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Chapter 2

Coronary Heart Disease

The heart in itself is not the beginning of life;
but it is a vessel formed of thick muscle,
vivified and nourished by the artery and vein
as are the other muscles.
Leonardo da Vinci (1452–1519)
The Notebooks of Leonardo

Introduction

Coronary heart disease (CHD) is a term used to identify several cardiac disorders resulting from inadequate circulation of blood to local areas of heart muscle. This deficiency is nearly always a consequence of focal narrowing of the coronary arteries by atherosclerosis. Atherosclerosis is a progressive disease that often begins in childhood. The earliest lesions probably arise in the lining of the coronary arteries or in the aorta, often by ages 10 to 15. They appear first as fatty streaks, some of which may later progress to fatty or fibrous plaques and, eventually, large complicated lesions (Berenson 1986). The result of the progressive narrowing of the vessels may be angina pectoris, myocardial infarction (heart attack), or sudden death. These are the most common manifestations of CHD. Elsewhere in the body, the same process may lead to serious and sudden decrease of the blood supply to the brain (ischemic stroke), peripheral vascular disease, or serious problems caused by weakening of the lower abdominal aorta. The development of CHD is a silent process generally lasting decades before the onset of symptoms. Of the half-million heart attack deaths that occur annually, approximately 60 percent occur suddenly or outside of a hospital before treatment can be administered (Kannel and Thom 1984). Thus, much attention is directed at the prevention of CHD by identifying and modifying risk factors before clinical disease develops.

The causes of CHD are multifactorial. It is generally accepted that high blood cholesterol, high blood pressure, and cigarette smoking play causal roles in the development of atherosclerosis, which leads in turn to narrowing of the arteries and development of CHD. Diet plays an important role in

the regulation of blood cholesterol levels and influences other risk factors for CHD as well. For millions of Americans, the most effective CHD preventive strategies are to avoid smoking cigarettes, to control high blood pressure, and to lower high blood cholesterol.

This chapter focuses on the influence of diet on the development, treatment, and prevention of CHD. The role of diet in hypertension is reviewed in the chapter on high blood pressure.

Historical Perspective

Interest in atherosclerosis and its relationship to dietary factors can be traced to observations made in 18th and 19th century medicine. During that period, the fatty nature of the plaque was described and cholesterol was identified in the blood (see historical review, Stamler 1967). In the early 20th century, atheromatous aortas were found to contain excessive amounts of cholesterol (Windaus 1910). These observations led to a series of experiments to induce atherosclerosis in animals by feeding them a diet rich in fats and cholesterol. In 1912–13, typical arterial atherosclerosis was produced in rabbits by feeding pure cholesterol dissolved in vegetable oil (Anitschkow 1967).

At that time, another line of investigation was based on the theory that atherosclerosis was caused by toxic products of protein metabolism. Nutritional experiments, in which large amounts of foods rich in animal protein were fed to rabbits, produced changes in the aorta similar to those in humans. The observed effects were later attributed to the high cholesterol content of the experimental diets (Anitschkow 1967).

Early observations by clinicians and pathologists working in the colonies of British India, Indonesia, Africa, and Latin America were consistent with the pathologic and experimental findings. More than 50 years ago, these workers observed the relative rarity of CHD among the native populations compared with European and North American populations and associated this finding with the nature of the habitual diets. Whereas native groups consumed diets composed mainly of vegetable products, the Westernized population consumed large quantities of eggs and butter (Raab 1932).

Subsequent epidemiologic studies, including long-term prospective studies, of CHD mortality among many national, occupational, racial, and

religious subgroups have established three major modifiable risk factors for developing CHD: cigarette smoking, high blood pressure, and high levels of blood cholesterol.

Significance for Public Health

Deaths from CHD are declining in this country, and this decline has been attributed both to improved medical care and changes in lifestyle. Thus, from 1964 to 1985, the age-corrected CHD death rate has dropped by more than 42 percent, resulting in 350,000 fewer deaths in 1986 than would otherwise have occurred. A recent analysis of the effects of changes in medical intervention and changes in lifestyle attributes 30 percent of this decline to reductions in plasma cholesterol (Goldman and Cook 1984).

Despite this decline, however, CHD still accounts for more deaths annually than any other disease or group of diseases. More than 1.25 million heart attacks occur each year (two-thirds occur in men), and more than 500,000 people die as a result (NHLBI 1984). Death rates for CHD in men under age 65 and in women under age 75 are higher among blacks than among whites, the reverse being true in older persons (Tables 2-1 and 2-2). Available data show lower rates for CHD in the Hispanic population than in non-Hispanic whites (Heckler 1985).

Table 2-1
Death Rate for Coronary Heart Disease by Age, Race, and Sex, United States, 1985

	Death Rate per 100,000 Population[a]			
Age (years)	White Men	Black Men	White Women	Black Women
Total	180.8	164.9	82.9	100.8
Under 45	8.2	13.2	1.7	4.3
45–64	294.5	317.8	85.1	161.1
65–74	1,132.6	990.6	506.0	645.9
75 and over	3,071.8	2,205.0	2,010.2	1,717.5

[a]Age-adjusted to the U.S. population, 1940.

Source: National Center for Health Statistics. In press.

Table 2-2
Prevalence of Coronary Heart Disease by Age, Race, and Sex, United States, 1985

	Prevalence per 1,000 Persons			
Age (years)	Men	Women	White	Black
Total	32.9	24.7	31.8	11.3[a]
Under 45	0.9[a]	1.6[a]	1.3[a]	1.1[a]
45–64	80.9	44.4	65.1	46.3
65–74	175.6	107.0	143.9	62.2
75 and over	169.0	124.6	154.7	[a]

[a]Figure does not meet standards of reliability or precision.

Source: National Center for Health Statistics 1986a.

CHD ranks first as the reason for Social Security disability (Social Security Administration 1982), third after arthritis and hypertension for limitation of activity (Collins 1986), and third after mental illness and all forms of cancer for total hospital bed days (NCHS 1987). According to information from the National Heart, Lung, and Blood Institute (NHLBI), morbidity and mortality from CHD cost the United States an estimated $49 billion a year in 1985 in direct health care expenditures and lost productivity. Furthermore, it has been estimated that unless there are reductions in risk factors or improvements in the efficacy of therapies, CHD prevalence and incidence will increase in the future because of the aging of the population, especially with maturation of the post World War II baby boom generation (Weinstein et al. 1987).

High Blood Cholesterol (Hypercholesterolemia) and CHD Risk

An extensive body of clinical evidence supported by animal, epidemiologic, and metabolic studies has established the relationship between high blood cholesterol and increased CHD risk (Grundy 1986). The relationship is strong, continuous, and graded.

Until recently, it was unclear whether this relationship held only for blood cholesterol levels above a threshold value of about 200 to 220 mg/dl. However, data from the 361,000 men ages 35 to 57 screened for the Multiple Risk Factor Intervention Trial indicate that the association is apparent at even lower levels—about 180 mg/dl (Stamler, Wentworth, and Neaton 1986; Martin et al. 1986).

Average blood cholesterol levels for adult American men and women are 211 and 215 mg/dl, respectively (NCHS 1986b). Individuals whose cholesterol levels are within the top 25 percent of the cholesterol distribution

(above 240 mg/dl) have been defined as being hypercholesterolemic and at substantially higher risk (Consensus Development Panel 1985).

Scientific Background

The effects of dietary factors on circulating lipids in blood were among the earliest observations of factors influencing lipid metabolism and the atherogenic process. A voluminous literature has accumulated over the past 75 years on the relationship between diet, lipoproteins, atherogenesis, and CHD. The primary conclusions of this research are (1) that the higher the total blood cholesterol level, the greater the severity of atherosclerosis and the greater the risk for CHD, (2) that dietary saturated fat and cholesterol raise total blood cholesterol and low density lipoprotein (LDL) cholesterol levels, and (3) polyunsaturated fat lowers total blood cholesterol and LDL cholesterol levels (Levy et al. 1979). Monounsaturated fat also appears to lower blood cholesterol (Grundy et al. 1986).

Atherogenesis

Atherosclerosis is a combination of changes in the inner lining of arteries that occur in response to vessel injury and repair. These changes, as well as elevations in the blood lipids, including cholesterol, permit the excessive entry of proteins and lipoproteins, especially LDL, from the blood into focal regions of the artery wall. In general, LDL is thought to enter intact, but some may have been modified by oxidation or by glycosylation (as in diabetes). They may also undergo alteration, which makes them more atherogenic, after entering the artery wall. Some evidence suggests that very low density lipoproteins (VLDL) may also injure the vessel wall in some individuals with hyperlipidemia (Bradley, Gotto, and Gianturco 1985).

Injury of the blood vessel may also allow certain cells from the blood to adhere to its lining or to enter it, causing low-grade chronic inflammation, which helps to stimulate the proliferation of the arterial cells. The resulting arterial plaque is made up mostly of these modified and rapidly dividing arterial smooth muscle cells, proteins from the blood (especially lipoproteins and their transported fats, including cholesterol), and other cells such as platelets and monocyte/macrophages from the blood. Smooth muscle cells multiply in the plaque, apparently partly in response to growth factors carried to them by blood platelets and released at the site where the platelets adhere when they aggregate. The proliferating cells produce an excessive amount of collagen, elastin, and intercellular matrix. Thrombotic processes probably also participate in the progression of the plaque, especially when endothelial injury becomes more severe.

Figure 2-1 illustrates the microscopic appearance of arterial plaque created as a result of the interaction of these various mechanisms. The smooth muscle cell proliferation in conjunction with cellular accumulations of cholesterol and fat-filled macrophages or foam cells results in a tissue mass with a fibrous layer, or cap, on the lumen (interior) side of the artery. Within the plaque, dead cells and lipid debris, which represent the breakdown of earlier stages of plaque growth, form a central core. This is the soft cholesterol ester-rich component from which the lesion derives its name (athero-"gruel") (Wissler 1985).

Lipoprotein Metabolism

The link between high blood cholesterol and atherogenesis has been elucidated through studies of lipoprotein metabolism. Lipoproteins are the protein carriers of lipids in the blood. Four classes of plasma lipoproteins are generally recognized. They are designated according to their density, which depends on their relative proportions of protein and lipid; those that contain the greatest proportion of lipid are the lightest. Chylomicrons, the lightest lipoproteins, contain mostly triglyceride (90 percent) and originate when dietary fats are delivered to the blood stream via the intestinal lymph. Very low density lipoproteins mainly manufactured by the liver, are also rich in triglyceride (65 percent). The low density lipoproteins normally carry 60 to 70 percent of the circulating cholesterol. High density lipoproteins (HDL) are the heaviest lipoprotein particles because they contain a

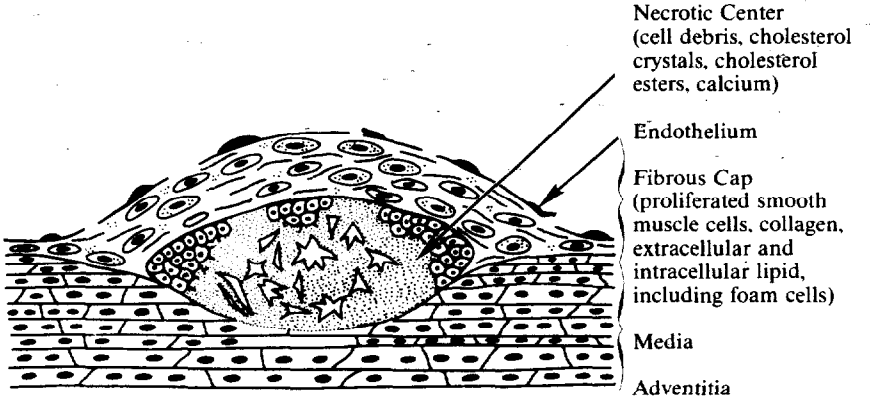

Figure 2-1. Diagram of an atherosclerotic plaque. The advanced atherosclerotic plaque has two important components—the cholesterol- and cholesterol ester-rich necrotic core and the fibrous cap.

Source: Conner, W.E., and Bristow, J.D., eds. 1985. *Coronary heart disease: Prevention, complications and treatment,* p. 194. Philadelphia, PA: Lippincott. Reprinted with permission.

relatively higher proportion of protein (approximately 50 percent by weight) (Rifkind 1982). All of these lipoproteins contain cholesterol but in varying amounts. All contribute to the total blood cholesterol level. An increase in any of them therefore contributes to high blood cholesterol. Lipoproteins are generally measured in the blood as the cholesterol fraction, for example, HDL cholesterol.

The metabolism of lipoproteins is largely determined by the composition of their protein components, or apoproteins. Some apoproteins serve primarily a structural role in lipid transport; others serve as functional units that are recognized by and bind to cell receptors. Still other apoproteins appear to act as cofactors for enzyme systems involved in catalyzing the intravascular changes in lipoproteins or their entry or exit from cells. Advances in techniques for measuring the composition and structure of lipoproteins are providing new insights into mechanisms controlling lipid metabolism and the process of atherogenesis. Although much information is available on how diet affects circulating levels of lipoproteins and the process of atherogenesis, less is known about its effects on the underlying mechanisms.

Low Density Lipoproteins. Low density lipoprotein is the major atherogenic lipoprotein and usually accounts for most of the CHD risk associated with elevated plasma total cholesterol (Gordon et al. 1977b). The level of LDL in the blood is an important determinant of the rate at which cholesterol is deposited in the artery walls. Low density lipoprotein levels are also influenced by other risk factors such as diabetes, cigarette smoking, and obesity (Schwarz et al. 1982).

The level of circulating LDL is determined by specialized proteins called LDL receptors, located on the surface of cells in the liver and other tissues (Goldstein, Kita, and Brown 1983). The number of receptors is determined by the cholesterol needs of the cell. Although cells are capable of making their own cholesterol, their receptors can also bind cholesterol-rich LDL particles and remove them from the circulation, leading to the incorporation of their cholesterol into the cell. If uptake of cholesterol by this route is decreased, as when the number of receptors is deficient, the cell increases its own synthesis of cholesterol. When the cholesterol is not withdrawn by the cells, LDL accumulates in the plasma and may be taken up by the arterial wall cells by mechanisms that do not involve LDL receptors.

Although the synthesis of cholesterol by the liver is under feedback regulation from dietary cholesterol, a reduction in dietary cholesterol intake to lower levels (<300 mg/day) will cause a net plasma cholesterol decrease

despite increased endogenous synthesis (Ernst and Levy 1980). The ability with which dietary cholesterol suppresses endogenous cholesterol synthesis varies greatly among individuals (Quintao, Grundy, and Ahrens 1971). Dietary cholesterol appears to suppress LDL receptor function in humans (Appelbaum-Bowden et al. 1984).

Much information about the consequences of diminished LDL receptor production has come from studies of individuals with familial hypercholesterolemia (FH) (Goldstein, Kita, and Brown 1983). This disease is caused by a genetic inability to synthesize normally functioning LDL receptor protein, causing very high circulating levels of LDL cholesterol, severe atherosclerosis, and often death in early adulthood from heart attack. In the most severe form of FH, accelerated and clinically catastrophic CHD occurs in early childhood in the absence of any other risk factors and is caused solely by elevated LDL cholesterol. Although the receptor defect in FH is genetically determined, other factors, such as increasing age and high-fat diets, may also lead to diminished receptor function in normal individuals (Brown, Kovanen, and Goldstein 1981).

Baboons, rabbits, and dogs maintained on low-fat diets have a high number of LDL receptors, and their circulating LDL levels are much lower than those of humans. When dogs and rabbits are fed high-fat diets, receptor activity is decreased by as much as 90 percent and circulating LDL levels rise (Brown and Goldstein 1984). At birth, infants have blood LDL concentrations similar to newborns of other species, apparently because of their ability to produce LDL receptors. In Western societies, LDL levels rise threefold to fourfold by adulthood. Clinical studies have suggested that this increase is attributable to a decrease in the number of receptors (Brown and Goldstein 1984). The cause of this receptor deficiency is not known, but a high-fat diet may be an important contributing factor. Diets high in saturated fat and cholesterol cause cholesterol to accumulate in cells and the liver, which could lead to a reduction in the number of LDL receptors. In some animals, dietary cholesterol has been reported to inhibit LDL receptor function by 30 percent, even in the presence of added polyunsaturated fat, and saturated fat may depress receptor function by as much as 90 percent (Spady and Dietschy 1985).

Experiments with cultured cells suggest that LDL receptor activity operates optimally at an LDL blood concentration of 25 mg/dl (Brown and Goldstein 1986). Average LDL cholesterol levels of 120 mg/dl in adult Western populations far exceed optimal levels (Goldstein and Brown 1977). This suggests that the human LDL receptor system evolved to function at low LDL levels and that a substantial portion of humanity may not be

genetically adapted to the relatively recent introduction of high dietary fat intake (Tiger 1980). This hypothesis is consistent with epidemiologic findings relating elevated LDL cholesterol to dietary fat intake (Brown and Goldstein 1984).

High Density Lipoproteins. High density lipoprotein is considered to protect against CHD. Numerous epidemiologic studies have shown that the higher the HDL cholesterol level, the lower the risk for CHD (Heiss et al. 1980). Female sex, estrogen use, exercise, moderate alcohol consumption, and weight loss have been associated with higher levels of HDL; in contrast, obesity and cigarette smoking have been associated with lower levels (Heiss et al. 1980). Some components of the HDL fraction may be involved in removing cholesterol from cells (reverse cholesterol transport) and inhibiting deposition of cholesterol in arteries, but the precise role of HDL is not well understood.

Very Low Density Lipoproteins. Very low density lipoprotein consists primarily of triglyceride of endogenous origin. The relationship between triglyceride and CHD is complex (NIH 1983). Although triglyceride levels are positively associated with an increased risk of CHD in most prospective population studies, they are closely associated with attributes such as obesity, total cholesterol, HDL levels, hypertension, and cigarette smoking and generally not independently predictive of CHD risk (Hulley et al. 1980). Elevated triglyceride may be an independent risk factor in older women (Gordon et al. 1977a).

However, almost all case-control studies of survivors of myocardial infarction have shown higher triglyceride levels in the affected patients, and many diseases associated with high triglyceride levels, such as diabetes mellitus, chronic renal disease, and certain primary hyperlipidemias, are associated with an increase in risk for cardiovascular disease (NIH 1983). Moreover, plasma triglyceride levels between 250 and 500 mg/dl may be a marker of lipoprotein abnormalities that are more directly associated with atherosclerosis, such as low HDL cholesterol. Alternatively, elevated triglycerides may reflect the presence of abnormal, triglyceride-rich lipoprotein particles or their metabolic products that may enhance atherogenesis. Whether or not triglycerides are directly involved in the atherogenic process, the identification of elevated levels may help to identify persons with increased CHD risk.

Expert Reports and Recommendations

Numerous expert bodies have examined the evidence relating diet to CHD and its implications for public health. Although there are many determi-

nants of blood cholesterol levels, no modifiable factor has been shown to influence cholesterol and LDL more profoundly than diet. The average adult American currently consumes a diet in which about 37 percent of the total calories is contributed by fat and 13 percent of calories by saturated fat. Dietary cholesterol is estimated to be about 300 to 400 mg/day (USDA 1985a, 1985b). These levels of saturated fat and cholesterol, the major determinants of blood cholesterol, exceed those in countries with low CHD rates, indicating the need for vigorous promotion and dissemination of appropriate dietary guidance.

Federal recognition of this need is demonstrated in the USDA/DHHS *Dietary Guidelines for Americans* issued in 1980 and revised in 1985 (USDA/DHHS 1985). The guidelines, which are being widely distributed and promoted in the public and private sectors, emphasize the reduction of fat, saturated fat, and cholesterol in diets for healthy Americans and suggest some ways to reduce these components through appropriate food selection.

A national preventive strategy to reduce the risk of CHD was enunciated in the 1980 DHHS report *Promoting Health, Preventing Disease: Objectives for the Nation* (DHHS 1981). Specific objectives are aimed at controlling high blood pressure, stopping smoking, lowering blood cholesterol levels, and reducing the prevalence of obesity. By 1990, the report states, the mean cholesterol level in the adult population ages 18 to 74 should be at or below 200 mg/dl.

In 1984, the NHLBI and the National Institutes of Health Office of Medical Applications of Research convened a consensus development conference on *Lowering Blood Cholesterol to Prevent Heart Disease* (Consensus Development Panel 1985). After reviewing much of the available data, the consensus panel of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, nutrition scientists, biostatisticians, experts in preventive medicine, and lay representatives unanimously concluded, despite consideration of some dissenting views (Ahrens 1985), that elevated blood cholesterol is a major cause of CHD and that the risk for heart attacks due to CHD should be reduced by lowering elevated blood cholesterol levels, specifically, blood levels of LDL cholesterol. The panel members suggested that although the benefits of blood cholesterol reduction had been demonstrated most conclusively in men with elevated levels, the evidence justified the conclusion that women with elevated levels would be afforded similar protection. The panel further recommended designation of individuals with blood cholesterol levels above the 75th percentile (the upper 25 percent of values) as being at special risk and requiring vigorous treatment

with dietary measures. It also recognized that dietary treatment of elevated blood cholesterol in children requires special consideration to ensure adequate nutrients for growth and development and to meet energy needs. Older persons, who are at increased risk for malnutrition, may also require special care to ensure adequate intake of essential nutrients.

The panel members asserted that the average blood cholesterol level in the United States is too high, largely because of high intakes of calories, saturated fat, and cholesterol. They recommended that all Americans, except children under age 2, adopt a diet with total dietary fat intake of 30 percent of total calories, with less than 10 percent of calories from saturated fatty acids; limit polyunsaturated fat intake to a maximum of 10 percent of calories; and limit daily cholesterol intake to 250 to 300 mg or less. These dietary recommendations are compatible with food intakes of countries with low CHD prevalence. The panel further advised that caloric intake be reduced if necessary to correct for obesity and that it be adjusted to maintain ideal body weight (Consensus Development Panel 1985).

Although the consensus panel considered the moderate-fat, moderate-cholesterol diet recommended for the general public to be suitable for all members of the family over 2 years of age, special concern was expressed about promotion of cholesterol-lowering diets for children because such diets might inadvertently compromise their nutritional needs (Ahrens 1985). The American Academy of Pediatrics has recommended moderation with respect to decreases in saturated fat and cholesterol, noting that 30 to 40 percent of calories from fat seems sensible for adequate growth and development (AAP Committee on Nutrition 1986; see chapter on maternal and child nutrition). Diets that avoid extremes, it states, are safe for children for whom there is no evidence of specific vulnerability.

National Cholesterol Education Program

The NHLBI is providing the focus for a national effort to reduce cholesterol levels through the National Cholesterol Education Program (NCEP), initiated in 1985. The NCEP has issued detailed guidelines for treatment of adults with high blood cholesterol (NCEP 1988a) and recommendations for improvements in the measurement of blood cholesterol (NCEP 1988b). Future panel reports will provide recommendations for the general public and for treatment of high blood cholesterol in children and adolescents (Lenfant 1987).

The report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP 1988a) defined categories of risk according to measurement of total cholesterol and, when

indicated, subsequent evaluation of LDL cholesterol (Table 2-3). Patients with borderline high blood cholesterol (200 to 239 mg/dl) and no other risk factors should be given cholesterol-lowering dietary information and should be reevaluated annually. Lipoprotein analysis is recommended for patients either with high blood cholesterol (240 mg/dl or greater) or with borderline high blood cholesterol and CHD, or with two other risk factors (one of which can be male sex). The LDL cholesterol is the basis for initiating treatment. Persons with borderline high LDL cholesterol levels (130 to 159 mg/dl) and CHD or two other risk factors and persons with LDL cholesterol levels of 160 mg/dl or greater should be treated to lower their cholesterol.

The report recognized that diet is the cornerstone of therapy to reduce borderline and high-risk blood cholesterol levels whether or not drug therapy is eventually added to the regimen; in general, drug therapy is not recommended without at least 6 months on optimal diet. The advent of highly effective drugs for the treatment of elevated blood cholesterol levels may stimulate widespread use as an alternative to diet therapy. Concerns have been raised about this potential trend because all lipid-lowering drugs have potential side effects, and adverse effects may not become manifest for many years (Grundy 1986). Many patients can reduce their cholesterol levels substantially with diet alone (see Dietary Guidance, Special Populations section). When drugs are required, concomitant modification of the diet may reduce their dosage requirements, cost, and potential side effects. Based on the NCEP adult treatment guidelines (NCEP 1988a), it is estimated that over 40 million adult Americans could be candidates for dietary education or treatment.

Other Reports

A compilation of 47 major reports addressing the public health issues of habitual diet and CHD risk issued since 1968 reveals a common theme—recommendations for less total fat, less saturated fat, and control of

Table 2-3
National Cholesterol Education Program
Adult Treatment Panel Classification

	Total Cholesterol	LDL Cholesterol
	mg/dl	mg/dl
Desirable	<200	<130
Borderline high	200–239	130–159
High	≥240	≥160

Source: National Cholesterol Education Program 1988a.

obesity—and most of the reports also recommend a reduction in dietary cholesterol and partial replacement of saturated with polyunsaturated fat (Truswell 1983).

In response to a congressional directive, DHHS and USDA jointly sponsored an assessment of the existing evidence relating dietary cholesterol to blood cholesterol and human health, as well as recommendations for further research. Their report to Congress, *The Relationship Between Dietary Cholesterol and Blood Cholesterol and Human Health and Nutrition* (1986), concluded that high blood cholesterol is one of the major risk factors for CHD and that cholesterol in the diet, but even more the amount and types of fat in the diet, affect blood cholesterol; dietary cholesterol raises blood cholesterol in most people; in some there is a small response and in others the increase is more pronounced. The prevalence of different degrees of response in the population is not known. A broad program of research was recommended.

The National Research Council of the National Academy of Sciences recently conducted a 3-year review of the role of animal products in the American diet (NRC 1988). Its report, *Designing Foods. Animal Product Options in the Marketplace,* concluded that nutrition-related health problems affect nearly every American family and recommended measures to reduce the quantity of animal fat in the diet and to increase consumers' access to fat and cholesterol information.

Key Scientific Issues

- Role of Dietary Fat and Cholesterol in CHD
- Role of Other Dietary Factors in CHD
- Efficacy of Dietary Interventions in CHD

Role of Dietary Fat and Cholesterol in CHD

Of the many dietary factors that have been studied, the strongest and most consistent evidence relates to dietary fat. Systematic examination of the diet-blood cholesterol-CHD link through clinical, epidemiologic, and animal research implicates both the amount and nature of dietary fats as important determinants of plasma cholesterol levels.

Clinical Studies

Clinical studies have addressed the role of dietary fat and cholesterol upon CHD through their effects upon blood cholesterol and by their effects upon

development and severity of heart disease. The latter type of clinical studies is summarized in the section on Efficacy of Dietary Interventions in CHD, while studies on blood cholesterol are summarized below.

A variety of clinical studies carried out over the past several decades have shown that the type of fat and amount of cholesterol in the diet affect blood cholesterol levels. In these studies, the composition of the diet is controlled so that the effects of single constituents can be tested. Fatty acid sources examined include butter fat, olive oil, cottonseed oil, sunflower oil, hydrogenated coconut oil, sardine oil, safflower oils, margarines, and cocoa butter (Keys, Grande, and Anderson 1974). Typically, saturated fatty acids were shown to raise and polyunsaturated fatty acids to lower plasma cholesterol levels in comparison with monounsaturated fatty acids, which were considered to be neutral. The degree of response to saturated fatty acids depends on the individual fatty acid content. Myristic (14 carbon atoms, C:14) and lauric acids (C:12) have a more powerful effect than palmitic acid (C:16), but palmitic acid is more abundant in the food supply. Saturated fatty acids with more than 18 or fewer than 10 carbon atoms appear to have little or no effect on plasma cholesterol levels (Keys 1967). Likewise, stearic acid (C:18) has been reported not to raise blood cholesterol levels or, when substituted for palmitic acid, to lower blood cholesterol levels (Bonanome and Grundy 1988). *Trans* fatty-acids are isomers of naturally occurring *cis* unsaturated fatty acids. They are produced in fats as a result of commercial hydrogenation of cooking oils and also occur in ruminant fats, including milk fat, beef fat, and lamb fat. *Trans* fatty acids as consumed in hydrogenated vegetable oil appear to be the equivalent of oleic acid in their cholesterolemic properties in humans. In this respect, they are similar to stearic acid, but dissimilar to palmitic, myristic, and lauric acids (LSRO 1985).

Equations to estimate the change in serum cholesterol from changes in dietary fats and cholesterol (Keys, Anderson, and Grande 1965; Hegsted et al. 1965) derived from such clinical experiments are presented in Table 2-4. They show that saturated fatty acids are about twice as powerful in raising plasma cholesterol levels as polyunsaturated fatty acids are in lowering them, while dietary cholesterol has a smaller effect (Blackburn 1979). It has been estimated that increasing the dietary cholesterol intake by 100 mg/1,000 kcal increases the plasma total cholesterol by about 10 mg/dl (Grundy et al. 1988). Thus, if a person consuming 2,000 calories per day increases his or her dietary cholesterol from 300 to 500 mg/day, plasma cholesterol will rise about 10 mg/dl.

Table 2-4
Estimates of Serum Cholesterol Change From Given Changes in Dietary Lipids Based on Isocaloric Controlled Experiments in Humans

Keys (Minnesota) equation:

$$\Delta \text{ CHOL} = 1.35 (2 \Delta \text{ S} - \Delta \text{ P}) + 1.52 \Delta \text{ Z}$$

Hegsted (Harvard) equation:

$$\Delta \text{ CHOL} = 2.16 \Delta \text{ S} - 1.65 \Delta \text{ P} + 0.0677 \Delta \text{ C} - 0.53$$

Where Δ CHOL = estimated change in serum cholesterol in mg/dl; Δ S = change in percent daily calories from saturated fat; Δ P = change in percent daily calories from polyunsaturated fat; Δ Z = change in the square root of daily dietary cholesterol in mg/1,000 calories; and Δ C = dietary cholesterol in mg/day.

Source: Blackburn, H. 1979. Diet and mass hyperlipidemia: public health considerations—a point of view. In *Nutrition, lipids, and coronary heart disease*, ed. R. Levy, B. Rifkind, B. Dennis, and N. Ernst, pp. 309–47. New York: Raven. Reprinted with permission from Raven Press, New York.

Numerous studies have predicted group mean plasma cholesterol levels on the basis of the dietary content of saturated and polyunsaturated fatty acids and cholesterol alone (Keys, Grande, and Anderson 1974). Other clinical studies have shown that although saturated fat raises and polyunsaturated fat lowers plasma cholesterol levels, the magnitude of the change differs from that predicted by the equations. Results of six European experiments were compared with those predicted by equations such as those shown in Table 2-4 (Grande 1983). The predicted changes in serum cholesterol were generally in agreement with the observed changes, with some variability. For example, in the Finnish Mental Health Study, a dietary change that was predicted to raise cholesterol 33 mg/dl produced an average elevation of 49 mg/dl. In another experiment, the cholesterol-lowering effect of corn oil and olive oil were compared with a control diet. Mean serum cholesterol reductions were 50 mg/dl and 38 mg/dl, respectively, whereas the equations predicted the same decrease for both diets, 43 mg/dl. In another experiment, the effect of dietary cholesterol added to a diet rich in polyunsaturated fat was in agreement with the predicted value but was underestimated when cholesterol was added to a diet high in saturated fat.

More recently, the effects of high-oleic safflower oil (monounsaturated), high-linoleic safflower oil (polyunsaturated), and palm oil (saturated) on

blood cholesterol levels were compared in normal and hypertriglyceridemic patients. Both the high monounsaturated and high polyunsaturated fatty acid oils achieved similar lowering of total cholesterol (35 mg/dl), compared with 78 mg/dl predicted for the high polyunsaturated and 45 mg/dl predicted for the high monounsaturated fat diets (Mattson and Grundy 1985).

In another study, beef fat, coconut oil, and safflower oil were isocalorically exchanged in the diets of healthy normal volunteers (Reiser et al. 1985). Mean plasma total cholesterol was 21 mg/dl lower on the safflower oil diet compared with the habitual diet. Mean plasma total cholesterol on the beef fat diet was 14 mg/dl higher than on the diet containing safflower oil and 13 mg/dl lower than on the diet containing coconut oil. The authors suggested that the relatively higher proportion of stearic acid in the beef fat might contribute to these differences.

Despite some inconsistencies in the degree of plasma cholesterol responses, clinical studies have generally shown a fall in response to polyunsaturated fat and a rise in response to saturated fat. However, the above two experiments suggest that the interaction of dietary factors in regulating blood cholesterol levels may be more complex than can be accounted for solely by the amount of saturated and polyunsaturated fats and dietary cholesterol. Other factors that might contribute to inconsistencies across studies include differences in baseline plasma cholesterol levels, composition and form (food vs. liquid formula) of the diet, age, metabolic status of the participants, and duration of the experiment (Mattson and Grundy 1985).

Most clinical studies have noted a high degree of individual variability in response to dietary cholesterol, a characteristic also noted among some animal species (Jokinen, Clarkson, and Prichard 1985). Humans are generally less sensitive to dietary cholesterol than most animal species, and the high degree of individual variability in plasma cholesterol responses to dietary cholesterol suggests that some people may be overly sensitive to dietary cholesterol while others are relatively resistant. The proportion of the population that might be cholesterol-sensitive and the factors that contribute to that sensitivity are not well understood. The response to dietary cholesterol may be affected by such factors as previous diet, age, or genetic makeup (McGill 1979) and the relative proportions of other nutrients in the diet. For example, one controlled clinical study compared the effects of adding three or six eggs to basal diets containing 40 percent fat and 300 mg of cholesterol and differing ratios of polyunsaturated to saturated fat (P/S). At P/S ratios of 0.25 and 0.4, the addition of three and six eggs raised LDL cholesterol by 16 mg/dl and 25 mg/dl, respectively. At P/S

ratios of 0.8 and 2.5, the addition of three eggs had little effect, but the addition of six eggs at the P/S ratio 0.8 raised LDL cholesterol 17 mg/dl. On the diet with a P/S of 2.5, neither three nor six eggs produced significant changes. Thus, both the cholesterol content and the P/S ratios were important in determining LDL level (Schonfeld et al. 1982). Another example suggests that type of protein may influence response to dietary cholesterol. In a controlled dietary study in Type II hypercholesterolemia patients, substitution of soybean for animal protein caused a reduction in serum cholesterol concentrations, and the decrease was about the same with or without the addition of 500 mg of cholesterol to the diet (Sirtori, Gatti, and Mantero 1979).

A total of 75 studies were carried out in 50 male outpatient volunteers fed high cholesterol (approximately 800 mg/dl) versus low cholesterol (approximately 250 mg/dl) in a diet containing 35 percent of calories as either polyunsaturated or saturated fat. In 69 percent of the studies, participants compensated for the increased dietary cholesterol by decreasing cholesterol absorption or endogenous synthesis. The type of dietary fat had a larger and more consistent effect on plasma cholesterol (McNamara et al. 1987).

The main effect of dietary cholesterol on lipoproteins is to raise LDL levels, but it also affects other lipoprotein fractions. For example, human volunteers who ate three to six eggs per day showed increased binding activity of an HDL subfraction that might be associated with increased risk for the development of atherosclerosis (Mahley et al. 1978). It is hypothesized that dietary cholesterol might increase the cholesterol content of chylomicron and VLDL remnants, making them more atherogenic; these changes would not be detected in fasting blood samples, indicating the need for information on postprandial lipoproteins (Grundy et al. 1988).

Epidemiologic Studies

Extensive evidence relating diet to high blood cholesterol has been amassed in a variety of observational-epidemiologic studies. These investigations involve comparisons of different populations, comparisons of migrant with native populations, and comparisons of groups within populations.

Between-Population Studies (International Comparisons). In one type of international analysis, nutrient and food commodity data from Food and Agriculture Organization food balance sheets have been compared with World Health Organization CHD mortality data for sets of countries (Stamler 1983). Univariate analyses consistently showed statistically sig-

nificant positive associations of CHD mortality with calories, total fat, animal fat, saturated fat, dietary cholesterol, total protein, animal protein, animal products (dairy products, meat, poultry, and eggs), and refined sugars. Similar analyses have also shown an inverse association between vegetable products and CHD mortality. Since many of these variables occur together, the independent effect of a single nutrient cannot be determined in such analyses. When the data were reanalyzed, combining the saturated and polyunsaturated fatty acids and dietary cholesterol into a single score based on defined equations (see Table 2-4) and using analysis of variance to control separately for the influence of sugar, vegetable products, and fat, the significant effects of dietary fats persisted while sugar and vegetable products no longer related to CHD mortality (Liu et al. 1982).

In a second type of international comparison, autopsy records were used to compare the degree of atherosclerosis with dietary data. The most systematic study was the International Atherosclerosis Project (McGill 1968), in which severity of atherosclerosis was quantified in autopsies of 23,000 people in 12 countries. The percent of calories consumed as fat ranged from 10 to 15 percent in Costa Rica and Guatemala to nearly 50 percent in the United States. Dietary composition was estimated from available survey data and subjective judgment. The countries were ranked on the basis of severity of disease, dietary indices, and serum cholesterol. The results showed that the percentage of calories from dietary fat was related to the severity of the atherosclerosis ($r = 0.67$) and to population levels of blood cholesterol ($r = 0.74$).

A third type of international comparison involves the direct measurement of cardiovascular risk factors and dietary assessment. These epidemiologic surveys provide further descriptive data on dietary factors associated with the prevalence of heart disease in the populations studied. For example, the Seven Countries Study (Keys 1970) has involved 12,000 men from 18 populations sampled in Finland, Greece, Italy, Japan, the Netherlands, the United States, and Yugoslavia. Fourfold differences in prevalence and incidence of CHD were shown among these populations. The highest incidence rates were recorded for Finland and the United States and the lowest for Japan and three populations in Greece (Corfu, Crete, and Dalmatia). Seven-day food records supplemented by chemical analyses of the diets consumed by study participants showed wide variability across population samples in both amount and type of fat. Saturated fat intake was highest in Finland, the United States, and the Netherlands (17 to 22 percent of calories, compared with 5 to 9 percent of calories in the other countries). Saturated fat intakes and 5-year CHD incidence rates for these populations were highly and significantly correlated ($r = 0.84$), as were saturated fat and