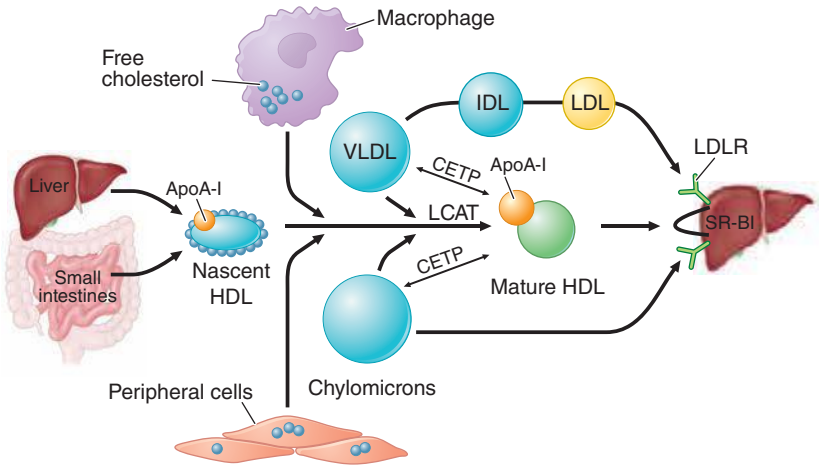

FIGURE 421-3 High-density lipoprotein (HDL) metabolism and reverse cholesterol transport. This pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDLs. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by lecithin-cholesterol acyltransferase (LCAT), forming mature HDLs. HDL cholesterol can be selectively taken up by the liver via SR-BI (scavenger receptor class BI). Alternatively, HDL cholesteryl ester can be transferred by cholesteryl ester transfer protein (CETP) from HDLs to very-low-density lipoproteins (VLDLs) and chylomicrons, which can then be taken up by the liver. IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

of synthesis (intestine or liver) via efflux promoted by the membrane protein ATP-binding cassette protein A1 (ABCA1). This process results in the formation of discoidal HDL particles, which then recruit additional unesterified cholesterol from cells or circulating lipoproteins. Within the HDL particle, the cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL, and the more hydrophobic cholesteryl ester moves to the core of the HDL particle. As HDL acquires more cholesteryl ester, it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDLs during lipolysis.

HDL cholesterol is transported to hepatocytes by both an indirect and a direct pathway. HDL cholesteryl esters can be transferred to apoB-containing lipoproteins in exchange for triglyceride by the cholesteryl ester transfer protein (CETP). The cholesteryl esters are then removed from the circulation by LDL receptor–mediated endocytosis. HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class B1 (SR-B1), a cell surface receptor that mediates the selective transfer of lipids to cells.

HDL particles undergo extensive remodeling within the plasma compartment by a variety of lipid transfer proteins and lipases. The phospholipid transfer protein (PLTP) transfers phospholipids from other lipoproteins to HDL or among different classes of HDL particles. After CETP- and PLTP-mediated lipid exchange, the triglyceride-enriched HDL becomes a much better substrate for HL, which hydrolyzes the triglycerides and phospholipids to generate smaller HDL particles. A related enzyme called *endothelial lipase* hydrolyzes HDL phospholipids, generating smaller HDL particles that are catabolized faster. Remodeling of HDL influences the metabolism, function, and plasma concentrations of HDL.

DISORDERS OF ELEVATED CHOLESTEROL AND TRIGLYCERIDES

Disorders of lipoprotein metabolism are collectively referred to as "dyslipidemias." Dyslipidemias are generally characterized clinically by increased plasma levels of cholesterol, triglycerides, or both, variably accompanied by reduced levels of HDL cholesterol. Because plasma lipids are commonly screened (see below), dyslipidemia is frequently seen in clinical practice. The majority of patients with dyslipidemia have some combination of genetic predisposition (often polygenic) and environmental contribution (lifestyle, medical condition, or drug). Many, but not all, patients with dyslipidemia are at increased risk for ASCVD, the primary reason for making the diagnosis, as intervention may reduce this risk. In addition, patients with substantially elevated levels of triglycerides may be at risk for acute pancreatitis and require intervention to reduce this risk.

Although literally hundreds of proteins influence lipoprotein metabolism and may interact to produce dyslipidemia in an individual patient, there are a limited number of discrete "nodes" that regulate lipoprotein metabolism. These include: (1) assembly and secretion of triglyceride-rich VLDLs by the liver; (2) lipolysis of triglyceride-rich lipoproteins by LPL; (3) receptor-mediated uptake of apoB-containing lipoproteins by the liver; (4) cellular cholesterol metabolism in the hepatocyte and the enterocyte; and (5) neutral lipid transfer and phospholipid hydrolysis in the plasma. The following discussion will focus on these regulatory nodes, recognizing that in many cases these nodes interact with and influence each other.

DYSLIPIDEMIA CAUSED BY EXCESSIVE HEPATIC SECRETION OF VLDL

Excessive production of VLDL by the liver is one of the most common causes of dyslipidemia. Individuals with excessive hepatic VLDL production usually have elevated fasting triglycerides and low levels of HDL cholesterol (HDL-C), with variable elevations in LDL cholesterol (LDL-C) but usually elevated plasma levels of apoB. A cluster of other metabolic risk factors are often found in association with VLDL overproduction, including obesity, glucose intolerance, insulin resistance, and hypertension (the so-called metabolic syndrome, Chap. 422). Some of the major factors that drive hepatic VLDL secretion include obesity, insulin resistance, a high-carbohydrate diet, alcohol use, exogenous estrogens, and genetic predisposition.

Secondary Causes of VLDL Overproduction • ***HIGH-CARBOHYDRATE DIET*** Dietary carbohydrates are converted to fatty acids in the liver. Some of the newly synthesized fatty acids are esterified forming triglycerides (TGs) and secreted as constituents of VLDL. Thus, excessive intake of calories as carbohydrates, which is frequent in Western societies, leads to increased hepatic VLDL-TG secretion.

ALCOHOL Regular alcohol consumption inhibits hepatic oxidation of free fatty acids, thus promoting hepatic TG synthesis and VLDL secretion. Regular alcohol use also raises plasma levels of HDL-C and should be considered in patients with the unusual combination of elevated TGs and elevated HDL-C.

OBESITY AND INSULIN RESISTANCE (See also Chaps. 416 and 417) Obesity and insulin resistance are frequently accompanied by dyslipidemia characterized by elevated plasma levels of TG, low HDL-C, variable levels of LDL-C, and increased levels of small dense LDL. The increase in adipocyte mass and accompanying decreased insulin sensitivity associated with obesity have multiple effects on lipid metabolism, with one of the major effects being excessive hepatic VLDL production. More free fatty acids are delivered from the expanded and insulin-resistant adipose tissue to the liver, where they are reesterified in hepatocytes to form TGs, which are packaged into VLDLs for secretion into the circulation. In addition, the increased insulin levels promote increased fatty acid synthesis in the liver. In insulin-resistant patients who progress to type 2 diabetes mellitus, dyslipidemia remains common, even when the patient is under relatively good glycemic control. In addition to increased VLDL production, insulin resistance can also result in decreased LPL activity, resulting in reduced catabolism of chylomicrons and VLDLs and more severe hypertriglyceridemia (see below).

NEPHROTIC SYNDROME (See also Chap. 335) Nephrotic syndrome is a classic cause of excessive VLDL production. The molecular