diseases arising from deleterious mutations fall into one of a few familiar patterns:

1. *Those involved in regulation of complex metabolic pathways that are subject to feedback inhibition.* Membrane receptors such as the low-density lipoprotein (LDL) receptor provide one such example; in familial hypercholesterolemia, discussed later, a 50% loss of LDL receptors results in a secondary elevation of cholesterol that, in turn, predisposes to atherosclerosis in affected heterozygotes.
2. *Key structural proteins, such as collagen and cytoskeletal elements of the red cell membrane* (e.g., spectrin). The biochemical mechanisms by which a 50% reduction in the amounts of such proteins results in an abnormal phenotype are not fully understood. In some cases, especially when the gene encodes one subunit of a multimeric protein, the product of the mutant allele can interfere with the assembly of a functionally normal multimer. For example, the collagen molecule is a trimer in which the three collagen chains are arranged in a helical configuration. Each of the three collagen chains in the helix must be normal for the assembly and stability of the collagen molecule. Even with a single mutant collagen chain, normal collagen trimers cannot be formed, and hence there is a marked deficiency of collagen. In this instance the mutant allele is called *dominant negative*, because it impairs the function of a normal allele. This effect is illustrated by some forms of osteogenesis imperfecta, characterized by marked deficiency of collagen and severe skeletal abnormalities (Chapter 26).

Less common than loss-of-function mutations are *gain-of-function* mutations, which can take two forms. Some mutations result in an increase in a protein's normal function, for example, excessive enzymatic activity. In other cases, mutations impart a wholly new activity completely unrelated to the affected protein's normal function. The transmission of disorders produced by gain-of-function mutations is almost always autosomal dominant, as illustrated by Huntington disease (Chapter 28). In this disease the trinucleotide-repeat mutation affecting the Huntington gene (see later) gives rise to an abnormal protein, called *huntingtin*, that is toxic to neurons, and hence even heterozygotes develop a neurologic deficit.

Table 5-1 lists common autosomal dominant disorders. Many are discussed more logically in other chapters. A few conditions not considered elsewhere are discussed later in this chapter to illustrate important principles.

Autosomal Recessive Disorders

Autosomal recessive traits make up the largest category of Mendelian disorders. They occur when both alleles at a given gene locus are mutated. These disorders are characterized by the following features: (1) The trait does not usually affect the parents of the affected individual, but siblings may show the disease; (2) siblings have one chance in four of having the trait (i.e., the recurrence risk is 25% for each birth); and (3) if the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the affected individual (proband) is the product of a consanguineous marriage. The following features generally apply to most autosomal recessive disorders and distinguish them from autosomal dominant diseases:

Table 5-1 Autosomal Dominant Disorders

System	Disorder
Nervous	Huntington disease Neurofibromatosis Myotonic dystrophy Tuberous sclerosis
Urinary	Polycystic kidney disease
Gastrointestinal	Familial polyposis coli
Hematopoietic	Hereditary spherocytosis von Willebrand disease
Skeletal	Marfan syndrome* Ehlers-Danlos syndrome (some variants)* Osteogenesis imperfecta Achondroplasia
Metabolic	Familial hypercholesterolemia* Acute intermittent porphyria

*Discussed in this chapter. Other disorders listed are discussed in appropriate chapters in the book.

- The expression of the defect tends to be more uniform than in autosomal dominant disorders.
- Complete penetrance is common.
- Onset is frequently early in life.
- Although new mutations associated with recessive disorders do occur, they are rarely detected clinically. Since the individual with a new mutation is an asymptomatic heterozygote, several generations may pass before the descendants of such a person mate with other heterozygotes and produce affected offspring.
- Many of the mutated genes encode enzymes. In heterozygotes, equal amounts of normal and defective enzyme are synthesized. Usually the natural "margin of safety" ensures that cells with half the usual complement of the enzyme function normally.

Autosomal recessive disorders include almost all inborn errors of metabolism. The various consequences of enzyme deficiencies are discussed later. The more common of these conditions are listed in Table 5-2. Most are presented elsewhere; a few prototypes are discussed later in this chapter.

Table 5-2 Autosomal Recessive Disorders

System	Disorder
Metabolic	Cystic fibrosis Phenylketonuria Galactosemia Homocystinuria Lysosomal storage diseases* α_1-Antitrypsin deficiency Wilson disease Hemochromatosis Glycogen storage diseases*
Hematopoietic	Sickle cell anemia Thalassemias
Endocrine	Congenital adrenal hyperplasia
Skeletal	Ehlers-Danlos syndrome (some variants)* Alkaptonuria*
Nervous	Neurogenic muscular atrophies Friedreich ataxia Spinal muscular atrophy

*Discussed in this chapter. Many others are discussed elsewhere in the text.