CHAPTER 4

THE ROLE OF CHOLESTEROL

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INTRODUCTION

Since the mid-1980s, when the National Cholesterol Education Program and the American Heart Association began a nationwide campaign to lower this country's average blood cholesterol level, the role of cholesterol in coronary heart disease (CHD) has come under scrutiny. In the public realm, manufacturers and advertisers played on consumer concerns by using oversimplified claims for products ranging from fish oil to breakfast cereals. Within the medical and scientific communities, the debate continues on what levels are truly "high" and on how best to approach the issue of controlling this major risk factor for cardiovascular disease.

One thing remains certain: A high level of cholesterol in the bloodstream is one of the major factors, along with smoking and high blood pressure, contributing to coronary heart disease, the nation's leading cause of death. How this risk factor relates to any one individual's health and life-style, however, is a far more complex matter. Cholesterol is not an immediate threat to the entire population, as some would claim; nor is it a "myth" generated by overzealous public health officials and medical experts, as others have contended.

In reality, elevated blood cholesterol does impart an increased risk for the development of coronary heart disease. The extent of this increase in risk depends on the degree of the cholesterol abnormality, together with other factors, including heredity, age, and gender. The presence of other coronary heart disease risk factors, such as high blood pressure, smoking, or diabetes, will also affect risk. The final determination of how to handle the cholesterol question rests with an individual and his or her physician.

In this chapter, we will examine the evidence that cholesterol does indeed pose a health risk and that control over cholesterol levels can lower that risk. The government's guidelines for cholesterol levels will be reviewed, and approaches to cholesterol control will be compared. First, however, it is essential to understand just what cholesterol is and what role it serves in the body.

THE NATURE OF CHOLESTEROL

Cholesterol has been portrayed by some as tantamount to a poison. In fact, cholesterol is a versatile compound that is vital (in small amounts) to the functioning of the human body. Only animals produce it; no plant product contains cholesterol unless an animal-based product, such as lard, has been added to

Triglycerides: What Is Their Role in Risk?

The exact role of triglycerides, or blood fats, in the development of coronary heart disease is uncertain. Unlike blood cholesterol, these fats must be measured after fasting, because the level of triglycerides in the blood goes up after a fatty meal. Whether a high level of fasting triglycerides in the blood is a definite risk factor for heart disease remains open to question. The international committee for the evaluation of hypertriglyceridemia as a vascular risk factor classified the hypertriglyceridemias into three groups: isolated moderate hypertriglyceridemia (triglycerides 200-400 mg/dl, total cholesterol <200 mg/dl); mixed hypertriglyceridemia (triglycerides 200-400 mg/dl, LDL cholesterol >130 mg/dl); and severe hypertriglyceridemia (triglycerides >400 mg/dl).

High triglycerides often appear along with other known risk factors, such as high blood cholesterol, obesity, and diabetes. But whether a high level of triglycerides is an independent risk factor is still being debated. Triglyceride level, unlike LDL cholesterol level, does not appear to have a continuous, graded relationship to coronary disease risk. There are subgroups of individuals with elevated triglycerides who are more susceptible to heart disease and others, with similar elevations, that are not. How to identify these subgroups is the subject of much research. An extremely high level of triglycerides—a relatively rare condition—poses an immediate risk to the pancreas and should be treated.

As it stands now, physicians tend to assess the risk of high triglycerides based on "the company they keep" in the bloodstream and on the rest of a patient's risk profile. Many lipid (blood fat) experts believe that a high level of triglycerides, along with a low level of HDL ("good") cholesterol, is a warning sign that merits further investigation and possible treatment. High triglycerides plus high LDL cholesterol is an important clue in diagnosing some inherited lipid disorders that carry a high risk of coronary heart disease. And high triglycerides in a person who already has coronary heart disease, or a family history of it, must be taken seriously. High triglycerides in a diabetic patient must be addressed. It is also possible that the testing of triglycerides only in a fasting state may present a deceptively low level and that an abnormally high increase in triglycerides after meals may pose risks of its own.

If treatment is deemed necessary, it will usually consist of dietary changes. Restriction of calories to reduce excess weight, a decrease in saturated fat and cholesterol, and reduced consumption of alcohol are the main dietary goals. Drug treatment is usually reserved for patients with high triglyceride levels, who have other risk factors and who do not respond to dietary changes.

it in processing. In humans, cholesterol serves three main functions. It is used by certain glands to manufacture steroid or cortisone-like hormones, including sex hormones; it helps the liver to produce bile acids, which are essential to the digestion of fats; and, most important, it is a main component of cell membranes and structures, a kind of building block for bodily tissues. Without it, mammalian life would not be possible.

The problem with cholesterol arises when the body has too much of it, or has deposits of it in the wrong places. Coronary heart disease results when cholesterol is deposited inside the walls of the heart's coronary arteries, the main suppliers of oxygen to the heart's own muscle tissue. There it contributes to the formation of fatty, toughened blockages called *plaque.* This buildup of plaque is variously called *arteriosclerosis,* hardening *of the arteries,* and atherosclerosis. Cholesterol can also be deposited within arteries elsewhere in the body, where it may contribute to the occurrence of stroke (from blocked arteries in the brain) and peripheral vascular disease (from arterial blockage in the legs).

How does cholesterol end up where it may do harm? Scientists have learned much about how it travels through the body and is deposited in the arterial walls. Cholesterol metabolism is based on the fact that oil and water don't mix. Cholesterol, a fatty or oily substance, cannot blend smoothly with blood, which is water-based. In order to travel throughout the body, cholesterol must be packaged in special molecules called lipoproteins. The lipids, or fatty cholesterol components, are wrapped inside a water-soluble protein coat. Different types of lipoproteins contain varying proportions of fat to protein.

The various lipoproteins form a dynamic economy within the body, transporting cholesterol to some tissues and removing it from others. The main cholesterol-carrying compound in the body is low-density lipoprotein, or LDL, cholesterol. LDL is often referred to as the "bad cholesterol because it appears to play a key role in depositing cholesterol within arteries. (It's called low-density because it has very little protein, the densest substance in the molecule, and is composed mainly of fats.) High levels of LDL are linked to an increased risk of coronary heart disease.

High-density lipoprotein, or HDL, is termed "good' cholesterol because it appears to help remove

cholesterol from artery walls and transport it to the liver for excretion. In contrast to LDL cholesterol, low levels of HDL are associated with an increased risk of coronary heart disease, while higher levels of HDL appear to protect against the disease.

Other subtypes of cholesterol particles include *chylomicrons,* which are produced by intestinal cells when fat is digested, and very-low-density lipoprotein, or VLDL, manufactured by the liver as an important precursor of LDL cholesterol production. VLDL is the major lipoprotein that transports the triglycerides, another type of fat, produced by the liver. (See box, "Triglycerides: What Is Their Role in Risk?")

For the purpose of determining heart disease risk, LDL and HDL are key. *Total blood cholesterol* is actually a composite number, made up of an individual's

Table 4.1
Average Total Serum Cholesterol Levels of U.S. Population Divided by Age and Sex

Race and age	Average	Race and age	Average
Men ***All*** *races*		***Women*** *All races*	
20-74 years	211	20-74	215
20-24 years	180	20-24	184
25-34 years	199	25-34	192
35-44 years	217	35-44	207
45-54 years	227	45-54	232
55-64 years	229	55-64	249
65-74 years	221	65-74	246
White		White	
20–74 years	211	20–74 years	216
20–24 years	180	20–24 years	184
25–34 years	199	25–34 years	192
35-44 years	217	35–44 years	207
45–54 years	227	45–54 years	232
55–64 years	230	55–64 years	249
65-74 years	222	65–74 years	246
Black		Black	
20-74 years	208	20–74 years	212
20-24 years	171	20–24 years	185
25-34 years	199	25–34 years	191
35-44 years	218	35–44 years	206
45–54 years	229	45–54 years	230
55–64 years	223	55–64 years	251
65–74 years	217	65–74 years	243
Age-adjusted *values:* *All races,*		Age-adjusted *values:* *All races,*	
20-74 years	211	20-74 years	215
White,		White,	
20-74 years	211	20–74 years	215
Black,		Black,	
20-74 years	209	20–74 years	214

Sources: **National Center for Health Statistics; R. Fulwood, W. Kalsbeck, B. Riftkind, et al., Total serum cholesterol levels of adults 20-74 years of age: United States, 1976–80. Vital and** *Health Statistics, Ser. 11, No. 236.* **DHHS Pub. No. (PHS) 86-1686. Public Health Service. Washington, D. C.: U.S. Government Printing Office, May 1986,**

Table 4.2
Mean Levels of Serum LDL Cholesterol

Sex and age	Mean
Male	
20–74 years	140
20–24 years	109
25-34 years	128
35-44 years	145
45–54 years	150
55–64 years	148
65–74 years	149
Female	
20-74 years	141
20–24 years	114
25–34 years	121
35–44 years	129
45–54 years	157
55-64 years	159
65–74 years	162

Source: National Center for Health Statistics, Division of Health Examination Statistics, unpublished data from the second National Health and Nutrition Examination Survey, 1976-80.

LDL cholesterol, HDL cholesterol, and VLDL cholesterol. (See Tables 4.1 and 4.2 for mean levels in the United States.) The ratio of LDL to HDL or total cholesterol to HDL may be as helpful as or more helpful than a simple measure of total cholesterol alone in estimating risk, a point that will be explored further in the section on cholesterol testing.

DIET, CHOLESTEROL, AND HEART RISK

Despite persistent doubts and controversy, there is overwhelming evidence that high blood cholesterol is associated with an increased risk of coronary heart disease, and furthermore, that the association is not merely coincidental but causative. Gaps remain, to be sure, in the understanding of how diet, cholesterol, and atherosclerosis interrelate, and research continues to fill those gaps. Meanwhile, ample data from vastly different types of research support the theory that high cholesterol levels in the blood are associated with increased risk. The most revealing avenues of research include the following.

STUDIES OF PLAQUE WITHIN ARTERIES

More than a century ago, pathologists in Russia analyzed the content of atherosclerotic plaque and discovered it to be composed of up to 70 percent cholesterol by weight. Since then, it has been determined that this cholesterol is brought to the arteries via the bloodstream and is not manufactured within the arteries themselves.

Inherited High Cholesterol: A Rare But Serious Risk

For many of the 25 percent or so of Americans who have high-risk levels of blood cholesterol, a high-fat, high-cholesterol diet is at least partially responsible. But for a small percentage, the cause is an inherited metabolic defect in the way their bodies clear cholesterol from the bloodstream. In individuals with normal cholesterol metabolism, special receptors on the surface of liver cells take up LDL cholesterol from the bloodstream. People with a disorder called *familial hypercholesterolemia* may lack some or almost all of these receptors entirely, or they may not function normally, causing extremely high levels of LDL cholesterol to circulate in the blood plasma.

This disorder causes elevated cholesterol levels (and thus higher-than-average heart disease risk) in about 1 out of every 500 Americans as the result of a gene inherited from one parent. A much more rare and more severe form of the disorder occurs when a child inherits the defective gene from both parents. This *hornozygous* form of the disease, which occurs only once in a million births, causes coronary heart disease in childhood and adolescence and may require liver transplantation as a last treatment resort.

There are many other types of familial hyperlipidemia (inherited lipid disorders), causing abnormalities in various aspects of the blood lipid profile (LDL, HDL, triglycerides). People who are diagnosed with extremely high levels of cholesterol (above 300 mg/dl) or triglycerides (above 400 mg/dl) should encourage other members of their families, especially their children, to undergo testing. Patients with this disorder may be referred to a lipid clinic, a facility (usually in a major medical center) that specializes in treating blood cholesterol disorders. 1 n cases of inherited cholesterol problems, diet therapy is usually necessary, but it may not be sufficient to bring cholesterol down to safe levels. Medication may be needed indefinitely to prevent premature coronary heart disease.

STUDIES OF LABORATORY ANIMALS

In most species of animals studied, atherosclerosis develops only when the animals' blood cholesterol levels are raised through a high-cholesterol, high-fat diet, no matter what other risk factors are present.

STUDIES OF HUMANS WITH INHERITED HIGH CHOLESTEROL

In a rare inherited disorder, the body accumulates extremely high levels of blood cholesterol from early childhood onward. People who have this condition develop coronary heart disease in youth, even when they have no other risk factors such as smoking or high blood pressure. (For more information on this rare disorder, called familial hypercholesterolemia, see box, "Inherited High Cholesterol: A Rare But Serious Risk.")

COMPARATIVE STUDIES OF HUMAN POPULATIONS

This type of research compares the rate of occurrence of various diseases among different populations. For decades, this epidemiologic research has shown a strong connection between a high-fat, high-cholesterol diet, such as that consumed in most industrialized Western countries, and high levels of blood cholesterol and heart disease.

Some of these studies compare risk among different population groups. In the Seven-Countries Study (see Table 4.3), the dietary intake and heart disease rates of seven countries and 16 population subgroups were examined. A high correlation was found between the intake of dietary cholesterol and saturated fat and blood cholesterol levels (and, ultimately, heart disease rates). For example, the inhabitants of western Finland, who are active, outdoor people, not part of an industrialized society, have a high incidence of heart disease; their intake of dairy products is extremely high.

Other studies pinpoint the relationship of cholesterol to risk within a given population group. One famous example is the Framingham Heart Study, an ongoing research project that has tracked risk factors and heart disease occurrence among the residents of a small Massachusetts town for more than 40 years. Among the residents of Framingham, as cholesterol levels rose above 200 milligrams per deciliter (mg/dl), heart disease risk rose accordingly. This study showed that risk was essentially similar at all levels below 200 mg/dl. Another study, conducted on a far

Table 4.3
Results of Seven-Countries Study

Locality	Average serum cholesterol, mg per 100 ml	Coronary heart disease deaths, heart attacks, . per 100	Locality	Percent calories saturated fatty acids	Coronary heart disease deaths, heart attacks, per 100
Velika Krsna (Yugoslavia)	156	0.2	Corfu	5.4	1.3
			Crete	8.6	0.1
Dalmatia (Yugoslavia)	186	1.2	Velika Krsna	8.8	0.2
Montegiorgio (Italy)	196	1.7	Montegiorgio	8.9	1.7
Corfu (Greece)	198	1.3	Dalmatia	9.5	1.1
Slavonia (Yugoslavia)	198	2.0	Crevalcore	9.7	1.8
Crevalcore (Italy)	200	1.8	Zrenjanin	10.0	0.3
Crete (Greece)	203	0.1	Belgrade Faculty	10.0	0.9
Zrenjanin (Yugoslavia)	208	0.5	Slavonia	13.0	2.0
Belgrade Faculty (Yugoslavia)	216	0.9	U.S. railroad workers	17.0	3.2
			West Finland	18.8	2.2
Zutphen (Netherlands)	230	3.4	Zutphen	19.5	3.4
U.S. railroad workers	237	3.25	East Finland	22.2	4.4
West Finland	253	2.25			
East Finland	264	2.4			

Note: Japan (Kyushu) was the seventh country studied. The diet here was lowest in total fat (9 percent) with only 3 percent from saturated fats. The Japanese also showed one of the lowest incidents of coronary events or deaths.

larger group of men for a research project called the Multiple-Risk Factor Intervention Trial (MRFIT), questioned whether even this "threshold of risk exists. Among the 360,000 men screened for MRFIT, the relationship was simple and direct: The higher their blood cholesterol level, the higher their risk of coronary heart disease.

Finally, some researchers have tracked the patterns of blood cholesterol and coronary heart disease among groups of people who have migrated from countries or regions with low-fat diets to more developed areas with higher-fat eating patterns. For example, Japanese men living in Japan (where heart disease is rare despite a significant incidence of such risk factors as smoking and high blood pressure) were compared to Japanese men living in Honolulu and San Francisco. As these Japanese men moved eastward and adopted a progressively more American type of diet (and perhaps a different life-style), their blood cholesterol rates rose, as well as their rates of heart disease.

THE BENEFITS OF CONTROLLING CHOLESTEROL

Given all the evidence that high-fat, high-cholesterol diets contribute to elevated levels of cholesterol in the blood, and that high blood cholesterol is a definite risk factor for heart disease, it might seem natural to assume that lowering blood cholesterol, by diet or other means, would reduce that risk. To a scientist, however, this is nothing more than a hypothesis awaiting hard proof. Such proof has been time-consuming and expensive to gather. Not all subgroups of the population have been studied. Put into context, however, the evidence now points toward the conclusion that lowering cholesterol does have an impact on the process of plaque buildup in the blood vessels.

As such evidence continues to mount, it seems clear that lowering the average cholesterol level in Americans through moderate shifts in eating patterns may be an effective way to save thousands of lives over the next generation. At the very least, it is clear that people who already have coronary heart disease, or are at increased risk for developing it because of a poor family history, diabetes, high blood pressure, or a history of smoking, can benefit from lowering their blood cholesterol through diet and, if necessary, the use of cholesterol-controlling drugs.

A brief look at two landmark studies helps illustrate the scientific rationale for cholesterol control in healthy people. Both these studies are what scientists call primary prevention trials-studies of people who entered the research project without evidence of coronary heart disease. In the studies, one group of people was subject to a specific intervention, such as drug treatment or a special diet, and another group with similar characteristics to no intervention (in the case of drug treatment, members of the group were given a placebo, or sugar pill). Then, after a specified period of years, the groups were compared for their incidence of newly diagnosed heart disease or deaths.

In the Lipid Research Clinics Coronary Primary Prevention Trial, completed in the mid-1980s, two groups of middle-aged men with cholesterol levels above 265 mg/dl (average level of 290) were recruited from medical centers across the United States. These men were at the highest 5 percent of risk for a heart attack and probably are not representative of the entire population. Both groups were put on cholesterol-lowering diets. In addition, one group was given a cholesterol-lowering drug, cholestyramine, in high doses, while the others received a placebo. Despite the fact that many of the men treated with the drug took less of it than they were supposed to (because of its common side effects of gastrointestinal symptoms), this group showed a cholesterol level that was, on average, 9 percent lower—and a 19 percent reduction in risk of fatal and nonfatal heart attacks. Many other benchmarks of heart health were also better in this group, including lower rates of chest pain associated with heart disease, less need for bypass surgery, and fewer abnormal exercise stress tests. In general, the greater the cholesterol reduction achieved, the greater the risk reduction for coronary artery disease. Unfortunately, many of these patients were unable to tolerate the high doses of the drug used in this study.

Meanwhile, researchers in Finland—a nation with the highest rate of heart disease in the world—were reaching similar conclusions in a project called the Helsinki Heart Study. Again, middle-aged men at high risk were given medication, this time a drug called gemfibrozil, to lower their cholesterol levels, and compared over a five-year period with men on placebo. Drug treatment lowered cholesterol levels by about 8 percent, lowered triglyceride levels by 34 percent, and raised HDL cholesterol levels by 10 percent. The treated men had a 34 percent reduction in coronary heart disease rates.

Another kind of research, called *secondary prevention*, focuses on the question: If a person has al-

ready had a heart attack, can lowering cholesterol reduce the chances of another? The answer would appear to be yes. A study called the Coronary Drug Project compared the effect of several cholesterol-lowering drugs in people who had suffered a heart attack, The early results were encouraging, although hardly dramatic: After five years, the men receiving niacin (a B vitamin that lowers cholesterol when given in high doses) had a significantly lower rate of nonfatal heart attacks, but no difference in fatal cardiac problems. Interestingly, however, long-term follow-up of these men after 15 years has revealed that the treated group lived longer than those who were never treated—even though the treatment had been discontinued.

Perhaps the most compelling evidence that people with proven heart disease can benefit from lowered cholesterol levels comes from studies that use coronary angiography (X-ray pictures of the coronary arteries-those that supply blood to the heart muscle itself) to document the actual size and changes in the size of the fatty plaques. Several studies of people with known coronary artery disease, documented by angiography, have shown that a significant drop in blood cholesterol level can halt the growth of new coronary "lesions," as these blockages are called, and in some cases can cause some shrinkage of existing lesions. It appears from these studies that benefit can be demonstrated over a relatively short period of one to two years. However, in order to slow the progression of the disease, or better yet, try to reverse its effects, more extensive cholesterol lowering is necessary.

Does lowering cholesterol lengthen life? Critics of the cholesterol treatment recommendations have charged that the intervention studies failed to demonstrate a decrease in mortality. Indeed, in some major trials, *cardiovascular* death rates have been reduced, but overall death rates have been about the same for both the treated and the placebo group. However, none of these studies was designed to address the issue of total mortality. Such a study would have had to compare larger populations for longer periods.

A reduction in total mortality has, however, been demonstrated in some clinical trials. (The first was the Coronary Drug Project described above; the other two are Scandinavian projects called the Oslo Diet and Antismoking Study and the Stockholm Ischemic Heart Disease Study.) One more point deserves mention: Death rates are not the only issue in preventive health care. In all the intervention studies, the reduction in cardiac symptoms (such as angina) and "events" (such as heart attacks) has contributed to an improved quality of life for the treated patients, regardless of overall death rates.

How well the conclusions from this research can be applied to the general population is not certain. None of the studies included women, children, elderly subjects, or persons who were at low risk. When the intervention consists only of such prudent health measures as eating a diet lower in saturated fat and cholesterol and getting more exercise, however, it seems clear to many experts that such changes can do no harm and may do much good. More data are obviously needed before definitive conclusions can be drawn.

In people with high risk, the primary benefit may be to delay the onset of so-called premature heart disease (that which occurs before age 65); in people at normal or low risk, such measures over a span of many years may help prevent cardiovascular disease in old age. To prove the benefits of cholesterol-lowering over a lifetime takes research so extensive that it is prohibitively expensive and difficult. According to many public health authorities, there is nothing to be gained by waiting 30 years to see the outcome of these measures; there is, however, ample evidence that lives may be saved by beginning such changes now

MEASURING CHOLESTEROL

In 1987, an expert panel assembled by the U.S. government issued a set of guidelines for physicians in evaluating and treating patients for high blood cholesterol levels. (See box, "Cholesterol Testing and Treatment.") The purpose of such guidelines is to translate the vast accumulation of research data into relatively simple terms that busy doctors can use in practice.

Unfortunately, such guidelines can be easily presented to the public as a series of "magic numbers" determining one's medical fate. This is hardly the case. Throughout this discussion of risk evaluation and treatment, it is important to keep in mind that each person is treated as an individual, with a risk factor profile that may not easily fit a given mold. Treatment decisions, whether they relate to changing diet or taking medication, should be made in consultation with a physician and based on a thorough evaluation of an individual's total health profile.

Cholesterol Testing and Treatment

The following guidelines were issued in 1987 by the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute to help physicians in making decisions on treatment for high blood cholesterol levels. Note that other coronary heart disease risk factors play a crucial role. These include male gender, a family history of coronary disease, cigarette smoking, high blood pressure, a low level of HDL cholesterol, diabetes, stroke or peripheral vascular disease, and obesity.

Blood cholesterol level	Treatment recommendations
Desirable (under 200 mg/dl)	Repeat test within five years; eat a prudent diet (low in total and saturated fat and cholesterol).
Borderline high risk (200 to 239 mg/dl)	No coronary disease and fewer than two other risk factors: Follow prudent diet and have cholesterol retested annually.
	Coronary disease or two other risk factors: Have LDL and HDL measured, and base further action on LDL level.
High risk (above 240 mg/dl)	Have LDL and HDL measured; further action based on LDL level.

Note: Some experts believe that HDL cholesterol should be tested along with total cholesterol as an initial test to screen for heart disease risk.

According to the governments guidelines, all adults should have their total blood cholesterol tested, or "screened (a term that refers to widespread testing to uncover a hidden medicaI condition). A total blood cholesterol level of 200 mg/dl or below is considered "desirable." In this range, the only recommendation is for a repeat test every five years or so, along with ongoing health care as appropriate—including, ideally, a prudent diet that is lower in fat, cholesterol, and calories than the typical American diet.

Although this figure of 200 mg/dl has emerged in many studies as the point at which coronary risk starts to rise, as a cutoff point it is somewhat arbitrary. A person with a level of 195 and one with a level of 205 clearly have similar risks. Tests themselves have a margin of error; cholesterol values may vary by 15-20 mg/dl when determined by different tests on the same sample of blood. Similar variations are possible in blood samples taken from the same person over a period of weeks or months, even with no change in diet, medication, or activity. Thus, any test value should be understood as an indicator of possible risk, not an absolute determinant. Unfortunately, printouts of laboratory results may categorize a reading of 245 as "high risk," creating what is possibly unnecessary anxiety for a patient. This reading may be 20 or 25 points lower on a follow-up analysis.

For people with total blood cholesterol levels between 200 and 239 mg/dl, the expert panel recommended the same measures as for people under 200 mg/dl, provided they have no evidence of coronary disease and fewer than two other coronary risk factors. However, if they fall into this "borderline high" range and have two or more coronary risk factors, further testing is recommended. Those risk factors include being male; having a family history of coronary heart disease; cigarette smoking; diabetes; high blood pressure; and severe obesity. If total cholesterol is more than 240 mg/dl further testing and possible treatment is definitely recommended, even if no other risk factors are present. (Incidentally, about 25 percent of adult Americans have cholesterol levels in this high-risk range.)

LIPOPROTEIN MEASUREMENT

It is recommended that patients with a total cholesterol in the borderline-high or high range have a second, more complete, test that measures high- and low-density lipoproteins. The measurement of HDL and LDL gives the physician a clearer picture of actual risk than does the total cholesterol level alone. Inmost cases, total cholesterol gives a fairly good picture of coronary risk, but not always.

For instance, it is possible that a somewhat high total cholesterol level may be due to a high proportion of protective HDL. For example, a cholesterol level of 250 may seem high, but if the HDL is 60 to 65 (a high level that is frequently seen in women), the risk of a heart attack may not be increased. High HDL levels are also seen in people who exercise a great deal. In this case, vigorous cholesterol control would be unjustified. In a number of cases, a desirable total cholesterol level can conceal an abnormally low !evel of HDL (below 30 to 35) and even occasionally a high level of LDL. For this reason, some experts have strongly contested the government's recommenda-

tion that total cholesterol alone be used as a screening test; they advocate the use of HDL testing in all people, especially those at high risk, as part of the initial testing. There are problems related to the measurement of HDL as well as conceptual problems of what to do with the isolated low HDL. Until these issues have been clarified, the decision to measure the lipoprotein tractions in someone with a total cholesterol in the "desirable" range rests with the individual and his or her physician.

Further decisions about how to treat elevated cholesterol are often based on the levels of LDL cholesterol, HDL cholesterol, and triglycerides in the blood. Triglycerides are often elevated to high levels in people with diabetes or in those who consume a great deal of alcohol. Ideally, LDL levels should be below 130 mg/dl, and HDL levels should be above 35 mg/dl. In patients with evidence of coronary heart disease, studies have demonstrated that reducing the LDL levels to around 100 mg/dl can slow the progression of the disease and even partially reverse its effects. If follow-up testing is needed to chart the progress of cholesterol control, the physician may just use total cholesterol testing for purposes of cost and convenience.

Can cholesterol be too low? Except in the case of some extremely rare inherited metabolic defects, it's unlikely. The body manufactures virtually all the cholesterol it needs, even on a low-fat, low-cholesterol diet. The suggestion has been made that low levels of cholesterol may be associated with certain types of cancer, based on limited evidence that people with unusually low cholesterol levels develop these cancers at higher than usual rates. There is little scientific proof for this assertion, however; in fact, populations that eat a lower-fat diet than North Americans also have lower rates of several types of cancer, including those of the breast and colon. If any relation is present between very low cholesterol levels and cancer, it may stem from the possibility that cancer changes many bodily components, including cholesterol, and may begin doing so even before the cancer is diagnosed. A marked weight loss may also result in low cholesterol levels. If cholesterol levels are 140 to 150, it is usually a good rather than a bad sign.

CONTROLLING CHOLESTEROL

If a person's cholesterol level is above the desirable range, the challenge for patient and doctor is to set a target for blood cholesterol that is both realistic and likely to provide benefit.

The cutoff points described above serve only as guidelines. Therapy must be planned in accordance with the entire lipid profile (total cholesterol, LDL, HDL, and triglycerides; personal and family medical history; life-style and dietary habits, including smoking, drinking, and exercise; and the person's own commitment to change).

Cholesterol can be lowered primarily through two approaches: diet and drugs. These modes of action are complementary, not mutually exclusive. As a rule, dietary change is recommended initially. (See box, "Strategies to Lower High Cholesterol," and see Chapter 5.) If cholesterol doesn't come down sufficiently, drug therapy may be added to—not substituted for—dietary modifications. The length of the trial period for diet alone depends on individual factors such as the presence of CHD and the person's responsiveness to dietary change.

Strategies to Lower High Cholesterol

- Lose excess weight. This is best accomplished by a modest reduction in caloric intake coupled with an increase in physical exercise. Avoid crash diets; instead, strive for a loss of 1 or 2 pounds a week until you achieve your desired weight goal. Then maintain that weight by a combination of exercise and moderate eating habits.
- Increase intake *of dietary fiber.* Studies show that soluble fibers help lower blood cholesterol. These fibers include pectin (found in apples and other fruits), guar (used in gum and as a thickener), and the fiber found in oats, corn, rice, and dried beans and other legumes. All types of dietary fiber have the added advantage of producing a feeling of satiety, thereby helping reduce total food intake.
- Lower *your total fat and cholesterol intake.* Use a cookbook that features low-fat, low-cholesterol recipes. Serve smaller portions of meat dishes and emphasize vegetables, pasta, and other low-fat, cholesterol-free foods. At the same time, reduce consumption of high-cholesterol foods like eggs, liver, and fatty meat.
- *Exercise regularly.* This helps in weight control and may also raise levels of HDL cholesterol.

(For more specific guidelines, see Chapter 5.)

DIET

Dietary therapy for elevated blood cholesterol consists of the same prudent eating habits recommended for the public at large (both adults and children over age 2): no more than 30 percent of total calories from fat, and no more than 10 percent from saturated fat, the kind found primarily in animal fats and in some vegetable oils such as coconut. The average American diet includes 37 percent of calories from fat. In addition, intake of dietary cholesterol (found in all animal products, including meat, poultry, egg yolks, and fish) should not exceed 300 milligrams per day. It is important to note that while fish contains cholesterol, it is low in saturated fat and maybe eaten instead of certain cuts of beef, lamb, and other meats that are high in saturated fat. Poultry falls between fish and meat with respect to saturated fat content. (See Tables 4.4 and 4.5.) One of the major sources of cholesterol is egg yolk. (See box, "Sources of Cholesterol in the American Diet.") One large egg yolk contains about 213 to 220 mg of cholesterol, almost 75 percent of a total day's ration.

If this level of dietary modification does not accomplish cholesterol control sufficiently, a "step two" diet that further restricts saturated fat to 7 percent of total calories may be recommended. At this level of restriction, the advice of a registered dietitian is usually needed to adopt eating patterns that are tasty, nutritious, and practical. (For a complete discussion of dietary goals, see Chapter 5.)

A key component of dietary therapy is the restriction of total calories to a level consistent with appropriate weight. Just losing excess pounds can help lower total cholesterol—and, as an added benefit, it can also help raise the level of protective HDL. For-

Table 4.4
Cholesterol/Fat/CaIorie Content of Common Foods

Food	Calories	Cholesterol (mg)	Fats (gin) Polyunsaturated	Monounsaturated	Saturated*
Meat/fish/poultry:					
Beef, 1 oz lean chuck	71	26	0.1	0.8	0.9
Beef, 1 oz fatty	110	27	0.2	2.0	2.2
Beef liver, 1 oz	46	83	0	0	0.1
Chicken, 1 oz dark	58	26	0.6	1.0	0.6
Chicken, 1 oz white	47	22	0.2	0.3	0.3
Fish, 1 oz lean (sole)	40	27	0.1	0.1	0
Fish, 1 oz fatty (trout)	58	25	1.1	1.1	0.9
Lamb, 1 oz lean	53	17	0.2	0.2	0.1
Pork, 1 oz lean chop	60	28	0.1	0.8	0.9
Tuna, 1 oz water pack	45	11	0.1	0.1	0
Turkey, 1 oz white	48	22	0.2	0.3	0.3
Veal, 1 oz cutlet	51	28	0.1	0.8	2.2
Dairy products:					
Butter, 1 T	100	31	0.4	2.8	3.2
Cheese, 1 oz cheddar	115	28	0.3	3.0	6.0
Cheese, cottage (4% fat) ½ cup	110	16	0.1	1.0	1.6
Egg, 1 large	79	213	0.7	2.2	1.7
Ice cream, 1 cup (115 fat)	270	56	0.3	9.6	16.8
Milk, 1 cup whole	150	34	0.1	2.4	4.8
Milk, 1 cup 2% fat	120	22	0.1	2.0	2.4
Milk, 1 cup 1% fat	100	10	0.1	0.8	1.2
Milk, 1 cup skim	85	4	0	0.1	0.3
Yogurt, 1 cup plain, 1% fat	145	14	0.1	1.0	2.3

*Avoid foods with a high level of saturated fats.

Table 4.5
Types of Fats According to Saturation

Type	% Polyunsaturated	% Monounsaturated	% Saturated
Mostly polyunsaturated:			
Corn oil	59	24	13
Cottonseed oil	52	18	26
Saftlower oil	75	12	6
Soybean oil	59	23	14
Sunflower oil	66	20	10
Mostly monounsaturated:			
Canola oil	32	62	6
Chicken fat	22	47	31
Lard	12	47	41
Margarine, hard[1]	29	35-66	17-25
Margarine, soft[1]	61	14-36	10-17
Margarine, tub	46	22-48	15-23
Olive oil	9	72	14
Peanut oil	32	46	17
Sesame seed oil	40	40	18
Vegetable shortening, hydrogenated'	33	44-55	22-33
Mostly saturated:			
Beef fat	11	4	52
Butter	4	30	66
Coconut oil	2	6	87
Palm/palm kernel oil	2	10	80

[1]Ranges derived from manufacturers' data; check labeIing,
Source: United States Department of Agriculture.
Note: In instances where total percentages are less than 100, water or other substances make up the difference.

tunately, a "fringe benefit' of prudent eating habits is that high-fat foods, the most concentrated source of calories, are replaced by lower-fat foods such as complex carbohydrates (found in grains, fruits, vegetables, and products made with them). Because gram for gram, fat contains more than twice as many calories as proteins or carbohydrates (9 calories versus 4), such dietary changes can facilitate weight loss without excessive deprivation. In addition, there is evidence that increasing dietary fiber intake also helps lower cholesterol. If obesity is one of a person's cardiovascular risk factors, an eating plan that combines weight control and cholesterol control without "crash" diets or gimmicks can usually be devised.

Sources of Cholesterol in the American Diet

Meat, poultry, fish	38%
Eggs	36%
Dairy foods	15%
Animal fats	11%

How much can diet lower cholesterol? The answer varies from one individual to another. The amount of cholesterol and fat produced by the liver and how efficiently these substances are broken down depend not only on diet but also on other factors determined by heredity. The liver contains certain receptors that are capable of getting rid of LDL cholesterol. A person who has an adequate number of these receptors may have a normal cholesterol level despite a high-fat diet; if there is a deficiency in these receptors, high lipid levels may occur even on a moderately low-fat diet.

On average, dietary changes like those outlined tend to reduce total cholesterol some 5 to 10 percent, but this average figure does not predict how a given individual will respond to diet therapy. The only sensible course, then, is to give dietary modification a fair try, have cholesterol levels remeasured within six weeks to six months, and take it from there. It is important to remember that having a high cholesterol

level is not an emergency—there is almost always time to work on lowering it. If diet modification alone does not complete the task, and the physician believes that other factors point toward an increased risk, drug therapy may be the next step. But medication is not a panacea to counteract the effects of a high-fat diet. Continued dietary changes, in fact, can help the medication to do its job and may allow for the use of lower dosages, thus lessening the possibility of side effects.

OTHER LIFE-STYLE MEASURES

In addition to diet changes, other changes can have a positive impact on cholesterol levels and on the proportion of "good" to "bad lipoproteins. One important step is for cigarette smokers to quit smoking; in addition to causing injury to blood vessel walls, smoking appears to lower the level of HDL ("good") cholesterol. (See Chapter 6.) If triglycerides are elevated, alcohol intake should be curtailed. While one or two drinks a day may indeed raise HDL levels, as has been reported, this is not a justification for excessive drinking, which has severe negative effects on the cardiovascular system, brain, and liver. (See Chapter 6.)

Finally, there is some evidence that regular exercise has a beneficial effect on HDL cholesterol levels. Just how much exercise is needed to achieve this effect is uncertain, but given the other benefits of moderate exercise on the heart, it certainly cannot hurt. Exercise can help keep weight down, and weight reduction can certainly help maintain a "desirable" lipid profile. (See Chapter 7.)

MEDICATION

The decision to prescribe a cholesterol-lowering drug should not be taken lightly. For one thing, such drugs may need to be taken indefinitely in order to maintain their benefits. For another, no drug is without risk, particularly when taken over the long term. The benefits of drug treatment must be weighed against its cost, inconvenience, and potential side effects.

The types of medication in longest use (and thus with the longest record of safety and effectiveness) have tended to produce a fairly high rate of inconvenient, if usually harmless, side effects. Recently, newer drugs have been developed that may produce similar benefits with a lower rate of side effects. Choosing a type of medication also depends on the composition of a person's lipoprotein profile, because various agents have differing impacts on total cholesterol, LDL, HDL, and triglycerides. The major drugs are summarized in Table 4.6. (For a more detailed discussion of cholesterol-lowering medications, see Chapter 23.)

In deciding whether or not to put a patient on cholesterol-lowering drugs, a doctor must consider, first and foremost, whether the patient already has heart disease, and if not, what his or her risk is of getting it, and what factors might complicate drug treatment (for example, other health problems, other medications, difficulty in remembering to take medication). More vigorous therapy is recommended in patients who have heart disease and whose cholesterol levels are high. On the other hand, a nonsmoking, thin, active woman with normal blood pressure may not derive much benefit from lowering a mildly elevated cholesterol level. In this case, the possible risk of drug treatment may outweigh the potential benefit.

The person who takes cholesterol-lowering medications should be a partner with his or her physician, reporting any side effects or other problems. Often a change in dosage or a different type of medication may be able to solve the problem. It is usually possible to establish a regimen using a single drug or a combination of drugs that will improve the lipid profile with minimal side effects.

CHOLESTEROL, RISK, AND COMMON SENSE

If cholesterol control is to be a rational part of preventive health care, it must be treated as one element in the entire risk factor profile. Smoking, for example, raises the coronary heart disease risk of a person with a cholesterol level of 200 mg/dl to that of a person with 250 to 300 mg/dl. To focus exclusively on cholesterol reduction while continuing to smoke, then, would be poor judgment. Age, sex, family history, blood pressure, weight, presence or absence of diabetes, and amount of regular exercise are other risk factors that must, to varying degrees, be taken into account. (See Chapter 3.)

Unanswered questions remain. For example, should cholesterol control be pursued as aggressively in women as in men, and should treatment for both sexes be the same? Women have not been included in any of the major cholesterol intervention studies. Before menopause, they have lower heart disease rates than men do, apparently because of the protection of female hormones. After menopause, however, they catch up quickly: Cardiovascular disease

Table 4.6
Major Cholesterol-Lowering Drugs

Drugs	Long-term safety	LDL-cholesterol lowering	Special precautions
Cholestyramine (Questran, Colestid, Questran Light, Cholybar)	**Yes**	**10%-25%**	Can alter absorption of other drugs. Can increase triglyceride levels and should not be used by people with an excess of triglycerides in the blood. May cause constipation.
Gemfibrozil (Lopid)	Preliminary evidence	5%–1570	Should be used with caution by people with gallbladder or kidney disease.
Lovastatin (Mevacor)	Not established	25%–50%	Monitor for liver function and muscle enzyme abnormalities.
Nicotinic acid or niacin (Nia-Bid, Nicolar, and others)	**Yes**	15%–30%	Monitor liver function abnormalities and uric acid and blood sugar levels.
Probucol (Lorelco)	Not established	10%-15%	Lowers HDL-cholesterol; significance of this has not been established.

is the biggest killer of American women as well as of American men, albeit some eight to ten years later. Major, long-term studies of the effects of hormone therapy after menopause are now under way to answer some of these gender-related questions. (See Chapter 19.)

Age is another variable in need of further study. What does elevated cholesterol mean for the elderly? The relative risk of a high cholesterol level declines as an individual gets older. However, the absolute death rate from coronary heart disease increases with advancing age, so that treatment may have an impact on death rates in the elderly. But how much should we disturb the life-style of a 75- or 80-year-old person for a benefit that is possible but has not been proved for those of advanced age? There areas yet no answers; common sense and good science suggest that a modified diet that does not prove too burdensome to an elderly person is a reasonable approach to therapy. A more aggressive approach, using drug therapy, may be appropriate in an older individual with heart disease or one who has very high cholesterol levels, is unresponsive to dietary intervention, and is otherwise healthy. Although we do not have specific intervention data in the elderly, a case can be made for giving these individuals the benefit of the doubt, assuming they will behave like a middle-aged population, until it is proven that they do not. (See Chapter 21.)

At what age should we start intervening? Cholesterol levels are lower in children than in adults, but tend to rise with age—at least in societies with high-fat diets. The benefits of preventing this rise may not be evident for a generation. But here, too, are there some dangers in rigidly restricting cholesterol intake in younger children? We have no answers, but an across-the-board restriction of high-fat junk foods and bacon-and-egg breakfasts probably will not hurt and may do some good. (See Chapter 20.)

In many respects, the American diet is more healthful than it was several decades ago. Consumption of red meat, whole milk, and eggs is down (by about 40 percent); people are eating more fish, poultry, fruits, vegetables, and low-fat dairy products. Most sectors of American society are also smoking less. The results, whether direct or indirect, can be seen in our gradually receding rate of coronary heart disease deaths, even when adjusted for the aging of the population. Dietary changes, along with better control of hypertension, have probably played a major role in the decrease in heart disease. Based upon the evidence, it is reasonable to assume that even better results may be expected if we adjust our dietary patterns even further to control cholesterol levels.