deficiency. In addition, genetic variation in a number of genes influences LDL clearance, and mutations in some of these genes cause several discrete Mendelian disorders of elevated LDL-C (Table 421-3).

Secondary Causes of Impaired Hepatic Uptake of Lipoproteins • ***HYPOTHYROIDISM*** (See also Chap. 405) Hypothyroidism is associated with elevated plasma LDL-C levels due primarily to a reduction in hepatic LDL receptor function and delayed clearance of LDL. Thyroid hormone increases hepatic expression of the LDL receptor. Hypothyroid patients also frequently have increased levels of circulating IDL, and some patients with hypothyroidism also have mild hypertriglyceridemia. Because hypothyroidism is often subtle and therefore easily overlooked, all patients presenting with elevated plasma levels of LDL-C, especially if there has been an unexplained increase in LDL-C, should be screened for hypothyroidism. Thyroid replacement therapy usually ameliorates the hypercholesterolemia; if not, the patient probably has a primary lipoprotein disorder and may require lipid-lowering drug therapy with a statin.

CHRONIC KIDNEY DISEASE (See also Chap. 335) Chronic kidney disease (CKD) is often associated with mild hypertriglyceridemia (<300 mg/dL) due to the accumulation of VLDLs and remnant lipoproteins in the circulation. TG lipolysis and remnant clearance are both reduced in patients with renal failure. Because the risk of ASCVD is increased in end-stage renal disease, subjects with hyperlipidemia, they should usually be aggressively treated with lipid-lowering agents, even though there is inadequate data at present to indicate that this population benefits from LDL-lowering therapy.

Patients with solid organ transplants often have increased lipid levels due to the effect of the drugs required for immunosuppression. These patients can present a difficult clinical management problem, since statins should be used cautiously in these patients due to untoward muscle-related side effects.

Primary (Genetic) Causes of Impaired Hepatic Uptake of Lipoproteins Genetic variation contributes substantially to elevated LDL-C levels in the general population. It has been estimated that at least 50% of variation in LDL-C is genetically determined. Many patients with elevated LDL-C have *polygenic hypercholesterolemia* characterized by hypercholesterolemia in the absence of secondary causes of hypercholesterolemia (other than dietary factors) or a primary Mendelian disorder. In patients who are genetically predisposed to higher LDL-C levels, diet plays a key role; indeed increased saturated and *trans* fats in the diet shifts the entire distribution of LDL levels in the population to the right. Inheritance of several variants that together elevate LDL-C, coupled with diet, is generally the cause of this condition; <10% of first-degree relatives themselves have hypercholesterolemia. However, single-gene (Mendelian) causes of elevated LDL-C are relatively common and should be considered in the differential diagnosis of elevated LDL-C.

FAMILIAL HYPERCHOLESTEROLEMIA (FH) FH, also known as autosomal dominant hypercholesterolemia (ADH) type 1, is an autosomal codominant disorder characterized by elevated plasma levels of LDL-C in the absence of hypertriglyceridemia. FH is caused by loss-of-function mutations in the gene encoding the LDL receptor. The reduction in LDL receptor activity in the liver results in a reduced rate of clearance of LDL from the circulation. The plasma level of LDL increases to a level such that the rate of LDL production equals the rate of LDL clearance by residual LDL receptor as well as non-LDL receptor mechanisms. More than 1600 different mutations have been reported in association with FH. The elevated levels of LDL-C in FH are primarily due to delayed removal of LDL from the blood; in addition, because the removal of IDL is also delayed, the production of LDL from IDL is also increased. Individuals with two mutated LDL receptor alleles (FH homozygotes, or compound heterozygotes) have much higher LDL-C levels than those with one mutant allele (FH heterozygotes).

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele. The population frequency of heterozygous FH due to LDL receptor mutations was originally estimated to be 1 in 500 individuals, but recent data suggest it may be as high as approximately 1 in 250 individuals, making it one of the most common single-gene disorders in humans. FH has a higher prevalence in certain founder populations, such as South African Afrikaners, Christian Lebanese, and French Canadians. Heterozygous FH is characterized by elevated plasma levels of LDL-C (usually 200–400 mg/dL) and normal levels of TGs. Patients with heterozygous FH have hypercholesterolemia from birth, and disease recognition is usually based on detection of hypercholesterolemia on routine screening, the appearance of tendon xanthomas, or the development of symptomatic cardiovascular disease. Inheritance is dominant, meaning that the condition was inherited from one parent and ~50% of the patient's siblings can be expected to have hypercholesterolemia. The family history is frequently positive for premature CHD on the side of the family from which the mutation was inherited. Physical findings in many, but not all, patients with heterozygous FH include corneal arcus and tendon xanthomas particularly involving the dorsum of the hands and the Achilles tendons. Untreated heterozygous FH is associated with a markedly increased risk of cardiovascular disease. Untreated men with heterozygous FH have an ~50% chance of having a myocardial infarction before age 60 years, and women with heterozygous FH are at substantially increased risk as well. The age of onset of cardiovascular disease is highly variable and depends on the specific molecular defect, the level of LDL-C, and coexisting cardiovascular risk factors. FH heterozygotes with elevated plasma levels of Lp(a) (see below) appear to be at greater risk for cardiovascular disease.

No definitive diagnostic test for heterozygous FH is available, except in certain founder populations where selected mutations predominate. Most LDL receptor mutations are private and require sequencing of the LDL receptor gene for identification. Sequencing for clinical diagnosis is available but not standard of care and is rarely performed in the United States, because the clinical utility of identifying the specific mutation has not been demonstrated. A family history of hypercholesterolemia and/or premature coronary disease is supportive of the diagnosis. Secondary causes of significant hypercholesterolemia such as hypothyroidism, nephrotic syndrome, and obstructive liver disease should be excluded.

Heterozygous FH patients should be aggressively treated to lower plasma levels of LDL-C, starting in childhood. Initiation of a diet low in saturated and *trans* fats is recommended, but heterozygous FH patients virtually always require lipid-lowering drug therapy for effective control of their LDL-C levels. Statins are effective in heterozygous FH and are clearly the drug class of choice, and usually a more potent member of the class. However, some heterozygous FH patients cannot achieve adequate control of their LDL-C levels even with high-dose statin therapy and require additional drugs; a cholesterol absorption inhibitor and/or a bile acid sequestrant are the next-line classes of drugs. Currently, heterozygous FH patients whose LDL-C levels remain markedly elevated (>200 mg/dL with cardiovascular disease [CVD] or >300 mg/dL without CVD) on maximally tolerated drug therapy are candidates for LDL apheresis, a physical method of purging the blood of LDL in which the LDL particles are selectively removed from the circulation; LDL apheresis is usually performed every 2 weeks. A new class of drugs known as PCSK9 inhibitors is under clinical development and has the potential to effectively control LDL-C levels in the vast majority of patients with heterozygous FH who are inadequately controlled on a statin alone or who are statin intolerant.

Homozygous FH is caused by mutations in both alleles of the LDL receptor and therefore much rarer than heterozygous FH. Patients with homozygous FH have been classified into those patients with virtually no detectable LDL receptor activity (*receptor negative*) and those patients with markedly reduced but detectable LDL receptor activity (*receptor defective*). LDL-C levels in patients with homozygous FH range from about 400 to >1000 mg/dL, with receptor-defective patients at the lower end and receptor-negative patients at the higher end of the range. TGs are usually normal. Many patients with homozygous FH, particularly receptor-negative patients, present in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, or