CHAPTER 41

Nutrition, Lipids, and Cardiovascular Disease

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OUTLINE

Atherosclerotic Cardiovascular Disease
  Pathophysiology of Atherosclerosis
  Dietary Lipids
  Antioxidants
  Nutrient Intake Deficiency Associated with Homocysteinemia
    Iron
    Selenium
    Chromium
  Dietary Treatment of Hypercholesterolemia

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COMMON ABBREVIATIONS

ASCVD (atherosclerotic cardiovascular disease)*
CAD (coronary artery disease)*
CHD (coronary heart disease)*
HDL (high density lipoproteins)
IDL (intermediate density lipoproteins)
LDL (low density lipoproteins)
VLDL (very low density lipoproteins)
ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Atherosclerotic cardiovascular disease is the number one cause of death in Western nations and is rapidly becoming a prominent cause of death in economically "underdeveloped" countries as well. It was recognized more than 100 years ago that the atherosclerotic lesion was laden with lipids. In 1908, Ignatowski first showed that rabbits fed meat, dairy, and egg products developed lesions resembling human atherosclerosis (Ignatowski, 1908). Anitschkow and Chalatow (1913) followed soon after with proof that dietary cholesterol was the key nutrient responsible for hypercholesterolemia and atherosclerosis in this animal model. Following these groundbreaking investigations, numerous epidemiological studies of diet, nutrition, and atherosclerotic cardiovascular disease have generated an enormous database linking diets high in saturated fat and cholesterol to human diseases (U. S. Department of Health and Human Services, 1988; National Research Council, 1989). These observational studies were paralleled by the rapid development of the field of lipid and lipoprotein metabolism, with studies stretching from human dietary investigations to studies of diet and atherosclerosis in transgenic and "knockout" mouse models of human dyslipidemia. The epidemiological and basic studies were followed by intervention trials, culminating in two studies in which changes in diet alone were associated with less progression of coronary artery disease and fewer coronary events (Ornish et al., 1990; Watts et al., 1992). The evidence linking diet and atherosclerotic disease, with a particular focus on effects of diet on lipid and lipoprotein metabolism, is reviewed in this chapter.

Pathophysiology of Atherosclerosis

Despite a rapidly growing base of knowledge regarding the cellular and molecular biology of the vessel wall, plasma lipids and lipoproteins still occupy the central and key role in our understanding of atherogenesis. Present concepts concerning the development of the atherosclerotic lesion and a brief overview of lipoprotein transport are summarized in this chapter. Detailed reviews of the pathologic cell biology of atherosclerosis are available (Ross, 1985; Steinberg et al., 1989).

Plasma cholesteryl esters and triacylglycerols, two classes of hydrophobic neutral lipids, are transported through the plasma core of lipoprotein particles, as discuss Chapters 7 and 14. The surface of the lipoprotein consists of amphipathic molecule including free cholesterol, phospholipids, and apoproteins. There are two major classes of triacylglycerol-rich lipoproteins: chylomicrons and very low density lipoproteins (VLDL). Chylomicrons are assembled in the small intestine and carry dietary triacylglycerols and cholesterol, whereas VLDL are assembled in the liver and transport mainly endogenously derived core lipids. In the plasma, chylomicrons and VLDL lose their triacylglycerols interacting with lipoprotein lipase at the vessel wall, they become, respectively, chylomicron remnants and VLDL remnants (also called or intermediate density lipoproteins). Chylomicrons and VLDL also can be modified by the exchange of their core triacylglycerols for core cholesteryl ester from high density lipoproteins (HDL) and low density lipoproteins (LDL). Although the chylomicron remnants are under normal conditions, almost quantitatively removed from plasma by the liver, remnants can be converted to low density lipoproteins (LDL) in addition to being taken up by the liver. Once LDL are formed, they can be removed from plasma by LDL receptors.

The major protein on chylomicron VLDL, their remnants, and LDL is apoprotein B (apo B). The liver makes a full-length 210-kDa version of this polypeptide, which is called in the body by both the liver and intestinal apo B-containing lipoproteins. The intestine makes a shortened 210-kDa version of the protein as a result of mRNA editing; although these short proteins are required for chylomicron secretion into the circulation, it lacks the receptor-binding domain present in full-length apo B. The apo B-containing lipoproteins are partially atherogenic if their metabolism is regulated properly. In contrast, HDL, which have a very different protein, apo A-I, as their major protein, are antiatherogenic under...
conditions. (See Chapter 14 for a more detailed description of the assembly, secretion, and plasma metabolism of lipoproteins.)

The role of the apo B-containing lipoproteins is to transport exogenously and endogenously derived lipids to peripheral tissues: in the case of triacylglycerols, for energy utilization or storage; in the case of cholesterol, for sterologenesis and cell membrane structural integrity. To carry out their role, lipoproteins must be able to move across the endothelial covering of blood vessels and reach the extracellular space. LDL is the predominant lipoprotein passing through the endothelial layer, but there is evidence that both chylomicron remnants and VLDL remnants can do so as well. Much of this transendothelial migration occurs in the capillaries, but some occurs in all vessels, including the large arteries. Present concepts of atherogenesis consider the passage of lipoproteins into the subendothelial space as the first critical step in the process. It appears that during a brief period of contact with the endothelial cell barrier, the lipoprotein may be "modified" (Steinberg et al., 1989). Modification may be in the form of oxidation of phospholipid, particularly phosphatidylcholine. Modified apo B-containing lipoproteins may be more liable to aggregate or to stick to extracellular matrix molecules in the subendothelial space. Alternatively, unmodified apo B lipoproteins may stick to matrix molecules in the subendothelial space, triggering interaction with overlying endothelial cells and subsequent modification of the lipoprotein. In either scheme, greater numbers of circulating lipoproteins will infiltrate the endothelium and be retained.

As illustrated in Figure 41–1, once modification/retention of apo B-containing lipoproteins occurs, signals to the endothelial cells result in synthesis and display of several cell adhesion molecules and of monocyte chemotactic proteins and in the secretion of monocyte colony-stimulating factor. Together, these molecules stimulate the formation, sequestering, and transmigration of circulating monocytes at the site of retained subendothelial lipoproteins (Gimbrone et al., 1995). Once the monocytes enter the subendothelial space, they are activated and transformed into macrophages. These macrophages further oxidize the retained lipoproteins, internalize them through one or more receptors, and develop into foam cells. They also secrete factors, such as transforming growth factor beta, which can stimulate smooth muscle cell proliferation and migration. Both the monocytes/macrophages and the activated smooth muscle cells begin to secrete extracellular matrix molecules as well. At this point, all the components of the advanced lesion are in place, and atherogenesis is well under way.

Lipoprotein (a) [Lp(a)] is composed of LDL with a second protein, apo(a), covalently linked to apo B. Apo(a) is a large protein with a highly variable size (200 to 700 kDa) that is synthesized in the liver. It is believed that apo(a) binds to LDL apo B in plasma. High plasma levels of Lp(a) have been linked in several studies to increased risk for atherosclerotic cardiovascular disease, and recent studies have suggested that certain diet components may affect Lp(a) levels (Berglund, 1995).

HDL, or the apo A-I–containing lipoproteins, appear to have protective effects against atherosclerosis. Two major hypotheses have been presented to explain the negative association of HDL cholesterol levels with atherosclerotic cardiovascular disease. First, a large body of data indicates a role for HDL in the reverse transport of cholesterol from tissues throughout the body back to the liver. Because the apo B–containing lipoproteins, particularly LDL, are thought to deliver several hundred milligrams of cholesterol to peripheral tissues daily, there must be some mechanism to balance that delivery system. HDL is thought to be the vehicle for such balance. Small, cholesterol-poor HDL particles (either spherical or disc-like) are good acceptors of free cholesterol from the extracellular surface of membranes. These HDL particles, enriched in free cholesterol, can be modified by the enzyme lecithin:cholesterol acyltransferase (LCAT); this enzyme esterifies the free cholesterol with a fatty acid (e.g., linoleate) from lecithin. The cholesterol ester moves from the surface of the lipoprotein to the core (because of its hydrophobicity), allowing more free cholesterol to be adsorbed onto the surface. This process results in enlargement of the HDL particles. As HDL become enriched
in cholesteryl esters, they become significant vehicles for delivery of those esters to the liver, where the cholesterol can be converted to bile acids or excreted as biliary cholesterol. How this final step in the reverse cholesteryl transport pathway is achieved is unclear at this time: either the HDL delivers the cholesteryl esters via selective uptake or endocytosis of the entire HDL particle occurs. Recently, a potential receptor for selective delivery of HDL cholesteryl esters to hepatocytes and certain other cells, called scavenger receptor B1 (SRB1), was identified. Alternatively, HDL can transfer the cholesteryl esters to triacylglycerol-rich VLDL or chylomicrons via cholesteryl ester transfer protein (CETP). The latter transfer, which is bimolecular with a triacylglycerol going to HDL, can be followed by uptake of the chylomicron or VLDL remnant by the liver.

The second potential antiatherogenic activity of HDL relates to its role as an antioxidant and/or antiaggregant in the vessel wall. Much fewer data are available to support this activity. Of particular interest is the striking ability of human apo A-I to reduce atherosclerosis in mice lacking apo E, an apoprotein that is a key ligand for several hepatic receptors, including the LDL receptor. In this mouse model of severe hyperlipidemia and atherosclerosis, overexpression of the gene for apo A-I results in significant reductions in atherosclerosis despite very small increases in plasma HDL cholesterol levels. Additionally, it has been shown that apo A-I can directly protect LDL against oxidative modification in vitro. These recent reports support the finding of an antiatherogenic effect of apo A-I infusions into swine despite no measurable
change in plasma HDL levels. This will be an exciting area of research to follow over the next few years.

Pathophysiology of Dyslipidemia

Despite the complexity of the atherosclerotic process and the multicomponent nature of the advanced lesion, a key initiator of atherogenesis appears to be the presence of increased amounts of retained and/or modified lipoproteins in the subendothelial space. The latter is a direct consequence of increased quantities of atherogenic lipoproteins in the circulation. It is, therefore, important to understand the pathophysiology of the various dyslipidemias. The more common types of hyperlipidemias and their clinical characteristics are summarized in Table 41–1.

Isolated Hypercholesterolemia. Elevated levels of fasting plasma total cholesterol are, in general, associated with increased concentrations of plasma LDL cholesterol, because LDL carries about 65% to 75% of total plasma cholesterol. If plasma triacylglycerol levels are markedly increased, VLDL cholesterol, which is usually 5% to 10% of total plasma cholesterol, may be high enough to elevate total plasma cholesterol concentrations even when LDL cholesterol levels are normal. VLDL cholesterol may be a major component of total cholesterol in dysbetalipoproteinemic subjects (with the apo E2/2 phenotype) as well. Finally, the rare individual with significantly elevated HDL cholesterol (>80 mg/100 mL) may appear to have moderately increased total plasma cholesterol.

Elevations of LDL cholesterol can result from single gene defects, polygenic disorders, and environmental effects on lipoprotein metabolism. Familial hypercholesterolemia (FH), which occurs in the heterozygous form in approximately 1 in 300 to 500 individuals, is associated with mutations in the gene for the LDL receptor (Brown and Goldstein, 1984). Plasma total and LDL cholesterol concentrations are increased at birth in FH subjects and remain so throughout life. In heterozygous FH adults, total cholesterol levels range from 300 to 500 mg/100 mL in the untreated state, and both tendon xanthomas (accumulations of cholesteryl ester–filled macrophages over tendons, particularly the Achilles tendon) and premature atherosclerosis with coronary artery disease (CAD) are common. Plasma triacylglycerol concentrations are typically normal, whereas HDL cholesterol levels may be normal or reduced. Metabolic studies have demonstrated decreased fractional clearance of LDL apo B in subjects with FH, consistent with reduced numbers of LDL receptors, although increased production of LDL has also been observed. The latter may be the result of more efficient conversion of VLDL to LDL in the FH patients as a concomitant of reduced LDL receptor function and reduced VLDL remnant removal from plasma. On the other hand, increased assembly and secretion of VLDL (or denser apo B–containing lipoproteins) may be a concomitant of defective hepatic catabolism of circulating LDL. In any event, markedly elevated levels of LDL cholesterol are the hallmark of FH and are associated with increased risk for CAD in these patients. The homozygous form of FH occurs in 1 of 1 million individuals and is associated with plasma cholesterol levels >500 mg/100 mL, large tendon and planar xanthomas, and very aggressive, premature CAD. These individuals almost always develop clinically significant CAD by early adulthood, often during adolescence.

Recently, a second single gene disorder that causes significant elevations of LDL cholesterol has been identified. A mutation in apo B, in the region of the protein associated with binding to the LDL receptor, has been linked to defective catabolism of LDL in vivo and to hypercholesterolemia. It is transmitted in an autosomal dominant fashion. Finally, subjects with familial combined hyperlipidemia, which is discussed later, can present with isolated elevations of LDL cholesterol (Goldstein et al., 1973).

Polygenic causes of hypercholesterolemia are much commoner than FH. In polygenic hypercholesterolemia, the environment plays a greater role in determining plasma LDL cholesterol concentrations. Most evidence indicates that both overproduction and reduced fractional catabolism of LDL play significant roles in the pathophysiology of this disorder. Both abnormal variables are probably affected...
## Characteristics of Common Hyperlipidemias

<table>
<thead>
<tr>
<th>Type</th>
<th>Plasma Lipid Levels</th>
<th>Lipoproteins</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated Hypercholesterolemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Heterozygotes</td>
<td>LDL</td>
<td>Usually develop xanthomas in adulthood and vascular disease at 30-50 y</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol = 300–500 mg/100 mL</td>
<td></td>
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<tr>
<td>Homozygotes</td>
<td></td>
<td>LDL</td>
<td>Usually develop xanthomas ar vascular disease in childhood</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol = 400–800 mg/100 mL</td>
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</tr>
<tr>
<td>Polygenic hypercholesterolemia</td>
<td></td>
<td>LDL</td>
<td>Usually asymptomatic until vascular disease develops; xanthomas</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol = 225–350 mg/100 mL</td>
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<td></td>
</tr>
<tr>
<td><strong>Isolated Hypertriglyceridemia</strong></td>
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<tr>
<td>Mild</td>
<td>Triacylglycerols = 250–750 mg/100 mL (plasma may be cloudy)</td>
<td>VLDL</td>
<td>Asymptomatic; may be associated with increased risk of vascular disease</td>
</tr>
<tr>
<td>Severe</td>
<td>Triacylglycerols &gt; 750 mg/100 mL (plasma may be milky)</td>
<td>Chylomicrons, VLDL</td>
<td>May be asymptomatic; may be associated with pancreatitis, abdominal pain, hepatosplenomegaly</td>
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<tr>
<td><strong>Hypertriglyceridemia and Hypercholesterolemia</strong></td>
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<td></td>
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<tr>
<td>Combined hyperlipidemia</td>
<td>Triacylglycerols = 250–750 mg/100 mL</td>
<td>VLDL</td>
<td>Usually asymptomatic until vascular disease develops; familial form (FCHL) may also present as isolated high triacylglycerols or as isolated high LDL cholesterol</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol = 250–500 mg/100 mL</td>
<td>LDL</td>
<td></td>
</tr>
<tr>
<td>Dysbetaalipoproteinemia</td>
<td>Triacylglycerols = 250–500 mg/100 mL</td>
<td>VLDL, IDL</td>
<td>Usually asymptomatic until vascular disease develops; may have palmar or tuberous xanthoma</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol = 250–500 mg/100 mL</td>
<td>VLDL, IDL</td>
<td></td>
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<tr>
<td><strong>Low HDL Cholesterol</strong></td>
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<tr>
<td>Associated with hypertriglyceridemia</td>
<td>HDL = 20–35 mg/100 mL</td>
<td>HDL</td>
<td>Usually asymptomatic; may increase risk for vascular disease</td>
</tr>
<tr>
<td></td>
<td>Total triacylglycerols &gt; 250 mg/100 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hypoalphalipoproteinemia</td>
<td>HDL = 5–25 mg/100 mL</td>
<td>HDL</td>
<td>Depending on etiology, may be asymptomatic; often associated with increased vascular disease</td>
</tr>
<tr>
<td></td>
<td>Total triacylglycerols &lt; 250 mg/100 mL</td>
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HDL, high density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; VLDL, very low density lipoproteins.

By dietary saturated fat and cholesterol consumption, by age, and by level of physical activity. Plasma total cholesterol levels are in the 250- to 350-mg/100 mL range. Plasma triacylglycerol and HDL cholesterol levels are usually normal. Tendon xanthomas are not present in these individuals. It is very likely that as genes related to regulation of cholesterol metabolism are identified, some of the polygenic forms of hypercholesterolemia will be found to be due to the interaction of two or more specific genes.

**Hypertriglyceridemia.** Elevated levels of fasting plasma triacylglycerol—in the range of 250 to 750 mg/100 mL—are generally associated with increased concentrations of VLDL triacylglycerols. When VLDL triacylglycerol levels are markedly elevated (regardless of etiology) or when lipoprotein lipase is either
significantly reduced or totally deficient, chylomicron triacylglycerols may also be present, even after a 14-hour fast. Elevations in plasma triacylglycerols most often are associated with the synthesis and secretion of excessive quantities of VLDL triacylglycerol by the liver (Ginsberg et al., 1985). Hepatic triacylglycerol synthesis is regulated by substrate flow (particularly the availability of free fatty acids), by energy status (particularly the level of glycogen stores in the liver), and by hormonal status (particularly the balance between insulin and glucagon levels). Obesity, excessive consumption of simple sugars and saturated fats, inactivity, alcohol consumption, and glucose intolerance or diabetes mellitus commonly have been associated with hypertriglyceridemia. Although no single gene disorder associated with increased hepatic synthesis of triacylglycerols has been identified, recent studies have suggested a link between abnormal bile acid metabolism and overproduction of triacylglycerols in some subjects with hypertriglyceridemia. It is believed that in this group of disorders, sometimes referred to as primary hypertriglyceridemia, only triacylglycerol synthesis is increased, and therefore the liver secretes a normal number of large, triacylglycerol-enriched VLDL particles. The secretion of a normal number of VLDL particles limits the rate of production of LDL particles, and these subjects may not be at increased risk for coincident elevations of LDL cholesterol. It should be noted, however, that subjects with familial combined hyperlipidemia, who will be described later, can present with isolated hypertriglyceridemia.

The degree of hypertriglyceridemia present in any individual will also depend on the quantity and activity of the two key triacylglycerol hydrolases, lipoprotein lipase and hepatic lipase. Most data suggest that lipoprotein lipase is normal in the majority of subjects with moderate hypertriglyceridemia (250 to 500 mg triacylglycerol/100 mL plasma), but lipoprotein lipase activity may be reduced in more severely affected individuals (>750 mg/100 mL). Several recent studies have suggested that heterozygosity for lipoprotein lipase deficiency, derived from specific mutations, occurs in about 5% to 10% of the hypertriglyceridemic population. Additionally, when VLDL triacylglycerol concentrations are markedly elevated (>1000 mg/100 mL), lipoprotein lipase may be saturated with substrate so that, in effect, the subject is relatively deficient in the enzyme during the postprandial period. Chylomicron triacylglycerols may then add to hypertriglyceridemia. If lipoprotein lipase is totally deficient, plasma triacylglycerol concentrations greater than 2000 mg/100 mL are commonly seen, with both chylomicrons and VLDL making significant contributions to the hyperlipidemic state. Hepatic lipase activity is frequently elevated in hypertriglyceridemic subjects, but the significance of this association is unclear; the high hepatic lipase activity may be relevant to the reduced HDL cholesterol levels found in this condition because hepatic lipase can hydrolyze HDL phospholipids and destabilize the HDL particle. Additionally, HDL can be elevated in subjects with a deficiency of hepatic lipase, a rare disorder in humans that results in defective final catabolism and/or abnormal remodeling of small VLDL and LDL.

**Hypertriglyceridemia with Hypercholesterolemia.** Hypertriglyceridemia can also occur in association with hypercholesterolemia in two phenotypes. In the first, called combined hyperlipidemia, both total plasma triacylglycerols and LDL cholesterol concentrations must, by definition, be greater than the 90th percentiles for age- and sex-matched controls (Goldstein et al., 1973). Although it is likely that a variety of combinations of regulatory defects in lipid metabolism account for a significant number of individuals with this phenotype, a familial form of combined hyperlipidemia (FCHL) has been identified in which probands (the initial case discovered within the family) may present with combined hyperlipidemia, with only hypertriglyceridemia, or with only elevated levels of LDL cholesterol. In the familial disorder, which appears to be transmitted as an autosomal dominant gene, the diagnosis must rest on the presentation, at some point in time, of combined hyperlipidemia in the proband or, alternatively, the presence of various lipid phenotypes in first-degree family members, along with either isolated hypertriglyceridemia or an isolated elevation of LDL cholesterol in the
proband. FCHL is not associated with abnormalities in LDL receptors. Thus, FCHL is not related to FH pathophysiology.

From available studies, FCHL appears to be associated with secretion of increased numbers of VLDL particles (as determined by the flux of VLDL apo B) (Arad et al., 1990). Hence, individuals with FCHL will be predisposed to high levels of plasma VLDL triacylglycerols if, for any other reason (see earlier), they synthesize triacylglycerols at an increased rate. Once they have assembled and secreted increased numbers of large, triacylglycerol-rich VLDL, these individuals will attain varying levels of plasma triacylglycerols, dependent upon their ability to hydrolyze VLDL triacylglycerol (via lipoprotein lipase and, to a lesser degree, hepatic lipase). The ability to hydrolyze VLDL triacylglycerols will also regulate the generation of LDL in plasma. Thus, subjects with FCHL who have very high VLDL triacylglycerol concentrations might have normal or actually reduced numbers of LDL particles in the circulation and a normal LDL cholesterol concentration (if they are not able to catabolize VLDL efficiently). On the other hand, if individuals with FCHL are able to efficiently catabolize the increased numbers of VLDL particles that are entering their plasma, they will generate increased numbers of LDL particles and present with both hypertriglyceridemia and a high LDL cholesterol level. Finally, subjects with FCHL who are synthesizing only normal quantities of triacylglycerols, but secreting increased numbers of VLDL carrying normal triacylglycerol loads, will generate increased numbers of LDL particles and present with only elevated plasma LDL cholesterol concentrations. FCHL may occur in as many as 1 in 50 to 100 Americans; it is the most common familial lipid disorder found in survivors of myocardial infarction (Goldstein et al., 1973). Recent studies have demonstrated links between combined hyperlipidemia and insulin resistance (Reaven, 1988); the pathophysiological basis for this link is undefined presently.

The second disorder in which elevations of both plasma triacylglycerols and cholesterol can occur is dysbetalipoproteinemia. In this rare disorder affecting 1 in 10,000 people, mutations in the gene for apo E result in synthesis of defective forms of this protein. Apparently, because apo E plays roles in the catabolism of chylomicron VLDL remnants (Mahley, 1988), sube defective apo E accumulate these cholesterol-enriched remnant lipoproteins plasma. Hence, both VLDL triacylglycerols and cholesterol are elevated and cholesterol remnants are present in fasting plasma. From dysbetalipoproteinemic subjects, cholesterol levels are not elevated in order. Therefore, the data indicate that apo E (the apo E2 isoform) is the most important element. Ninety percent of these apo E2/2 subjects have normal plasma triacylglycerol and cholesterol levels; they also have reduced LDL cholesterol levels, possibly as a consequence of an enhanced ability to process VLDL normally. Therefore, the defect in lipid metabolism, not apo E2/2 genotype, must be present in 10,000 individuals with the clinically entity, dysbetalipoproteinemia.

Reduced HDL Cholesterol. Low concentrations of HDL cholesterol are most often seen in subjects with coexistent hypertriglyceridemia, although "primary hypoalphalipoproteinemia" has been identified in both males and females. The pathophysiological basis of reduced HDL cholesterol concentrations is not well defined and is probably complex (Horowitz et al., 1993; Tall). The relationship between hypertriglyceridemia and low HDL levels probably derive from HDL catabolism, (1) the cholesteryl ester transfer (CETP)-mediated transfer of cholesteryl esters from HDL to VLDL, (2) the surface components, particularly phospholipids and apolipoproteins C-II and C-IV, and (3) HDL to VLDL, and (4) the increased HDL cholesterol concentrations, by the catabolism of the cholesteryl ester-poor HDL that results from these processes. The complexity of the situation is highlighted, in most patients who partially with hypertriglyceridemia and low HDL cholesterol concentrations, by the HDL levels to normalize when fasting triacylglycerols are significantly reduced.