INTRODUCTION

Lipoproteins are complex molecular assemblies with highly evolved, diverse functions. Lipoproteins are synthesized by the jejunum, liver, and periphery and serve to shuttle lipids (phospholipids and triglycerides), cholesterol, and cholesterol esters between a large number of cell types. Although cholesterol is pathogenic when available in excess, this crucial sterol functions to modulate cell membrane fluidity, is a precursor to steroid hormones and bile salts, and can modulate the activity of a variety of membrane-bound enzymes. Therapeutic modulation of lipid metabolism has become one of the cornerstones for preventing the development and progression of atherosclerotic disease in both the primary and the secondary prevention settings. Reducing the burden of such atherogenic lipoproteins in serum as very low-density and low-density lipoproteins (VLDLs and LDLs, respectively) is a major focus of cardiovascular medicine. Precisely defined, evidence-based targets for atherogenic lipoproteins have been promulgated by the National Cholesterol Education Program (1,2).

Atherogenic lipoproteins promote the net uptake and deposition of cholesterol within macrophages localizing to the subendothelial space of arteries. A large number of clinical trials have shown that LDL reduction is associated with significant attenuation of risk for cardiovascular morbidity and mortality (3–5). However, even with very aggressive reductions in serum LDL, the majority of acute cardiovascular events are still not prevented (6,7). Consequently, a major focus of current investigation is to
further elucidate the role of emerging risk factors in atherogenesis and how they interact with or amplify the deleterious effects of established risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, and cigarette smoking.

One of the most important risk factors for myocardial infarction (MI), stroke, sudden death, premature coronary artery disease (CAD), and peripheral arterial disease is a low serum level of high-density lipoprotein (HDL) (8, 9). Unlike atherogenic lipoproteins, the HDLs exert a large number of beneficial, vasculoprotective effects. This chapter will review HDL metabolism, the epidemiology linking low levels of this lipoprotein to increased risk for acute cardiovascular and cerebrovascular events, as well as established and investigational means by which to raise the serum levels of this important lipoprotein.

ANTIATHEROGENIC EFFECTS OF HDL

Reverse Cholesterol Transport

HDL particles are comprised of a charged, hydrophilic phospholipid surface. Triglycerides and cholesteryl esters (CEs) are concentrated within the hydrophobic core of these particles. HDLs carry a variety of apoproteins, the most important being apoprotein A-I (apoA-I). Other apoproteins bound to HDLs include apoproteins A-II, C-I, C-II, C-III, E, and J (clusterin). HDLs are also able to bind a variety of enzymes that perform diverse catalytic functions, such as lipid transfer and exchange, peroxide reduction, and cholesterol esterification. In older nomenclature, HDLs were described as α-lipoproteins, because of their mobility patterns in electrophoretic fields.

All somatic cells have the capacity to synthesize cholesterol. Cholesterol plays many important roles in metabolism. Cholesterol is soluble in cell membranes and modulates the fluidity of the hydrocarbon phase of phospholipid bilayers and the activity of membrane-bound enzymes. Cholesterol is a precursor to steroid hormone biosynthesis in steroidogenic organs and bile salts in hepatocytes. Cholesterol derived from the gut, liver, and systemic tissues is exchanged among lipoproteins which shuttle lipids and sterols among the various somatic lipid pools.

Unlike hepatocytes, somatic cells are unable to catabolize cholesterol. During atherogenesis, LDL migrates into the intima and subendothelial space of blood vessel walls in response to a variety of inflammatory, histologic, and thermodynamic driving forces. When exposed to modified LDL particles, macrophages upregulate scavenger receptors (SRs) (CD36, SR A) and take up LDL, promoting foam cell formation. Unless these cells can externalize intracellular cholesterol, net uptake will continue until the macrophage dies.

The HDLs regulate cholesterol balance in systemic tissues. These lipoproteins are able to interact with macrophages, promote cellular exporting of cholesterol, and deliver the cholesterol back to the liver for elimination or for repackaging into apoB-100-containing lipoproteins via a pathway defined as reverse cholesterol transport (RCT). The HDLs also deliver cholesterol to steroidogenic organs such as the adrenal, ovaries, testes, and placenta. If serum HDL levels are low or if any of the multiple steps of RCT are impaired, the capacity for systemic cholesterol clearance is reduced and risk for atherosclerotic disease is frequently increased.

ApoA-I is produced by both the jejunum and the liver and is secreted into blood in either its free or nonlipidated state or as a surface coat component of chylomicrons and VLDL. Nonlipidated apoA-I binds phospholipids and forms nascent discoidal HDL