Role of Low-Density Lipoproteins in Atherogenesis and Development of Coronary Heart Disease

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There is a strong association between increased blood concentrations of low-density lipoprotein (LDL) and severity of coronary atherosclerosis. Multiple mechanisms affect hypercholesterolemia, e.g., diet, aging, hormones, and genetics. LDL receptors apparently are also important—through down-regulation, defects in structure, or decreased numbers—as are changes in LDL binding characteristics caused by alterations in apolipoprotein B content or structure. Current concepts of LDL metabolism are extensively reviewed, including the role of modified or oxidized LDL in atherogenesis.

Indexing Terms: apolipoproteins/metabolism/heritable defects/risk factors/cholesterylamine/LDL receptors

A high concentration of serum cholesterol is a major risk factor for coronary heart disease (CHD). Growing evidence indicates that this risk is mediated through the major cholesterol-carrying lipoprotein of serum, low-density lipoprotein (LDL), and has led the National Cholesterol Education Program (NCEP) to identify LDL as the major atherogenic lipoprotein and the primary target of cholesterol-lowering therapy (1). As a result, the biochemistry and metabolism of LDL have received increasing attention. In the discussion to follow, current concepts of LDL metabolism and the role of LDL in atherogenesis will be reviewed.

LDL Metabolism and Atherogenic Effects

LDL, a spherical lipoprotein particle, contains mostly cholesteryl ester in its nonpolar core; its surface apolipoprotein consists almost exclusively of apolipoprotein B-100 (apo B-100, or apo B), one apo B molecule per LDL particle. Apo B-100 contains 4563 amino acids and is synthesized in the liver. In contrast, apo B-48, which is present on triglyceride-rich chylomicrons, is produced by the intestine as a truncated form of apo B-100; i.e., only the first 48% of the apo B-100 molecule is synthesized. This is the result of “editing” of the messenger RNA for apo B-100 by the insertion of a stop codon at the truncating site of the molecule. The liver employs apo B-100 in the formation of triglyceride-rich lipoproteins called very-low-density lipoproteins (VLDL).

VLDL particles are responsible for transporting triglyceride fatty acids from the liver to peripheral tissues for utilization. When VLDLs enter capillaries, they come into contact with lipoprotein lipase (LPL), an enzyme that hydrolyzes the triglycerides and releases fatty acids for tissue utilization. VLDL carry two other groups of apolipoprotein, the apo Cs and apo Es. Apo CII is a cofactor for the activation of LPL. Apo E plays a role in the disposition of VLDL. After most of the triglycerides are removed from VLDL, a residual particle, called a VLDL remnant, remains in the circulation. Some of the circulating VLDL remnants are removed directly by the liver in a process mediated by apo E. Cell surfaces of liver cells contain receptors that recognize and bind to the apo E on remnants; the remnant lipoprotein is then internalized and removed from the circulation. However, another fraction of VLDL remnants remains in the circulation and is converted to LDL. Thus the proportion of VLDL remnants converted to LDL greatly influences the concentration of serum LDL. Usually, about two-thirds of remnants is taken up by the liver, and one-third goes to LDL. If a greater fraction of VLDL is transformed to LDL, the concentrations of the latter will rise. More VLDL also will go to LDL if the number of VLDL particles secreted by the liver increases. Factors determining rates of hepatic secretion of VLDL particles are currently the subject of intense investigation.

Another factor affecting LDL concentrations is the fractional removal rate of LDL from the circulation. This rate is determined in large part by the availability of cell-surface receptors for LDL (LDL receptors), particularly on liver cells. At least 75% of circulating LDL is removed via the liver, with the remainder going to other tissues (6). Most of LDL is cleared by way of LDL receptors, although a smaller fraction is removed by nonreceptor pathways. The latter mechanism probably represents bulk-phase endocytosis. Steady-state concentrations of LDL thus depend on rates of conversion of VLDL to LDL and the fractional clearance rate for LDL.

Evidence That LDL Is Atherogenic

The NCEP has designated LDL as the major atherogenic lipoprotein and the primary target of cholesterol-lowering therapy (1). Let us therefore ask: What is the evidence to support this claim? In fact, several lines of evidence underlie the conclusion that LDL is a major cause of atherosclerosis: studies in laboratory animals, epidemiologic evidence, genetic hypercholesterolemias,
pathologic investigations, and studies in model systems. Each can be reviewed briefly.

Animal research. Numerous studies in laboratory animals indicate that increases in circulating lipoproteins resembling human LDL produce atherosclerosis (3-6). Increases in serum lipoproteins can be produced either by dietary cholesterol or by genetic defects. It is true that in many animals the cholesterol-rich lipoproteins are not identical to those of human, but there is a close resemblance, particularly in some nonhuman primates, in whom LDL increases clearly are accompanied by enhanced atherogenesis (6). These findings, while perhaps not definitive, lend support to the concept that human LDL has an atherogenic potential.

Epidemiologic evidence. Many investigations worldwide reveal a positive correlation between concentrations of total cholesterol and rates of CHD (7, 8). Likewise, since LDL is the major cholesterol-carrying lipoprotein in serum, the concentrations of LDL cholesterol are highly correlated with those of total cholesterol; therefore, it seems likely that the total cholesterol-CHD link extends to LDL. Moreover, when LDL is measured in epidemiologic studies (9), the LDL cholesterol concentrations are found to be "independently" associated with CHD rates. Although epidemiologic surveys are always subject to confounding variables, the consistency of the data accumulated from a large series of studies strongly supports the concept that LDL is an atherogenic lipoprotein.

Pathologic investigations. Studies of atherosclerotic plaques obtained at necropsy provide additional evidence. Results of chemical analysis of plaques are consistent with a plasma origin of cholesterol; the fatty acid composition of plaque cholesterol esters closely resembles that in plasma (10). Further, apo B-100 has been detected in atherosclerotic lesions (11) and, indeed, LDL particles have been identified in plaques (12). Finally, a recent and ongoing study of young adults dying accidently, Pathologic Determinants of Atherosclerosis in the Young, reveals a strong positive correlation between the severity of atherosclerosis and the concentrations of LDL+VLDL cholesterol at the time of death (13).

Clinical hypercholesterolemia. Very strong evidence that LDL is atherogenic comes from two independent forms of hypercholesterolemia in which the LDL concentration is increased. In one of these, familial hypercholesterolemia (FH) (14), the LDL receptors are deficient on a genetic basis; as a result, LDL cholesterol concentrations are greatly increased, atherogenesis is enhanced, and premature CHD is common. This is true even when affected individuals are devoid of other CHD risk factors. A related condition, familial defective apo B-100 (FDB) (15, 16), involves a mutation in the apo B-100 molecule that precludes its recognition by the LDL receptors. Consequently, LDL particles are retained in plasma, and LDL cholesterol concentrations are high. Patients with FDB likewise are prone to premature CHD (17), again pointing to the potential of high concentrations of LDL to promote atherosclerosis.

Model systems. Among the in vitro systems developed to study the atherogenic process are various cultures of macrophages and smooth muscle cells, the major cellular components of the plaques. Such systems have shown that LDL has the potential to transform these cells into cholesterol-enriched foam cells, which are the hallmark of atherosclerotic lesions (18, 19). The precise mechanisms whereby LDL produces foam cells will be discussed in more detail below, but the recognition of this potential supports the perception that LDL participates importantly in atherogenesis.

Clinical trial evidence. A final line of evidence supporting an LDL-atherosclerosis link comes from clinical trials of cholesterol-lowering treatments. Among these the strongest example is the Lipid Research Clinics Coronary Primary Prevention Trial (20, 21). In this trial, LDL cholesterol concentrations were reduced in hypercholesterolemic middle-aged men through use of a bile acid sequestrant, cholestyramine. Compared with placebo administration, cholestyramine therapy produced a significant reduction in CHD rates. This change could be attributed almost exclusively to a lowering of LDL cholesterol concentrations.

Although one might question whether any single line of evidence presented above "proves" that LDL is atherogenic, little doubt remains when the combined evidence is considered. Further, this evidence is far stronger than that for an atherogenic effect of other lipoproteins—VLDL and high-density lipoprotein (HDL). Even though these other lipoproteins probably also participate in the atherogenic process, the evidence supporting this possibility does not impart the same level of confidence as that for LDL.

How LDL Produces Atherosclerosis

Although the multiple lines of evidence discussed above provide almost incontrovertible evidence that high concentrations of LDL produce atherosclerosis, the precise mechanism(s) whereby this occurs is not fully understood. In recent years a great interest has developed as to the nature of such mechanisms. Several possibilities exist and, in fact, multiple mechanisms may be involved (Fig. 1). The various theories currently under investigation include the following:

1) Endothelial damage. One theory holds that endothelial damage is the first step in atherogenesis (22). According to this theory, endothelial damage results in platelet aggregation on the injured endothelial surface, where, in turn, the platelets release growth factors that cause proliferation of smooth muscle cells. Furthermore, in vitro model systems suggest that high concentrations of LDL may be toxic to the endothelial surface (23), with the resulting damage leading to the initiation of atherogenesis. Although the endothelial-injury theory is less in vogue than some years ago, it has never been disproved. Even if it is not the only mechanism for the initiation and propagation of atherosclerosis, endothelial damage still could be one mechanism in the overall process.

2) Filtration into the arterial wall. According to the above theory, LDL might promote atherosclerosis with-
out ever entering the arterial wall. However, because atherosclerotic plaques contain large amounts of cholesterol, seemingly derived from circulating LDL cholesterol, the entrance of LDL into the arterial wall would appear to be a requirement for cholesterol deposition. LDL particles have been shown to be small enough to penetrate into the arterial wall by passing between (or through) endothelial cells, with the rate of penetration appearing to depend on the plasma concentrations of LDL (24). Once LDL passes through the endothelial surface, it may set into motion a train of events that accelerate atherogenesis. The first visible stage of atherosclerosis is the fatty streak, characterized by the presence of large amounts of cholesterol in the intima. This cholesterol is present both between and within cells (10). The next stage of atherosclerosis is the fibrous plaque, which appears to arise out of the fatty streak. The potential role of LDL in the various stages of atherogenesis therefore can be considered.

Intercellular accumulation of cholesterol. The deposition of cholesterol in the intracellular matrix of the arterial wall could result from the interaction of LDL with proteoglycans and elastin. Because the apolipoprotein of LDL, apo B-100, seemingly has a high affinity for proteoglycans (25–27) and elastin (28–31), these interactions could trap and retain LDL within the arterial wall. Not only might this process lead to deposition of cholesterol in the intracellular matrix of the intima, it could also render LDL susceptible to cellular engulfment followed by intracellular deposition of cholesterol.

Macrophage formation of foam cells. Most of the cholesteryl ester-enriched foam cells in fatty streaks appear to be derived from macrophages. The processes by which foam cells form have become a subject of intense investigation. Apparently, intact LDL particles are not taken up directly by macrophages; instead, some type of modification of LDL is probably required for cellular uptake. For example, entrapment of LDL in the intracellular matrix may lead to slow degradation of LDL particles such that they are recognized by macrophages. Another popular theory holds that LDL particles within the arterial wall become partially oxidized, which renders them susceptible to macrophage recognition and uptake (32, 33). Other modifications of LDL also may occur, e.g., self-aggregation (34) or chemical modification (18, 19, 35, 36). Thus, there is a strongly likelihood that some type of LDL modification is required for macrophage foam cell formation, but the details of the modification remain to be elucidated.

Smooth muscle cell conversion to foam cells. As atherosclerotic plaques advance, more and more cholesterol is accumulated in smooth cells. Possibly, cholesteryl ester enrichment of smooth muscle cells occurs, similarly to that of macrophages; alternatively, other processes may be required. Regardless, the source of most of the cholesterol accumulating in smooth muscle cells almost certainly is LDL.

Macrophage recruitment. Fatty streaks are enriched in macrophage-derived foam cells. The large number of these cells in fatty streaks must have been derived from outside the intima. The chemotactic factors that draw macrophages into the early but growing lesion are not known, but evidence has been presented that oxidized LDL may be an important factor. In fact, to exert a chemotactic function for circulating monocytes, the LDL needs to be only minimally oxidized (37, 38). Minimally modified LDL appears to have additional properties that alter cellular metabolism within the artery wall and may promote atherogenesis.

Conversion of fatty streak to fibrous plaque. Apparently, high concentrations of circulating LDL are a critical factor in the formation of fatty streaks. In laboratory animals, most hypercholesterolemia-induced atherosclerosis is of the fatty streak type. On the other hand, humans with severely high concentrations of LDL (e.g., homozygous familial hypercholesterolemia) appear to develop fully developed fibrous plaques in the absence of the usual nonlipid risk factors (cigarette smoking, hypertension, and diabetes mellitus) (16). Thus, by whatever mechanism, LDL apparently can produce "full-blown" atherosclerosis without the need for concomitant risk factors. Just how LDL can set into motion all the elements of the atherosclerosis process remains to be determined.

Is LDL the "Prime" Risk Factor?

To understand the role of LDL in atherogenesis, one must keep in mind the two-stage process whereby atherosclerotic plaques develop (Fig. 2). LDL appears to be necessary for the formation of the fatty streak; and, without the formation of this lesion, there will be no progression to the fibrous plaque. Evidence is growing that other CHD risk factors (smoking, hypertension, diabetes) act mainly to promote conversion of fatty streaks into fibrous plaques (39). If this scenario is correct, then LDL, which is required for fatty streak formation, can be considered the prime risk factor. This concept is consistent with epidemiologic evidence. For example, in populations in which LDL cholesterol concentrations are low, the development of advanced atherosclerosis appears to be relatively rare, even when
other risk factors are frequent, e.g., cigarette smoking (40, 41), hypertension (42, 43), and diabetes mellitus (44–46).

In contrast to the other risk factors, low concentrations of HDL, in conjunction with high concentrations of LDL, may promote the formation of the fatty streak. This may be related to the ability of HDL to promote reverse cholesterol transport, i.e., to remove excess cholesterol from the surface of cells (47); or, a high concentration of HDL may exert its protective effect against the development of CHD through interaction with LDL. This may explain why low HDL cholesterol concentrations are a major risk factor for CHD, but only when LDL concentrations are relatively high (48–50).

Clinical Approach to High Blood Cholesterol

In the discussion to follow, the term “hypercholesterolemia” will be used synonymously with high concentrations of LDL cholesterol. In overall populations, LDL cholesterol concentrations are highly correlated with total cholesterol concentrations, although in individual patients this is not necessarily true. A classification of serum cholesterol concentrations, based on NCEP recommendations (1), is shown in Fig. 3, which presents the corresponding values for total cholesterol and LDL cholesterol and relates the serum cholesterol concentrations to the degrees of hypercholesterolemia. A brief discussion of the clinical significance and metabolic determinants of each of these categories follows.

Desirable Serum Cholesterol

Total cholesterol concentrations <200 mg/dL (LDL cholesterol <130 mg/dL) are called “desirable” (1). This term implies that concentrations in this range impart little increased risk for CHD, but is this, in fact, true? Are people who have cholesterol values in this range safe from CHD? Actually, even within the desirable range, cholesterol concentrations are associated with a graded risk for CHD from lower to higher values. People whose total cholesterol is <160 mg/dL have a lower CHD risk than those with cholesterol of 190 mg/dL (51). Nonetheless, in the absence of other risk factors, the risk for developing premature CHD in people with cholesterol values in this range is acceptably low. However, these concentrations may be high enough to lead to clinical atherosclerotic disease in some elderly persons, even in the absence of other risk factors.

In 1994, almost 50% of American adults had cholesterol concentrations in the desirable range (1). This proportion has been increasing and probably can be explained by a greater attention to dietary habits. However, the proportion with desirable cholesterol values is disproportionately weighted towards young adults, and there is a definite tendency for an individual’s cholesterol concentration to rise with age. Certainly an important goal for preventive medicine is to increase the proportion of the population with cholesterol in the desirable range.

Borderline-High Cholesterol

This range is defined as total cholesterol of 200–239 mg/dL (LDL cholesterol 130–159 mg/dL). Because patients with “borderline-high” cholesterol concentrations are at greater risk for CHD than are those with “desirable” values, this category also can be called “mild hypercholesterolemia” (51). About 30% of adult Americans have cholesterol concentrations in this range (1). An important question is, How much is the risk for CHD increased by having a borderline-high cholesterol? Epidemiologic studies (52) strongly suggest that, for a 1 mg/dL increase in cholesterol concentrations over moderate ranges, the risk for CHD increases by 1%. Thus an increase of cholesterol from 200 to 240 mg/dL should raise the risk for CHD ~40%. Although many more people have desirable cholesterol concentrations than borderline-high concentrations, the incidence of CHD is considerably higher in the latter group. This attests to the importance of borderline-high cholesterol as a significant risk factor for CHD.

Given that a borderline-high cholesterol (mild hypercholesterolemia) is an important risk factor, we might ask about its causes. What causes the concentrations to rise into this range? Fig. 4 outlines the major causes. One factor undoubtedly is genetics. Probably ~50% of the variability in cholesterol concentrations in the gen-
eral population has a genetic basis. The nature of this genetic variation is at present not known, but research currently underway may explicate this problem. Other recognized causes are also listed in Fig. 4: (a) relatively high intakes of saturated fat and cholesterol in the American population, (b) increasing obesity with age, (c) increases of serum cholesterol with aging per se, and (d) the postmenopausal increase in cholesterol in older women (53). The latter three factors, but not the first, help to explain why older people have higher cholesterol concentrations than do young adults. Intakes of saturated fats and cholesterol do not increase with age, and these nutrients exert their effects approximately equally throughout life. However, the other three factors come into play as people age, and definitely reinforce the increasing risk for CHD with aging.

How do these various factors lead to increased concentrations of serum cholesterol? Both dietary cholesterol and saturated fatty acids apparently suppress LDL-receptor expression in the liver (54). Beyond this, aging per se adds to LDL-receptor expression by means that are not understood (55–57). Increasing obesity, on the other hand, provokes an overproduction of VLDL particles by the liver (58) and the excess VLDLs are transformed into LDL (59). Finally, the loss of estrogens after the menopause removes the action of estrogens to stimulate the synthesis of LDL receptors (60, 61). Thus, borderline-high cholesterol concentrations are due to in large part to a decrease in LDL-receptor activity, from both dietary and aging factors.

Management. The management of borderline-high cholesterol concentrations flows logically from the causes. First on the list is to reduce the intakes of saturated fat and cholesterol. This can be achieved in large part by a reduction in the intake of animal fats: whole milk and its high-fat products and animal fats. Egg consumption also should be reduced. Animal products need not be eliminated from the diet, but choices should be restricted to low-fat commodities. Animal fats can be replaced by vegetable oils, particularly those high in monounsaturated fatty acids (e.g., olive oil and canola oil) (62). Weight reduction in obese patients is necessary to further reduce cholesterol values. Finally, estrogen replacement therapy can be considered for women with mild hypercholesterolemia, especially if their LDL cholesterol concentrations are high. In most people having borderline-high cholesterol, espousing these measures will reduce serum cholesterol concentrations into the desirable range.

High Serum Cholesterol

NCEP guidelines (1) rank total cholesterol concentrations >240 mg/dL as "high." As the concentration increases progressively beyond 240 mg/dL, the risk for CHD rises correspondingly. About 20% of all American adults have a high serum cholesterol concentration, increasing to 25–30% in older Americans. For practical purposes, I will divide the high cholesterol category into "moderately high" (240–320 mg/dL) and "severely elevated" (>320 mg/dL), values corresponding to LDL-cholesterol of 160–220 and >220 mg/dL, respectively. In the absence of secondary causes, the former range is designated "primary moderate hypercholesterolemia"; the latter, "primary severe hypercholesterolemia." These two categories will be discussed separately.

Primary moderate hypercholesterolemia. The causes of moderate increases of LDL cholesterol are presented in metabolic terms in Fig. 5. Although the foundation of primary moderate hypercholesterolemia is borderline-high cholesterol, which includes all of the causes depicted in Fig. 4, other contributors also have been identified (53, 63), most of which probably have a genetic basis. First, some patients have a further reduction in LDL-receptor activity beyond that produced by dietary cholesterol and saturated fats and by aging per se and, in postmenopausal women, by loss of estrogens. Some patients may have a genetic defect in the gene encoding for LDL receptors; however, because factors other than the primary gene regulate LDL-receptor expression, abnormalities may exist in these as well. Recently a protein has been described that modulates the promoter of the LDL-receptor gene (64); abnormalities in this protein could suppress the activity of LDL receptors. Further, because LDL-receptor synthesis is modulated by intracellular concentrations of cholesterol, abnormalities in cholesterol metabolism also can affect LDL concentrations.

The best therapy for a reduced activity of LDL receptors is to reverse the defect. A diet low in saturated fatty acids and cholesterol is the first line of therapy; this diet will partially relieve the suppression of receptor activity. In postmenopausal women, estrogen replacement therapy will further enhance receptor expression, and
may alleviate the need for drug therapy. But for patients with more marked LDL increases, drug treatment may be required. Two types of drugs are known to increase the synthesis of LDL receptors, and both act to lower hepatic concentrations of cholesterol: Bile acid sequestrants enhance the catabolism of hepatic cholesterol into bile acids, whereas HMG CoA reductase inhibitors (statins) suppress the synthesis of cholesterol. Both have proven effective in treatment of primary moderate hypercholesterolemia in which the LDL-receptor activity is reduced.

Other patients with primary moderate hypercholesterolemia have defective LDL particles, which bind poorly to LDL receptors. One abnormality responsible for defective LDL particles is the condition FDB, discussed earlier (15, 16). This disorder is characterized by a mutation in apo B-100 that prevents its being recognized by LDL receptors. The specific defect is an arginine to glutamine change at position 3500 of the apo B-100 molecule. As a result of not binding to the LDL receptors, the LDL particles accumulate in the circulation, and the patient develops hypercholesterolemia. Other patients with increased LDL concentrations probably have still other mutations in apo B-100; although none has been identified so far, isotope kinetic studies indicate that many patients without the 3500 defect still have defective LDL particles (15, 65). Interestingly, patients with FDB respond well to statin drugs (66), probably for two reasons. First, almost all patients with this condition are heterozygotes, and half of their LDL particles bind to LDL receptors; hence, increasing LDL receptors with statin therapy removes the normal LDL particles and lowers the LDL cholesterol concentration in blood. Second, precursors of LDL (i.e., VLDL) bind LDL receptors via another apoprotein, apo E, and thus are removed at an increased rate during statin therapy; because fewer VLDL particles are converted to LDL, the blood concentrations of LDL decrease.

In many patients with moderate hypercholesterolemia resulting from increased input rates for LDL, i.e., increased conversion of VLDL to LDL (63, 63), two mechanisms could be responsible: (a) an increase in hepatic secretion rates of VLDL particles and (b) a decrease in the direct removal of VLDL particles by the liver so that more VLDL particles are available to be converted to LDL. Both mechanisms are probably active, although current methodology is not sophisticated enough to differentiate with certainty between these two mechanisms. Further, the underlying causes of these two different causes of increased input of LDL remain to be determined. The ideal drug therapy for an increased input of LDL particles probably is nicotinic acid, which appears to inhibit hepatic secretion of VLDL. Unfortunately, many patients cannot tolerate nicotinic acid, which has a variety of undesirable side effects. An alternative approach is to use a statin drug, which enhances the clearance of VLDL particles (67). Although the statins do not attack the underlying defect, they do reduce the concentrations of LDL, and to a lesser extent, those of VLDL. Bile acid sequestrants are less desirable for these abnormalities in VLDL and LDL metabolism because they often increase VLDL concentrations and may thus aggravate the underlying defect.

Finally, some patients with moderate hypercholesterolemia have LDL particles that are enriched with cholesteryl esters (53, 63). In these patients the number of circulating LDL particles is not increased, but each LDL particle contains more cholesterol than usual. Consequently, LDL cholesterol concentrations are increased to abnormally high values. The underlying cause of this overloading of LDL with cholesteryl esters is not known. Treatment of hypercholesterolemia with either statins or bile acid sequestrants not only lowers the number of LDL particles (68), but also may decrease the cholesterol content of the LDL particles. However, the latter effect appears to be greater with bile acid sequestrants than with statins, leaving the former as the theoretically preferred approach. Also, low-fat diets appear to reduce the cholesterol content of LDL particles more than they reduce the concentrations of LDL particles (69); thus, in patients with cholesterol-overloaded LDL, low-fat diets may be especially beneficial.

**Primary severe hypercholesterolemia.** This condition is defined as an LDL cholesterol >220 mg/dL. Some patients with severe hypercholesterolemia have monogenic disorders of LDL metabolism, i.e., heterozygous FH and FDB; others apparently have polygenic abnormalities. Indeed, studies with my colleagues (53, 63) showed that most patients with severe hypercholesterolemia have at least two of the defects shown in Fig. 5, added to an underlying borderline-high cholesterol concentration. This finding conforms to the polygenic nature of many cases of severe hypercholesterolemia. Often, the concentrations of LDL cholesterol are increased so severely that two drugs in combination are required to produce an adequate decrease of LDL cholesterol. Perhaps the most desirable drug combination is a bile acid sequestrant plus a statin: This combination has the potential to reduce LDL cholesterol concentrations by as much as 50% (68).

**References**

40. Todd GP. Cigarette consumption per adult of each sex in various countries. J Epidemiol Community Health 1986;32:289–93.
52. Davis C, Riffkind B, Brenner H, Gordon D. A single cholesterol measurement underestimates the risk of coronary heart disease.