receptor-mediated endocytosis. A genetic defect in a receptor-mediated transport system is exemplified by familial hypercholesterolemia, in which reduced synthesis or function of LDL receptors leads to defective transport of LDL into the cells and secondarily to excessive cholesterol synthesis by complex intermediary mechanisms. In cystic fibrosis the transport system for chloride ions in exocrine glands, sweat ducts, lungs, and pancreas is defective. By mechanisms not fully understood, impaired chloride transport leads to serious injury to the lungs and pancreas (Chapter 10).

Alterations in Structure, Function, or Quantity of Nonenzyme Proteins

Genetic defects resulting in alterations of nonenzyme proteins often have widespread secondary effects, as exemplified by sickle cell disease. The hemoglobinopathies, sickle cell disease being one, all of which are characterized by defects in the structure of the globin molecule, best exemplify this category. In contrast to the hemoglobinopathies, the thalassemias result from mutations in globin genes that affect the amount of globin chains synthesized. Thalassemias are associated with reduced amounts of structurally normal α-globin or β-globin chains (Chapter 14). Other examples of genetic disorders involving defective structural proteins include collagen, spectrin, and dystrophin, giving rise to osteogenesis imperfecta (Chapter 26), hereditary spherocytosis (Chapter 14), and muscular dystrophies (Chapter 27), respectively.

Genetically Determined Adverse Reactions to Drugs

Certain genetically determined enzyme deficiencies are unmasked only after exposure of the affected individual to certain drugs. This special area of genetics, called *pharmacogenetics*, is of considerable clinical importance. The classic example of drug-induced injury in the genetically susceptible individual is associated with a deficiency of the enzyme G6PD. Under normal conditions glucose-6 phosphate-dehydrogenase (G6PD) deficiency does not result in disease, but on administration, for example, of the antimalarial drug primaquine, a severe hemolytic anemia results (Chapter 14). In recent years an increasing number of polymorphisms of genes encoding drug-metabolizing enzymes, transporters, and receptors have been identified. In some cases these genetic factors have major impact on drug sensitivity and adverse reactions. It is hoped that advances in pharmacogenetics will lead to patient-tailored therapy, an example of "personalized medicine."

With this overview of the biochemical basis of single-gene disorders, we now consider selected examples grouped according to the underlying defect.

Disorders Associated with Defects in Structural Proteins

Several diseases caused by mutations in genes that encode structural proteins are listed in Table 5-4. Many are discussed elsewhere in the text. Only Marfan syndrome and Ehlers-Danlos syndromes (EDSs) are discussed here, because they affect connective tissue and hence involve multiple organ systems.

Marfan Syndrome

Marfan syndrome is a disorder of connective tissues, manifested principally by changes in the skeleton, eyes, and cardiovascular system. Its prevalence is estimated to be 1 in 5000. Approximately 70% to 85% of cases are familial and transmitted by autosomal dominant inheritance. The remainder are sporadic and arise from new mutations.

Pathogenesis. **Marfan syndrome results from an inherited defect in an extracellular glycoprotein called *fibrillin-1*.** There are two fundamental mechanisms by which loss of fibrillin leads to the clinical manifestations of Marfan syndrome: loss of structural support in microfibril rich connective tissue and excessive activation of TGF-β signaling. Each of these is discussed below.

- Fibrillin is the major component of microfibrils found in the extracellular matrix (Chapter 1). These fibrils provide a scaffolding on which tropoelastin is deposited to form elastic fibers. Although microfibrils are widely distributed in the body, they are particularly abundant in the aorta, ligaments, and the ciliary zonules that support the lens; these tissues are prominently affected in Marfan syndrome. Fibrillin occurs in two homologous forms, fibrillin-1 and fibrillin-2, encoded by two separate genes, *FBN1* and *FBN2,* mapped on chromosomes 15q21.1 and 5q23.31, respectively. Mutations of *FBN1* underlie Marfan syndrome; mutations of the related *FBN2* gene are less common, and they give rise to *congenital contractural arachnodactyly*, an autosomal dominant disorder characterized by skeletal abnormalities. Mutational analysis has revealed more than 600 distinct mutations of the *FBN1* gene in individuals with Marfan syndrome. Most of these are missense mutations that give rise to abnormal fibrillin-1. These can inhibit polymerization of fibrillin fibers (dominant negative effect). Alternatively, the reduction of fibrillin content below a certain threshold weakens the connective tissue (haploinsufficiency).
- While many clinical manifestations of Marfan syndrome can be explained by changes in the mechanical properties of the extracellular matrix resulting from abnormalities of fibrillin, several others such as bone overgrowth and myxoid changes in mitral valves cannot be attributed to changes in tissue elasticity. Recent studies indicate that loss of microfibrils gives rise to abnormal and excessive activation of transforming growth factor-β (TGF-β), since normal microfibrils sequester TGF-β and thus control the bioavailability of this cytokine. Excessive TGF-β signaling has deleterious effects on vascular smooth muscle development and it also increases the activity of metalloproteases, causing loss of extracellular matrix. This schema is supported by two sets of observations. First, in a small number of individuals with clinical features of Marfan syndrome (MFS2), there are no mutations in *FBN1* but instead gain-of-function mutations in genes that encode TGF-β receptors. Second, in mouse models of Marfan syndrome generated by mutations in *Fbn1*, administration of antibodies to TGF-β prevents alterations in the aorta and mitral valves.