with electrocardio-

[1] Some authors use a longer time limit for sudden death, including all deaths that occur within 24 hours of the onset of symptoms in the definition.

graphic abnormalities, but lacking the chemical or electrocardiographic evidence of definite myocardial infarction.

CHD is the most common cause of death among adult Americans, and it is a very common disease. Most symptomatic CHD occurs in the elderly; more than 17 percent of men and 11 percent of women aged 65 and over who are not in nursing homes or other institutions report that they suffer from ischemic heart disease (120). In 1984, 8.4 percent of all men and 6.9 percent of all women aged 65 and over were admitted to a hospital because of heart disease (121). Most of these admissions were due to CHD or consequences of CHD, such as congestive heart failure. These admissions accounted for more than 7.6 million and 10 million days of hospital care for men and women, respectively (121). The National Vital Statistics system reported that in 1985 heart disease killed more than 1 percent of all Americans who were between the ages of 65 and 74, 2.7 percent of 75 to 84 year-olds, and 7.3 percent of Americans aged 85 and over (122).

The Distribution of Serum Cholesterol Levels Among Elderly Americans

According to a recent consensus statement from the National Heart, Lung, and Blood Institute (NHLBI) and other experts, serum cholesterol levels of 240 milligrams per deciliter of blood serum (mg/dl) and above are "high-risk" even in the absence of other cardiac risk factors. In the presence of other risk factors, a cholesterol level of 200 mg/dl or more should lead to further evaluation (1 16). As table 1 demonstrates, most adult Americans have cholesterol levels that exceed the "desirable" level of 200 mg/dl or less.

If the 240 mg/dl cutoff is used, about 30 percent of men and 50 percent of women aged 65 to 74 are at high risk. Even at the higher cutoff of 260 mg/dl for high risk proposed by an earlier NHLBI--sponsored consensus conference (11 4), 18 percent of men and 34 percent of women aged 65 to 74 fall into the high-risk category (121). If a "high-risk" cholesterol level mandates treatment, a vast number of elderly Americans will need to undergo therapy.

Evidence That hypercholesterolemia Is Associated With Increased Morbidity and Mortality

Although hypercholesterolemia may contribute to other illnesses, its most important impact is on CHD. Many studies of middle-aged and younger men have demonstrated that the cholesterol level predicts CHD incidence, CHD mortality, and mortality from all causes (39). The evidence comes from international comparisons of CHD incidence and death rates (66), as well as epidemiologic and clinical studies. This section describes the evidence that the cholesterol level is a predictor of the incidence of stroke, peripheral vascular disease, and CHD, and of mortality from CHD and from all causes.

Serum Cholesterol as a Predictor of Stroke Incidence

Because there are substantial similarities between the pathology of atherosclerosis of the coronary arteries and the lesions responsible for stroke, many authors have suggested that hypercholesterolemia may be an independent predictor of morbidity from stroke. Three main lines of evidence are available to test this hypothesis. First, several authors have compared the cholesterol levels in stroke victims to those without strokes. A binational cooperative study compared stroke victims to controls in Japan and Minnesota (14) and found no difference in the cholesterol levels of the cases and controls within each country. A report on stroke in adults less than 50 years old (35) found no difference between the cholesterol levels of the victims and local population averages.

More direct evidence comes from longitudinal studies that have examined cholesterol as a predictor of stroke. The Honolulu Heart

Table 1.-- Mean Serum Cholesterol Levels of Men and Women, SEM, Age-Adjusted Values, Selected Percentiles, Number of Examined Persons, and Estimated Population, by Race and Age: United States, 1978-1980

Age	Number of persons examined	Estimated population in thousands	Mean	SEM	Percentile[a] 5th	10th	15th	25th	50th	75th	85th	90th	95th
Men													
All races:													
20-74	5604	63611	211	1.2	144	156	165	179	206	239	258	271	291
20-24	676	9331	180	1.7	129	136	145	155	176	202	215	227	246
25-34	1067	15895	199	1.5	141	152	159	172	194	220	240	254	275
35-44	745	11367	217	2.0	153	166	173	187	215	244	262	275	293
45-54	690	11114	227	1.8	159	176	182	197	223	255	271	283	303
55-64	1227	9607	229	1.8	164	176	184	198	225	254	277	288	307
65-74	1199	6297	221	1.8	153	167	175	191	217	249	265	279	301
White:													
20-74	4883	55808	211	1.2	145	157	166	179	207	239	258	271	291
20-24	581	8052	180	1.8	131	138	146	155	176	202	216	229	244
25-34	901	13864	199	1.7	144	153	161	172	194	220	239	254	273
35-44	653	9808	217	1.8	153	166	173	187	214	244	260	272	291
45-54	617	9865	227	1.8	160	177	181	198	222	254	271	283	303
55-64	1086	8642	230	2.0	164	178	185	199	225	255	278	289	307
65-74	1045	5576	222	2.0	153	167	175	191	217	250	266	281	301
Black:													
20-74	607	6102	208	2.5	133	146	156	171	200	238	260	273	301
20-24	79	1043	171	3.7[b]	b	128	134	149	170	193	210	211	b
25-34	139	1546	199	4.1[b]	129	136	144	163	192	226	248	259	301
35-44	70	1112	218	8.3[b]	b	156	168	176	202	238	275	283	b
45-54	62	1044	229	7.1[b]	b	174	184	195	232	261	268	279	b
55-64	129	801	223	4.8[b]	157	168	172	183	218	254	271	299	312
65-74	128	555	217	4.2	149	163	173	183	216	244	261	277	299
Age-adjusted values:													
All races, 20-74	MA	MA	211	1.1	MA	MA	MA	MA	MA	NA	MA	MA	MA
White, 20-74	MA	MA	211	1.1	MA	NA	NA	MA	MA	MA	MA	MA	MA
Black, 20-74	MA	MA	209	2.5	MA	NA	MA	NA	NA	NA	MA	MA	MA
Women													
All races:[b]													
20-74	6260	69994	215	1.2	143	156	166	179	210	245	266	282	305
20-24	738	9994	184	1.9	132	140	145	157	180	204	216	230	250
25-34	1170	16856	192	1.4	135	145	154	164	188	215	233	243	263
35-44	844	12284	207	1.8	147	158	164	177	202	231	248	260	276
45-54	763	11918	232	2.2	164	178	188	199	228	257	275	290	306
55-64	1329	10743	249	2.0	180	193	203	215	242	277	299	314	336
65-74	1416	8198	246	1.6	173	189	198	214	241	274	295	309	327
White:													
20-74	5418	60785	216	1.3	143	156	166	179	210	246	267	282	305
20-24	624	8408	184	2.1	133	140	147	159	181	204	215	230	249
25-34	1000	14494	192	1.5	135	145	153	164	188	215	235	244	261
35-44	726	10584	207	1.9	147	157	164	177	203	231	248	250	277
45-54	647	10369	232	2.6	166	179	188	199	228	257	274	290	308
55-64	1176	9601	249	1.7	180	193	203	215	244	277	298	312	330
65-74	1245	7329	246	1.7	174	190	199	214	242	275	296	309	328
Black:													
20-74	729	7579	212	3.1	140	154	166	176	205	237	263	279	308
20-24	94	1304	185	4.9[b]	b	136	144	156	178	204	220	237	b
25-34	145	1953	191	4.1	129	144	156	167	190	212	226	235	267
35-44	103	1415	206	4.5[b]	143	158	170	175	194	233	254	274	279
45-54	100	1215	230	7.2[b]	150	172	181	200	226	263	277	291	306
55-64	135	959	251	8.0[b]	178	185	198	211	233	280	318	336	345
65-74	152	733	243	4.2	173	189	198	211	237	269	290	308	322
Age-adjusted values:													
All races, 20-74	MA	MA	215	1.2	MA	MA	MA	MA	MA	MA	MA	MA	NA
White 20-74	MA	MA	215	1.2	MA	MA	MA	MA	MA	MA	MA	MA	MA
Black 20-74	MA	MA	214	2.7	MA	MA	MA	MA	NA	MA	MA	MA	MA

[a]Serum cholesterol values are given in milligrams per deciliter. To convert values to millimoles per liter, multiply by 0.02586.

[b]Includes data for races not shorn separately.

ABBREVIATIONS: SEM = standard error of the mean, NA = not applicable.

SOURCE: Reproduced from Adult Treatment Panel, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institute of Health, U.S. Department of Health and Human Services, "Report of the National Cholesterol Education Program Expert Panel on Detection, Evacuation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern Med. 148:36-69, 1988.

Program reported a statistically significant U-shaped association between cholesterol and subsequent incidence of stroke (97). Stroke rates were higher at both very low and high cholesterol levels than for cholesterol levels in the middle range. However, in a similar analysis of transient ischemic attacks (a stroke-like syndrome that resolves within 24 hours), the predictive ability of cholesterol disappeared when hypertension and cigarette smoking were considered (98).

Westlund (127) and Balodimos (1 1) each reported that cholesterol is a significant predictor of stroke when examined alone (i.e., in a univariate analysis). Another univariate analysis, a 10-year followup of residents of Shikoku Island, Japan found no association between cholesterol and stroke (109). None of these reports included a multivariate analysis. Only a multivariate analysis, which measures the independent or separate effects of each of several risk factors, can distinguish the effect of cholesterol from the effect of other risks, such as cigarette smoking, that are also correlated with the cholesterol level.

Studies that control for the impact of other potential risk factors suggest that cholesterol is not independently associated with the risk of stroke. Two Italian reports of fatal and nonfatal strokes in men between 40 and 59 years of age found no independent role for cholesterol as a risk factor (33,86). A 7-year followup of a cohort of adults 35 to 39 years old in Eastern Finland found hypertension, age, tobacco use, prior stroke, and diabetes to be independent predictors of stroke, while the independent association with cholesterol was not significant (102), A 13-year study of 50-year-old men found that the diastolic blood pressure, smoking habits, and the erythrocyte sedimentation rate were significant predictors (3). Once again, the association with cholesterol was insignificant. An 8-year followup of adults 40 to 69 years of age in a farming village in Akita, Japan ascribed a similarly insignificant independent role to cholesterol (111). Finally, the Framingham Heart Study (an ongoing prospective epidemiologic study of several thousand adults from Framingham, Massachusetts, that was begun in the late 1940s) found that the cholesterol level was not associated with the risk of stroke except in subjects who also had other risk factors (65). In multivariate analyses of the 2-year risk of stroke from Framingham, the independent effects of the cholesterol level on the risks of stroke and transient ischemic attack were not statistically significant in either men or women with the exception of women aged 65 to 74.

In summary, case-control studies as well as multi variate longitudinal analyses have suggested that the serum cholesterol does not appear to be independently associated with the risk of stroke. The apparent relation between cholesterol and stroke is due to the relation between cholesterol and other variables, particularly smoking and hypertension, that appear to be much stronger predictors of stroke risk.

Serum Cholesterol as a Predictor of Peripheral Vascular Disease Incidence

Just as hypercholesterolemia would be expected to predispose individuals to stroke, it also is a potential risk factor for peripheral artery disease. Few studies have examined whether there is a significant association between cholesterol level and the incidence of PVD.

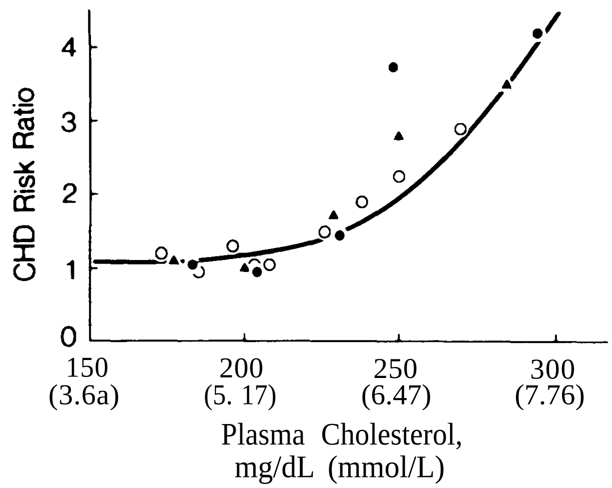
Two studies found that the cholesterol level was a significant predictor of the subsequent development of PVD in univariate analyses, but none of these studies controlled for the effect of other risk factors (1 1, 127), One report from the Framing ham Study found that intermittent claudication, a clinical marker for PVD, was more common in hypercholesterolemic subjects but failed to apply multivariate analysis (45). A recently reported 25-year evaluation of two rural Italian communities found that deaths from PVD were so rare (0,72 percent over 25 years) that no statistical relations to to cholesterol could be determined (86).

Studies could not be located that assessed whether the serum cholesterol level has an association with PVD that is independent of such confounding variables as cigarette smoking and the blood pressure level. Because the serum cholesterol level is associated at the population level with cigarette smoking, the association of cholesterol level and PVD independent of those factors is likely to be smaller than the association found in univariate analyses.

Serum Cholesterol as a Risk Factor for Coronary Heart Disease Incidence and Death

Numerous multi variate studies of middle-aged men have shown that, over a wide range of cholesterol values, the probability that an asymptomatic individual will subsequently develop angina or suffer a myocardial infarction or sudden cardiac death rises in an approximately exponential fashion with his or her cholesterol level. Thus, the same increment in cholesterol has a much more pronounced effect at higher levels than at lower levels of serum cholesterol. For example, among 361,662 men screened in the Multiple Risk Factor Intervention Trial (MRFIT), individuals whose cholesterol exceeded 263,[2] placing them at or above the 90th percentile, had four times the risk of coronary death of the bottom 20 percent, whose cholesterol level was less than 182 (85). In the Whitehall study, the 10-year CHD mortality ranged from 2.85 percent in the lowest quintile, to 3.44 percent in the next lowest quintile, to 5.37 percent in the highest quintile of cholesterol levels (99). A pattern of slowly rising risk of CHD at lower cholesterol levels and rapidly rising risk at higher levels was observed in the Framingham Study (63), which examined CHD incidence, and in a prospective study of Israeli

Figure 1---Relation Between Plasma Cholesterol Level and Relative Risk of Coronary Heart Disease (CHD) in Three Prospective Studies



Key: ● = Framingham Heart study
▲ = Pooling Project
0 = Israeli Prospective Study

SOURCE: Reproduced with permission from S. M. Grundy, "Cholesterol and Coronary Heart Disease," J. A.M.A. 256:2849-58, 1986. Copyright 1986, American Medical Association.

civil servants (41), which examined CHD mortality. The relation between cholesterol level and relative risk of developing CHD in three prospective studies is illustrated in figure 1 (48). Epidemiologic studies have also found that the effect of hypercholesterolemia is highly dependent on the presence of other risk factors. Cholesterol interacts in a synergistic fashion with other risk factors to increase the risk of coronary disease. Cigarette smoking and hypertension, in particular, produce greater increases in CHD mortality in people with hypercholesterolemia than would be predicted on the basis of each risk factor alone (64,93).

It is not certain that these results apply to the elderly. The relation between cholesterol and CHD risk in the elderly will

2 Unless otherwise noted, throughout this document "cholesterol" refers to the serum cholesterol level and is reported in units of mg/dl. Cholesterol levels in many countries are reported in units of mmol/L (S1 units); to convert from mg/dl to mmol/L, multiply by 0.02586.

undoubtedly be clarified when more data become available. Relatively few studies have addressed whether the cholesterol level predicts CHD risk at age 65 or older, although the Stockholm Prospective Study (22), Framingham, and a few others included elderly individuals. Investigators in the Framingham Study reported several years ago that total cholesterol is not a significant risk factor for the development of CHD in the elderly, despite its clear predictive power in younger individuals (44). Two later publications based on 30 years of followup from the Framing ham Heart Study indicated that cholesterol is a risk factor for CHD in elderly women, but not elderly men. In a multivariate logistic regression analysis, Framingham investigators reported that the cholesterol level was not a statistically significant independent predictor of the incidence of CHD among men aged 65 and over, although it was a significant predictor for women (1 15).

The second Framingham publication used Cox-type proportional hazards analysis[3] to relate the development of CHD to putative cardiac risk factors in individuals 65 years of age and over (5 1). For this study, the cholesterol level was divided into four categories: <200 mg/dl; 200 to 239 mg/dl; 240 mg/dl to the 90th percentile (306 mg/dl for women and 275 mg/dl for men); and 90th percentile and above. The risk of CHD was significantly elevated for those individuals whose cholesterol was at the 90th percentile or greater, when men and women were pooled; the elevated risk for those in the category between 240 mg/dl and the 90th percentile reached borderline statistical significance. The association between cholesterol category and risk of CHD was much stronger for women than for men. When men and women were analyzed separately, the risk of developing heart disease was 2.3 times as great for women whose cholesterol exceeded 305 mg/dl as for women whose cholesterol level was less than 200 mg/dl. This risk elevation was statistically significant. There was a trend toward increasing risk of CHD with increasing cholesterol level for both men and women, but aside from the single category of women whose cholesterol levels were in the top 10 percent, the association between cholesterol level and CHD risk did not achieve statistical significance. Thus both of these reports from the Framingham Heart Study suggest that very high cholesterol levels are associated with an elevated risk of developing CHD for elderly women, but not necessarily for the elderly men.

In the Glostrup prospective epidemiologic study of 230 men and 210 women aged 70 and above from nine Danish municipalities, the cholesterol level at age 70 did not predict the development of cardiovascular disease (CVD) during the succeeding ten years, when suspected risk factors that are correlated with cholesterol-- triglycerides, glucose intolerance (diabetes), and a prior history of CVD--were taken into account. CHD was not reported separately; CVD included CHD as well as cerebrovascular disease and intermittent claudication. These results were true for men and women (4,5). In univariate analyses of the Busselton (Australia) Study, the cholesterol level did not predict the development of CHD in the succeeding 6 years among men or women who were 60 years of age or older; multi variate results were not presented (126). A univariate 9-year fol-1OWUP study of Swedish men found that the serum cholesterol level did not predict the subsequent development of CHD among men who were aged 60 or over at the time the cholesterol was drawn (22).

The relation between cholesterol and CHD death rates is similar to the relation with CHD incidence. In the Glostrup study of 70 year-olds (5), the serum cholesterol was not a significant independent predictor of

3 Proportional hazards analysis is a biostatistical method for ana 1 yz i ng the association between r i sk factors and variation in survival (27).

cardiovascular mortality. In the Busselton study, total cholesterol did not predict CHD or CVD mortality in men or women aged 60 to 69, or in men aged 70 and above, although cholesterol was significant at the 5 percent level in predicting CHD mortality among women aged 70 and above (126). In the 30-year followup of the Framingham Study, the serum cholesterol predicted CHD death rates in elderly women, but not in elderly men (1 15).

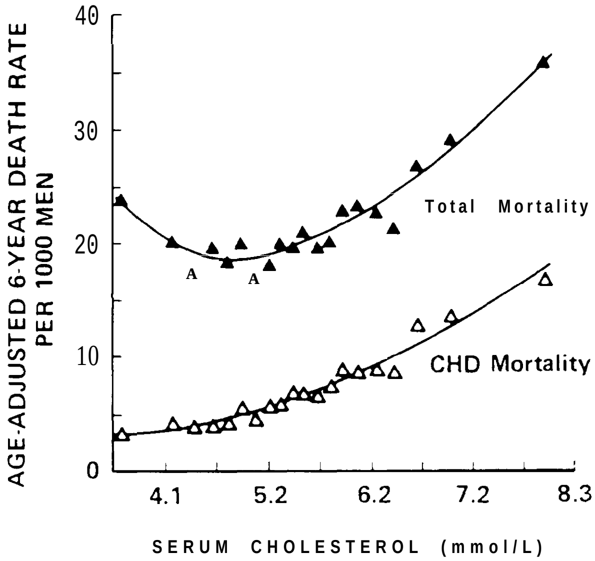
This review located only one published study that found cholesterol is a significant independent predictor of CHD death rates among both elderly men and women. This study, in adults between 50 and 79 years of age in Southern California, reported results of a Cox-type proportional hazards analysis that found that total cholesterol was a significant independent predictor ($p<0.01$) of CHD mortality among men and women aged 65 to 70. Among women aged 65 to 79, it was significant at the 5 percent level. The authors explained the disparity with other studies by noting that they conducted their investigation more recently. Because of falling CHD mortality rates, "subjects with high levels of risk factors [were] no longer weeded out by age 50 or even by age 65. Consequently, the impact of selective mortality may be delayed so that these risk factors still have expression at later ages" (13). Their hypothesis was supported by the low CHD mortality rate in their study population compared to other studies and compared to the general U.S. population (the risk ratios for men and women were 0,40 and 0.27, respectively). Unpublished observations from the Lipid Research Clinics followup study, a major epidemiologic study conducted by several collaborating institutions, also suggest that the total cholesterol level is a significant predictor of CHD incidence and mortality in the elderly (19).

Collectively, these studies demonstrate that the blood cholesterol level is an independent risk factor for the development of CHD in middle-aged men and elderly women. Although it is not certain why cholesterol seems to retain its importance as a risk factor in elderly women more than in elderly men, women begin to develop symptoms of CHD at more advanced ages than men, so from the standpoint of cardiac disease, an elderly woman may bear risks similar to those of a middle-aged man. It is possible that newer studies will confirm that cholesterol is a risk factor in elderly men and women, as the work of Barrett-Connor and colleagues and the results from the Lipid Research Clinics followup suggest. However, there is currently little evidence that cholesterol is a CHD risk factor in men who have reached the age of 65 without manifesting heart disease.

The Serum Cholesterol Level as a Risk Factor for All-Cause Mortality

Does the relation between overall mortality and cholesterol level parallel the relation between CHD risk and cholesterol level? Univariate analyses have found that, for individuals whose cholesterol is below the tenth or twentieth percentile, mortality actually decreases as cholesterol levels increase; at higher cholesterol levels, further increases in cholesterol are associated with rising mortality (see figure 2). The MRFIT study found that middle-aged men whose cholesterol levels were in the bottom decile had a significantly increased rate of cancer death early in the trial (before the intervention could have been responsible for an increased cancer risk). Adjusted for age, smoking status, and randomization group, the MRFIT participants who died of cancer experienced much greater falls in serum cholesterol levels after enrollment than did survivors. Furthermore, the drop in cholesterol was greatest among the men who died of cancer early in the trial, which has been interpreted to mean that cancer causes the serum cholesterol to fall (106), rather than that a falling cholesterol causes cancer. Other large studies have also found that at very low cholesterol levels, declines in cholesterol are associated with increased all-cause mortality. In the Israeli civil servants study, age-adjusted overall mortality at 15 years was

Figure 2--- Age-Adjusted 6-year CHD and Total Mortality per 1,000 Men Screened for MRFIT According to Serum Cholesterol



Entire cohort of 361,662 men was divided into approximate twentieths, and each point represents the mortality (either CHD or total) and the mean cholesterol level in one of those twentieths. Modified lines are drawn through the points.

ABBREVIATION: CHD = coronary heart disease.

SOURCE: Reproduced with permission from M.J. Martin, S.B. Hulley, and U.S. Browner, "Serum Cholesterol, Blood Pressure, and Mortality: Implications From a Cohort of 361,662 Men," Lancet 2:933-936, 1986.

lowest for individuals in the third decile, corresponding to a serum cholesterol of 177 to 187 mg/dl (41). All-cause mortality in the bottom decile, corresponding to a cholesterol level of less than 161 mg/dl, was about the same as mortality in the seventh decile, corresponding to a cholesterol level of 217 to 227 mg/dl,

Not all studies have found a negative association between cholesterol level and noncardiovascular mortality. The inconsistent findings of epidemiologic studies have led some experts to question whether a low cholesterol level is associated with elevated cancer mortality (34,107), but most of the studies were not designed to examine the relation between cardiovascular risk factors and noncardiovascular mortality. More controversial than the existence of an association is its interpretation; many cardiovascular experts doubt that a declining cholesterol level leads to elevated total mortality, while others (104) believe that a low cholesterol level may be more than a preclinical marker of cancer. Whether the low cholesterol level causes cancer or cancer causes the cholesterol level to fall, the relation with total mortality suggests that there is little reason to further reduce an already low cholesterol level in middle-aged men, while rises in their cholesterol levels clearly place them at higher risk if their cholesterol is already elevated.

In the elderly, the total cholesterol level does not appear to be an independent predictor of survival. The few studies that investigated this issue found either that the cholesterol level does not predict total mortality at all (5,8,13) or, in the case of the Framingham Study, that it is a statistically significant predictor of lower mortality for both men and women (l15). The insignificant or negative association may reflect the much higher incidence of death from noncardiovascular causes in old age. For example, among white males in 1985, the death rate from malignant neoplasms between the ages of 35 and 44 was 39.5 per 100,000, while the death rate was 1,061 per 100,000 at ages 65 to 74 and 1,820 per 100,000 between ages 75 and 84 (115). Cancer death rates for white females are lower than for white males but also rise dramatically with age. If cancer, occult or overt, lowers the serum cholesterol, it may cause the association between cholesterol and total mortality to weaken or reverse with age.

In the absence of studies that directly assess the effects of cholesterol reduction in the elderly, further investigation of the reasons for the lack of association (or negative association) between cholesterol level and total mortality in the elderly is important. If the cholesterol level is not associated with mortality in the elderly, and if the development of CHD is only weakly associated with the cholesterol level, the epidemiologic evidence does not confirm that detecting and treating hypercholesterolemia in the elderly will increase their longevity.

Do Other Lipoprotein Levels Predict Mortality and Morbidity in the Elderly?

Cholesterol and triglycerides are the two major lipids that circulate in blood. Both circulate as constituents of lipoproteins. Tests to detect hyperlipoproteinemia include serum cholesterol and triglyceride levels as well as measurements of specific lipoprotein classes (sometimes called "lipoprotein fractions"). Besides the serum cholesterol level, the triglyceride level and the levels of two classes of lipoproteins--HDL and low-density lipoprotein (LDL)--are widely used to assess hyperlipoproteinemia. What is the role of these tests in the identification of individuals at high risk of CHD?

Whether the triglyceride level is an independent risk factor for CHD at any age is controversial. In univariate analyses, the triglyceride level appears to predict CHD risk. However, hypertriglyceridemia is associated with cigarette smoking, obesity, diabetes mellitus, and other potential cardiac risk factors (such as a low HDL level). Among asymptomatic individuals who are not obese, who do not have diabetes or a family history of hyperlipidemia, and who do not have hypercholesterolemia, the triglyceride level does not appear to be an independent risk factor for CHD (12,58,59). Perhaps the most important confirmation of the importance of a risk factor comes from studies that show that health is improved by eliminating the risk factor. It appears that no randomized trials have been conducted of triglyceride reduction alone, but a randomized trial of gemfibrozil, a drug that raises HDL levels and lowers total and LDL cholesterol and triglyceride levels found that the decline in CHD incidence correlated with changes in HDL, LDL, and total cholesterol levels, but not with the fall in triglycerides (84).

Studies of (primarily) nonelderly populations have shown that the level of HDL (sometimes called the "scavenger" or "good" cholesterol) is inversely related to the risk of developing CHD, and that the LDL level is positively related to CHD risk (128). The ratio of LDL to HDL and the ratio of HDL to the serum cholesterol 1evel may also be reliable predictors of cardiac risk (62). Most commonly, the HDL and LDL levels are viewed as adjuncts to the measurement of serum cholesterol; many experts recommend first obtaining a serum cholesterol level and then determining HDL and LDL levels if the cholesterol is elevated. Usually the LDL is a calculated value that requires a serum cholesterol measurement (see below), so the LDL cannot be substituted for a cholesterol measurement. The serum cholesterol level is highly correlated with the LDL but not with the HDL level (table 2), so high-risk individuals who have a low HDL level in association with a low serum cholesterol may not be detected if LDL and HDL measurement (referred to as fractionation) is limited to hypercholesterolemic subjects (54,58,75).

Few studies have evaluated the HDL or LDL levels as risk factors for CHD incidence in the elderly, and this review did not locate any studies that reported on the relation between HDL or LDL and either CHD mortality or total mortality in the elderly. Investigators from the Framingham Study reported that HDL was a much better predictor of CHD incidence among the elderly than the total cholesterol level (43). Among men aged 60 to 69, the HDL level was a significant predictor ($p<0.05$) of CHD but it was not significant for men aged 70 to 79. Among women at age 60 to 69 or 70 to 79, the HDL level was not a significant predictor of CHD risk. In these analyses, the LDL level was significant ($p<0.05$) in predicting the risk of CHD among men aged 60 to 69 and 70 to 79, and significant at the 1 percent level in predicting CHD incidence among women aged 60 to 69. Another report from the Framingham Study (44) published the same year stated that both the HDL and LDL choles-

Table 2---Simple Pearson Correlation Coefficients Between Various Plasma Lipids and Lipoprotein Fractions From Various Studies

Study	Correlation between: HDL and TC	HDL and LDL	LDL and TC
Framingham:			
Men (n=1,025)	0.10	-0.04	0.84
Women (n=1,445)	0.07	-0.16	0.88
Ages 49-82 years			
Hawaii:			
Japanese men (n=2,019)	0.03	-0.01	0.78
Ages 50-72 years			
Cooperative Lipoprotein Phenotyping Study:[a]			
Men (n=4,898)	0.03 to 0.18	-0.01 to -0.31	0.78 to 0.88
Women (n=1,683)	0.06 to 0.24	-0.09 to -0.16	0.88 to 0.89
Ages 40-70 years			
MRFIT:			
Men (n=301)	NA	-0.08	NA
Ages 35-57 years			

[a]The correlation coefficients reported for the Cooperative Lipoprotein Phenotyping Study represent the range for the five geographic sites of the study.

ABBREVIATIONS: HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRFIT = Multiple Risk Factor Intervention Trial; TC = total cholesterol; NA = not applicable.

SOURCE: Office of Technology Assessment, 1989; adapted from C.E. Davis, D. Gordon, J. LaRosa et al., "Correlations of Plasma High Density Lipoprotein Cholesterol Levels With Other Plasma Lipid and Lipoprotein Concentrations: The Lipid Research Clinics Program Prevalence Study," Circulation 62(supp.IV):IV-24--IV-30, 1980.

terol levels were highly significant predictors of CHD risk among men and women aged 49 to 82 years. This study did not report the number of participants who were aged 65 and above, nor did it report results for the elderly (aged 65 and over) separately. Because the HDL and LDL levels were not measured as part of the Framingham Study until 1968, the results of both of these publications were based on only about 4 years of followup. A more recent publication from the Framingham investigators, based on 12 years of followup, reported that the HDL cholesterol is a particularly strong indepen-dent predictor of one form of CHD--myocardial infarction--among older women, and is of borderline significance for older men (1).

Taken as a whole, the evidence from the Framingham Study indicates that at least among some groups of the middle-aged and the elderly HDL and LDL levels predict CHD incidence.

Summary

Do the cholesterol level, HDL level, or LDL level predict the risk of significant cardiac events and death among the asymptomatic elderly? The epidemiologic studies that included elderly individuals have found, in some cases, that the total cholesterol level may predict CHD risk among the elderly, but the effect is not nearly as striking or as consistent as the relation among the middle-aged. The relation between cholesterol level and CHD mortality has not been reported as frequently, and here the relation is even weaker. Furthermore, some of the studies that report the relation between cholesterol level and CHD mortality include individuals who have already manifested symptoms (such as angina) or signs (such as hypertension) of heart disease, in whom the relation between cholesterol level and CHD death may be stronger. The HDL and LDL levels may be better predictors of CHD risk in the elderly than the total cholesterol level. The studies that have reported on the association between the total cholesterol level and overall mortality have found that the cholesterol level either is a significant negative predictor of mortality in the elderly (the opposite is observed in middle-aged and younger individuals), or does not predict overall mortality rates at all.

Why does the relation between cholesterol and CHD events weaken with age, and why does the association with total mortality reverse? One might speculate that individuals who have hypercholesterolemia and remain free of CHD when elderly may have a different mix of apolipoproteins,[4] or for some other reason may tolerate hypercholesterolemia better than those who went on to develop heart disease at earlier ages. Their selective CHD-free survival may explain why the individuals who survive to old age with hypercholesterolemia and no evidence of CHD subsequently seem to suffer few deleterious consequences from their hypercholesterolemia. At younger ages, the cholesterol level does not seem to be associated with non-CHD mortality, except at very low cholesterol levels, where non-CHD mortality may rise as the cholesterol level falls. Several studies have found that the elevated mortality at low cholesterol levels is associated with cancer, though this is not a uniform finding. The role of the serum cholesterol level at advanced age is of great concern because of the large potential attributable risk of hypercholesterolemia. Attributable risk refers to the expected number of excess deaths due to the presence of a risk factor. It is usually distinguished from the relative risk, or the ratio of the number of deaths in persons with the risk factor to the number of deaths in persons without the risk factor. The attributable risk is superior to the relative risk as a measure of the impact of a risk factor on overall survival, since the relative risk of an uncommon event can be very high without significantly affecting survival rates, For example, about 2.7 percent of Americans between the ages of 75 and 84 died of heart disease in 1985 compared to 0.15 percent of 45 to 54 year-olds (122). Suppose that a risk factor increases the relative risk of CHD death at all ages by 10 percent (i.e., the ratio of the rate of CHD death among individuals with the risk factor to the rate in individuals without it is 1.1). Then the attributable risk of the factor is about 0.27 percent among 75 to 84 year-olds (i.e., almost 27 additional deaths per 10,000 people in this age group would occur each year), but it is only 0.015 percent among 45 to 54 year-olds (i. e., 2 additional deaths per 10,000 people in the age group would occur).

Most of the epidemiologic studies cited in this paper indirectly measured the impact of cholesterol on attributable risk, not relative risk, but they did not find that it had a statistically significant effect. Because the estimates were often imprecise, they are consistent with a large impact on attributable risk of CHD, but they are also consistent with a small or even negative impact on attributable risk. With prolonged followup of larger numbers of elderly individuals, the attributable risk of CHD due to elevations in the cholesterol level may prove to be large, but existing studies provide weak support for such a speculation.

---

4 Apolipoproteins are parts of the lipoproteins to which cholesterol binds.