Table 5-4 Biochemical and Molecular Basis of Some Mendelian Disorders

Protein Type/ Function	Example	Molecular Lesion	Disease
Enzyme	Phenylalanine hydroxylase	Splice-site mutation: reduced amount	Phenylketonuria
	Hexosaminidase	Splice-site mutation or frameshift mutation with stop codon: reduced amount	Tay-Sachs disease
	Adenosine deaminase	Point mutations: abnormal protein with reduced activity	Severe combined immunodeficiency
Enzyme inhibitor	α_1-Antitrypsin	Missense mutations: impaired secretion from liver to serum	Emphysema and liver disease
Receptor	Low-density lipoprotein receptor	Deletions, point mutations: reduction of synthesis, transport to cell surface, or binding to low-density lipoprotein	Familial hypercholesterolemia
	Vitamin D receptor	Point mutations: failure of normal signaling	Vitamin D–resistant rickets
Transport			
Oxygen	Hemoglobin	Deletions: reduced amount	α-Thalassemia
		Defective mRNA processing: reduced amount	β-Thalassemia
		Point mutations: abnormal structure	Sickle cell anemia
Ion channels	Cystic fibrosis transmembrane conductance regulator	Deletions and other mutations: nonfunctional or misfolded proteins	Cystic fibrosis
Structural			
Extracellular	Collagen	Deletions or point mutations cause reduced amount of normal collagen or normal amounts of defective collagen	Osteogenesis imperfecta; Ehlers-Danlos syndromes
	Fibrillin	Missense mutations	Marfan syndrome
Cell membrane	Dystrophin	Deletion with reduced synthesis	Duchenne/Becker muscular dystrophy
	Spectrin, ankyrin, or protein 4.1	Heterogeneous	Hereditary spherocytosis
Hemostasis	Factor VIII	Deletions, insertions, nonsense mutations, and others: reduced synthesis or abnormal factor VIII	Hemophilia A
Growth regulation	Rb protein	Deletions	Hereditary retinoblastoma
	Neurofibromin	Heterogeneous	Neurofibromatosis type 1

consequences of an enzyme defect in such a reaction may lead to three major consequences:

- *Accumulation of the substrate*, depending on the site of block, may be accompanied by accumulation of one or both intermediates. Moreover, an increased concentration of intermediate 2 may stimulate the minor pathway and thus lead to an excess of M1 and M2. Under these conditions tissue injury may result if the precursor, the intermediates, or the products of alternative minor pathways are toxic in high concentrations. For example, in galactosemia, the deficiency of galactose-1-phosphate uridyltransferase (Chapter 10) leads to the accumulation of galactose and consequent tissue damage. Excessive accumulation of complex substrates within the lysosomes as a result of deficiency of degradative enzymes is responsible for a group of diseases generally referred to as *lysosomal storage diseases.*
- *An enzyme defect can lead to a metabolic block and a decreased amount of end product* that may be necessary for normal function. For example, a deficiency of melanin may result from lack of tyrosinase, which is necessary for the biosynthesis of melanin from its precursor, tyrosine, resulting in the clinical condition called *albinism.* If the end product is a feedback inhibitor of the enzymes involved in the early reactions (in Fig. 5-5 it is shown that the product inhibits enzyme 1), the deficiency of the end product may permit overproduction of intermediates and their catabolic products, some of which may be injurious at high concentrations. A prime example of a disease with such an underlying mechanism is the Lesch-Nyhan syndrome (Chapter 26).
- *Failure to inactivate a tissue-damaging substrate* is best exemplified by α_1-antitrypsin deficiency. Individuals who have an inherited deficiency of serum α_1-antitrypsin are unable to inactivate neutrophil elastase in their lungs. Unchecked activity of this protease leads to destruction of elastin in the walls of lung alveoli, leading eventually to pulmonary emphysema (Chapter 15).

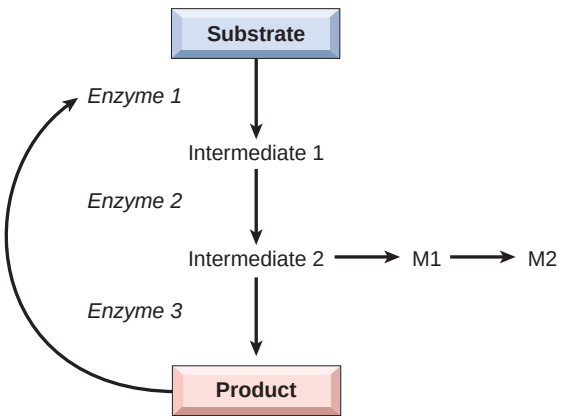

Figure 5-5 A possible metabolic pathway in which a substrate is converted to an end product by a series of enzyme reactions. M1, M2, products of a minor pathway.

Defects in Receptors and Transport Systems

As we discussed in chapter 1, biologically active substances have to be actively transported across the cell membrane. In some cases transport is achieved by