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third edition

临床病理生理学

Pathophysiology of Disease

An Introduction to Clinical Medicine

Stephen J. McPhee
Vishwanath R. Lingappa
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Pathophysiology of Disease: An Introduction to Clinical Medicine, 3/e

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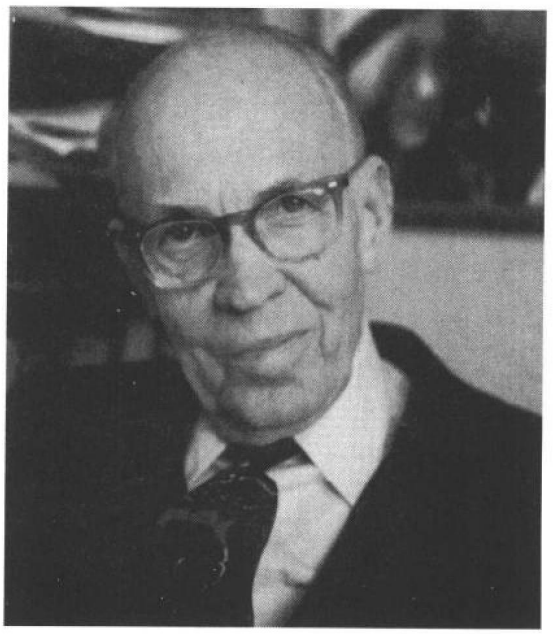
This book was set in Times Roman by Pine Tree Composition.
The editors were David Barnes, Jim Ransom, and Harriet Lebowitz.
The production supervisor was Frank Del Vecchio.
The production service was Pine Tree Composition.
The cover designer was Elizabeth Schmitz.
The art manager was Eve Siegel.
The art coordinator was Becky Hainz-Baxter.
The illustrators were Teshin Associates.
The index was prepared by Kathy Pitcoff.

图字：01-2001-3616

临床病理生理学（英文版）

编　　著： Stephen J. McPhee 等	**经　　销：** 新华书店
出版发行： 人民卫生出版社(中继线 67616688)	**开　　本：** 787×1092　1/16　**印张：** 42
地　　址： (100078) 北京市丰台区方庄芳群园 3 区 3 号楼	**字　　数：** 1562 千字
	版　　次： 2001 年 11 月第 1 版
网　　址： http://www.pmph.com	2001 年 11 月第 1 版第 1 次印刷
E - mail: pmph@pmph.com	**标准书号：** ISBN 7-117-04570-1/R·4571
印　　刷： 北京人卫印刷厂	**定　　价：** 88.00 元

Dedication



The editors and contributors wish to dedicate this third edition of *Pathophysiology of Disease* to Dr. Jack Damgaard Lange, who died at age 92 while this revision was under way. Jack was the president and one of the founding partners—with his wife DeLoris—of Lange Medical Publications. He retired in 1986 but maintained an active interest in medical book publishing with the goal of making inexpensive medical texts of high quality available to students and practitioners in the health science professions in all parts of the world. One of his goals late in life was to add a pathophysiology textbook to the Lange series. This book is the result.

Preface

WHAT THE BOOK IS

This is a text designed to present an orientation to disease considered as disordered physiology. It is intended to enable the student and practitioner to understand how and why the symptoms and signs of various conditions occur. In approaching disease as disordered physiology, this text analyzes the mechanism of production of the symptoms and signs of different diseases and syndromes. In so doing, it recognizes the student's and practitioner's need to understand the mechanisms underlying the disease and its clinical manifestations so that rational therapies can be offered.

WHAT THE BOOK IS NOT

We do not offer a standard textbook of medicine that proceeds in conventional sequence from etiology, pathology, symptoms and signs, laboratory findings, diagnosis, and differential diagnosis to treatment and prognosis. Nor is *Pathophysiology of Disease* intended to serve as a standard textbook of physiology, pathology, or physical diagnosis. Furthermore, the text is not intended to be all-encompassing in the disordered physiologic mechanisms or disease states taken up for discussion. Rather, the authors have selected examples of disordered physiology and disease states which seemed most relevant to the clinical practice of medicine.

INTENDED AUDIENCE

Medical students in basic pathophysiology courses will find that this text makes a useful contribution to their understanding of how disordered physiology produces common diseases and syndromes. Students taking courses on the introduction to clinical medicine or engaged in basic internal medicine and surgery clerkship rotations will find this work helpful in comprehending how and why the symptoms and signs of various disease states appear. House officers will find the concise, up-to-date descriptions of disease mechanisms, with citations to the current literature, of use in devising proper patient management. Practitioners (internists, family physicians, and other specialists who provide generalist care) will find *Pathophysiology of Disease* useful as a refresher text, designed to update their understanding of the mechanisms underlying disease. Nurses and other health practitioners will find that the concise format and broad scope of the book facilitate their understanding of basic disease entities.

ORGANIZATION OF THE BOOK

Pathophysiology of Disease is divided into 25 chapters, developed chiefly by organ system. Each chapter is divided into sections emphasizing normal structure and function, pathology and disordered physiology, common clinical presentations, and mechanisms underlying symptoms and signs. Text review questions are provided in boxes throughout the chapters. A list of pertinent recent references is provided at the end of each chapter as suggestions for further reading.

NEW TO THIS EDITION

The third edition of *Pathophysiology of Disease* contains two new chapters. One is on inflammatory rheumatic diseases. The other provides 38 illustrative cases with a brief discussion of each. Other chapters have been updated and revised, and recent references have been substituted.

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San Francisco, California
November, 1999

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Contents

Introduction 1

Jack D. Lange, MD

WHAT IS PATHOPHYSIOLOGY?

Pathophysiology may be defined as the physiology of disease, of disordered function, or derangement of function seen in disease that is produced by the action of an etiologic agent (eg, bacteria) on susceptible tissues or organs. The term "pathophysiology" emphasizes alterations in function—as distinguished from "pathology," which emphasizes structural changes. Pathophysiology includes also the study of the mechanisms underlying disease. The study of pathophysiology is an essential introduction to clinical medicine and serves as a bridge between the basic sciences and disease.

Pathophysiology differs from pathogenesis. Pathogenesis is the mode of origin or development of any disease process (eg, development of autoimmunity to the thyroid-stimulating hormone receptor). Pathophysiology describes the resulting disordered physiology and clinical consequences (eg, release of excess thyroid hormone, producing the syndrome of hyperthyroidism).

WHY IS PATHOPHYSIOLOGY IMPORTANT?

An orientation to disease as disordered physiology can enable the student and practitioner to understand how and why the symptoms and signs of various conditions appear. A pathophysiologic approach to disease as disordered physiology enables the clinician to analyze the mechanism of production of the symptoms and signs of different disease syndromes. In so doing, it recognizes the student's and practitioner's need to understand the mechanisms underlying the disease and its clinical manifestations so that rational therapies can be devised.

This book was written with the principles described above in mind. It summarizes the normal structure and function of each organ system, then discusses a number of the major diseases of each system, showing how symptoms and signs of the selected diseases are produced by disordered physiology. It also provides an introduction to clinical medicine by analyzing in the same way the broad topics of genetic abnormalities, neoplasia, and infectious disease.

2 Genetic Disease

Gregory Barsh, MD, PhD

Mechanisms of cellular and tissue dysfunction in genetic diseases are as varied as the organs they affect. To some extent, these mechanisms are similar to those that occur in nonheritable disorders. For example, a fracture due to the decreased bone density in osteoporosis heals in the same fashion as one caused by a defective collagen gene in osteogenesis imperfecta, and the response to coronary atherosclerosis in most individuals does not depend on whether they have inherited a defective LDL receptor. Thus, the pathophysiology of genetic diseases relates not so much to the affected organ system as to the mechanisms of mutation, inheritance, and molecular pathways from genotype to phenotype.

This chapter begins with a discussion of the terminology used to describe inherited conditions, the prevalence of genetic disease, and some major principles and considerations in clinical genetics. Important terms and key words used throughout the chapter are defined in Table 2–1.

Next, a group of disorders caused by mutations in collagen genes is discussed, ie, **osteogenesis imperfecta.** Though osteogenesis imperfecta is often considered a single entity, different mutations and different genes subject to mutation lead to a wide spectrum of clinical phenotypes. The different types of osteogenesis imperfecta exhibit typical patterns of autosomal dominant or autosomal recessive inheritance and are therefore examples of so-called **mendelian conditions.**

Recently, several genetic conditions have been found to depend not only on the gene being inherited but also on the phenotype or the sex of the parent. As an example of a condition that exhibits nonclassic inheritance, the **fragile X-associated mental retardation syndrome** is discussed. This syndrome is not only the most common inherited cause of mental retardation but also illustrates a recently discovered principle of molecular and cellular biology.

One of the most common types of human genetic disease that does not affect DNA structure per se is **aneuploidy,** or a change in the normal chromosome content per cell. The example that is considered, **Down's syndrome,** has had a major impact on reproductive medicine and reproductive decision making and serves to illustrate general principles that apply to many aneuploid conditions.

Finally, to show how environmental factors can influence the relationship between genotype and phenotype, we shall discuss **phenylketonuria,** which serves as the paradigm for newborn screening programs and treatment of genetic disease.

UNIQUE ASPECTS OF GENETIC PATHOPHYSIOLOGY

Although the phenotypes of genetic diseases are diverse, their causes are not. The primary cause of any genetic disease can be defined as a discrete event that affects gene expression in a group of cells related to each other by lineage. Most genetic diseases are caused by an alteration in DNA sequence that alters the synthesis of a single gene product. However, some genetic diseases are caused (1) by chromosome rearrangements that result in deletion or duplication of a group of closely linked genes or (2) by mistakes during mitosis or meiosis that result in an abnormal number of chromosomes per cell. In most genetic diseases, every cell in an affected individual carries the mutated gene or genes as a consequence of its inheritance via a mutant egg or sperm **(gamete).** However, mutation of the gametic cell may have arisen during its development, in which case somatic cells of the parent do not carry the mutation and the affected individual is said to have a "new mutation." In addition, some mutations may arise in somatic cells during early embryogenesis, in which case tissues of the affected individual contain a mixture, or **mosaic,** of mutant and nonmutant cells (Figure 2–1).

One must bear in mind the distinctions between gene, locus, and allele and between mutation, polymorphism, and phenotype since confusion about the terminology of genetics and genetic diseases can

Table 2–1. Glossary of terms and keywords.

Term	Definition
Acrocentric	Pertaining to the terminal location of the centromere on chromosomes 13, 14, 15, 21, and 22, which contain so-called satellite DNA on their short arms that encodes for ribosomal RNA genes.
Allele	Alternative forms of a gene that occupy the same locus on a specific chromosome.
Allelic heterogeneity	The state in which multiple alleles at a single locus can produce a disease phenotype or phenotypes.
Amorphic	Refers to a mutation that results in a complete loss of function.
Aneuploidy	A general term used to denote any unbalanced chromosome complement.
Antimorphic	Refers to a mutation which, when present in heterozygous form opposite a nonmutant allele, results in a phenotype similar to homozygosity for loss-of-function alleles.
Ascertainment bias	The problem that arises when individuals or families in a genetic study are not representative of the general population because of the way in which they are identified.
Autosomal	Located on chromosomes 1–22 rather than X or Y.
CpG island	A segment of DNA that contains a relatively high density of 5′-CG-3′ dinucleotides. Such segments are frequently unmethylated and located close to ubiquitously expressed genes.
Dictyotene	The end of prophase during female meiosis I in which fetal oocytes are arrested prior to ovulation.
Dominant	A pattern of inheritance or mechanism of gene action in which the effects of a variant allele can be observed in the presence of a nonmutant allele.
Dominant negative	Mutant alleles that give rise to structurally abnormal proteins that interfere with the normal function of the nonmutant gene products.
Dosage compensation	Mechanism by which a difference in gene dosage between two cells is equalized; for XX cells, decreased expression from one of the two X chromosomes results in a concentration of gene product similar to that of an XY cell.
End product deficiency	A pathologic mechanism in which absence or reduction in the product of a particular enzymatic reaction leads to disease.
Epigenetic	Refers to a phenotypic effect that does not depend on genotype. DNA methylation that occurs during gametogenesis can affect gene expression in zygotic cells, but the pattern of methylation can also be reversed in subsequent generations and thus does not affect genotype.
Expressivity	The extent to which a mutant genotype affects phenotype. A quantitative measure of a disease state that may vary from mild to severe but is never completely absent.
Fitness	The likelihood that an individual who carries a particular mutant allele will produce progeny that also carry the allele.
Founder effect	One of several possible explanations for an unexpectedly high frequency of a deleterious gene in a population. If the population was founded by a small ancestral group, it may have, by chance, contained a large number of carriers for the deleterious gene.
Gamete	The egg or sperm cell that represents a potential reproductive contribution to the next generation. Gametes have undergone meiosis and so contain half the normal number of chromosomes found in zygotic cells.
Gene dosage	The principle that the amount of product expressed for a particular gene is proportionate to the number of gene copies present per cell.
Genetic anticipation	A clinical phenomenon that occurs when the phenotype observed in individuals carrying a deleterious gene appears more severe in successive generations. Possible explanations include ascertainment bias or a multistep mutational mechanism such as expansion of triplet repeats.
Genetic heterogeneity	A situation in which mutations of different genes produce similar or identical phenotypes. Also referred to as locus heterogeneity.
Haplotype	A set of closely linked alleles that are not easily separated by recombination. Often refers to DNA sequence alterations such as restriction fragment length polymorphisms.
Heterochromatin	One of two alternative forms of chromosomal material (the other is euchromatin) as determined by the way in which chromosomal DNA is bound to proteins and condensed. Heterochromatin is highly condensed and usually does not contain genes that are actively transcribed.

(*continued*)

Table 2–1. Glossary of terms and keywords. (continued)

Term	Definition
Heterozygote advantage	One way to explain an unexpectedly high frequency of a recessively inherited mutation in a particular population. During recent evolution, carriers (ie, heterozygotes) are postulated to have had a higher fitness than homozygous nonmutant individuals.
Hypermorphic	Refers to a mutation that has an effect similar to increasing the number of normal gene copies per cell.
Hypomorphic	Refers to a mutation that reduces but does not eliminate the activity of a particular gene product.
Imprinting	As applied most commonly, the process whereby expression of a gene depends on whether it is transmitted through a female or male gamete.
Linkage disequilibrium	The situation occuring when certain combinations of closely linked alleles are present in a population at frequencies not predicted by their individual frequencies.
Monosomy	A reduction in zygotic cells from two to one in the number of copies for a particular chromosomal segment or chromosome.
Mosaicism	A situation in which a genetic alteration is present in some but not all cells of a single individual. In germline or gonadal mosaicism, the alteration is present in germ cells but not in somatic cells. In somatic mosaicism, the genetic alteration is present in some but not all of the somatic cells (and is generally not present in the germ cells).
Neomorphic	Refers to a mutation that imparts a novel function to its gene product and thus results in a phenotype distinct from an alteration in gene dosage.
Nondisjunction	Failure of two homologous chromosomes to separate, or disjoin, at metaphase of meiosis I; or the failure of two sister chromatids to disjoin at metaphase of meiosis II or mitosis.
Penetrance	In a single individual of a variant genotype, penetrance is an all-or-none phenomenon determined by the absence or presence of defined phenotypic criteria. In a population, reduced penetrance implies that an individual of a variant genotype is less likely to be recognized according to the same phenotypic criteria.
Phenotypic heterogeneity	The situation occurring when mutations of a single gene produce multiple different phenotypes.
Polymorphism	An allele that is present in 1% or more of the population.
Postzygotic	Refers to a mutational event that occurs after fertilization, and that commonly gives rise to mosaicism.
Premutation	A genetic change that does not itself result in a phenotype but has a high probability of developing a second alteration—a full mutation—that does cause a phenotype.
Primordial germ cells	The group of diploid cells set aside early in development that go on to give rise to gametes.
Recessive	A pattern of inheritance or mechanism of gene action in which a particular mutant allele gives rise to a phenotype only in the absence of a nonmutant allele. Thus, for autosomal conditions, the variant or disease phenotype is manifest when two copies of the mutant allele are present. For X-linked conditions, the variant or disease phenotype is manifest in cells, tissues, or individuals in which the nonmutant allele is either inactivated (a heterozygous female) or not present (a hemizygous male).
RFLP	Restriction fragment length polymorphism, a type of DNA-based allele variation in which different alleles at a single locus are recognized and followed through pedigrees based on the size of a restriction fragment. The locus is defined by the segment of DNA that gives rise to the restriction fragment; the different alleles are generally (not always) caused by a single change in DNA sequence that creates or abolishes a site of restriction enzyme cleavage.
Robertsonian translocation	A type of translocation in which two acrocentric chromosomes are fused together with a single functional centromere. A carrier of a Robertsonian translocation with 45 chromosomes has a normal amount of chromosomal material and is said to be euploid.
Substrate accumulation	A pathogenetic mechanism in which deficiency of a particular enzyme causes disease because the substrate of that enzyme accumulates in tissue or blood.
Triplet repeat	A three-nucleotide sequence that is tandemly repeated many times, ie, $(XYZ)_n$. Alterations in length of such simple types of repeats (dinucleotide and tetranucleotide as well) occur much more frequently than most other kinds of mutations; however, alterations in the length of trinucleotide repeats is the molecular basis for several heritable disorders.
Trisomy	An abnormal situation in which there are three instead of two copies of a chromosomal segment or chromosome per cell.

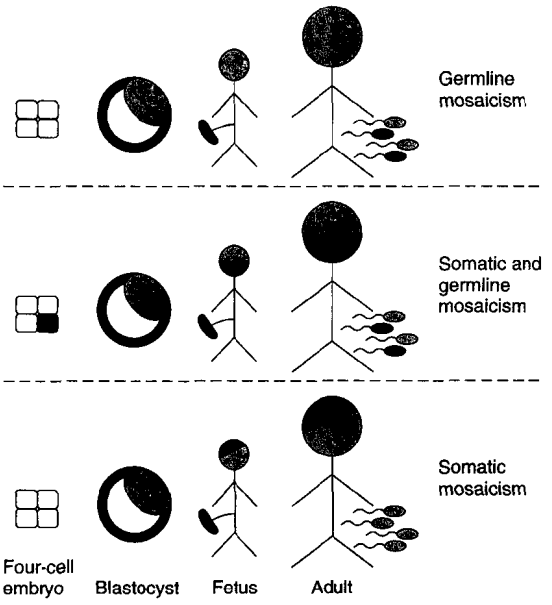

Figure 2–1. Cellular origin of mutations can lead to somatic mosaicism, germline mosaicism, or both. The effects of a mutation on mosaicism depend on the cell and the developmental stage in which the mutation occurs. The early blastocyst is composed of two different tissues: the inner cell mass (light-colored), which mostly gives rise to embryonic tissues, including somatic and germ cells; and the trophoblast (dark-colored), which gives rise to extraembryonic tissues cells such as the placenta. If a mutation (black) occurs in a portion of the inner cell mass whose daughter cells contribute exclusively to the germline, the adult will not exhibit phenotypic features of the mutation in somatic tissues but may produce germ cells both with and without the mutation (germline mosaicism; upper panel). However, if a mutation occurs in the four-cell embryo, the adult may also exhibit phenotypic features of the mutation in some but not all somatic tissues (somatic and germline mosaicism; middle panel). Finally, a mutation that occurs in a portion of the blastocyst or fetus that does not give rise to germ cells results only in somatic mosaicism (lower panel). (Adapted from Thompson MW et al: *Genetics in Medicine,* 5th ed. Saunders, 1991.)

have unfortunate consequences for patients and their families. Although genes were recognized and studied long before the structure of DNA was known, it has become common usage to regard a **gene** as a short stretch of DNA (usually but not always < 100 kb in length) that encodes a product (usually protein) responsible for a measurable trait. The **locus** is the place where a particular gene lies on its chromosome. A gene's DNA sequence nearly always shows slight differences when many unrelated individuals are compared, and the variant sequences are described as **alleles.** A **mutation** is a biochemical event such as a nucleotide change, deletion, or insertion that has produced a new allele. Many changes in the DNA sequence of a gene, such as those within introns or at the third "wobble" position of codons for particular amino acids, do not affect the structure or expression of the gene product; therefore, although all mutations result in a biochemical or molecular biologic phenotype—ie, a change in DNA—only some result in a clinically abnormal phenotype. The word **polymorphism** denotes an allele that is present in 1% or more of the population. At the biochemical level, polymorphic alleles are usually recognized by their effect on the size of a restriction fragment **(restriction fragment length polymorphism [RFLP]),** or the length of a short but highly repetitive region of DNA. On the other hand, at the clinical level, polymorphic alleles are recognized by their effect on a phenotype such as HLA type or hair color. The HLA system is an example where there are many polymorphic alleles; therefore, most individuals are heterozygous.

Finally, this discussion helps to illustrate the use of the word **phenotype,** which refers simply to any characteristic that can be described by an observer. Hair color is a phenotype readily apparent to a casual observer, whereas RFLPs are a phenotype that can only be detected with a laboratory test.

PENETRANCE & EXPRESSIVITY

It is an important principle of human genetics that two individuals with the same mutated gene may have different phenotypes. For example, in the autosomal dominant condition called type I osteogenesis imperfecta, pedigrees may occur in which there is both an affected grandparent and an affected grandchild even though the obligate carrier parent is asymptomatic (Figure 2–2). Given a set of defined criteria, recognition of the condition in individuals known to carry the mutated gene is described as **penetrance.** In other words, if seven out of ten individuals over age 40 with the type I osteogenesis imperfecta mutation have an abnormal bone density scan, the condition is said to be 70% penetrant by that criterion. Penetrance may vary both with age and according to the set of criteria being used; for example, type I osteogenesis imperfecta may be 90% penetrant at age 40 when the conclusion is based on a bone density scan in conjunction with laboratory tests for abnormal collagen synthesis. **Reduced penetrance** or **age-dependent penetrance** is a common feature of dominantly inherited conditions that have a relatively high **fitness** (likelihood of reproduction by the individual with the mutant allele), such as Huntington's disease or polycystic kidney disease.

Although the presence of a mutated gene can be observed in many individuals, their phenotypes may still be different. For example, blue scleras and lower than normal height may be the only manifestations of type I osteogenesis imperfecta in a particular individ-

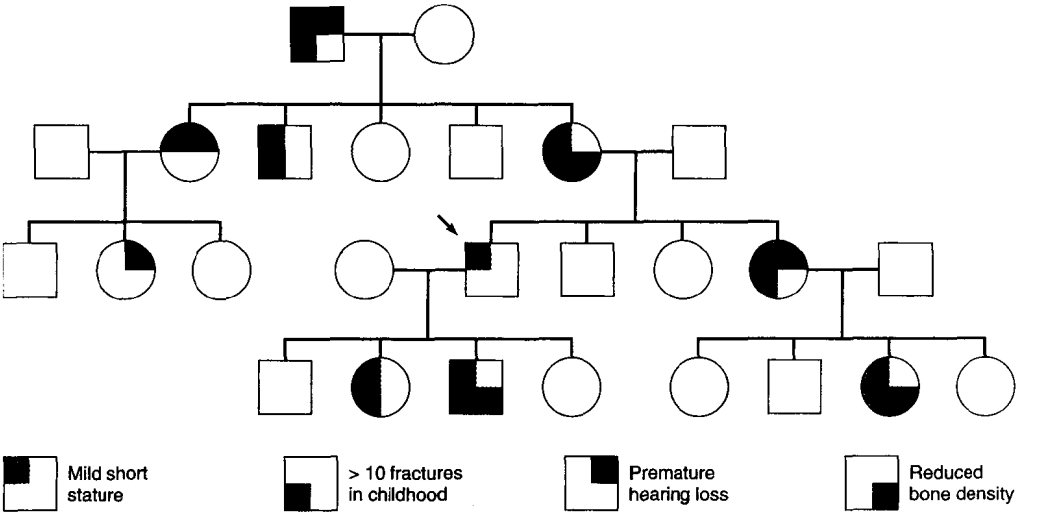

Figure 2–2. Penetrance and expressivity in type I osteogenesis imperfecta. In this schematic pedigree of the autosomal dominant condition type I osteogenesis imperfecta, nearly all of the affected individuals exhibit different phenotypic features that vary in severity (variable expressivity). As is shown, type I osteogenesis imperfecta is fully penetrant, since every individual who transmits the mutation is phenotypically affected to some degree. However, if mild short stature in the individual indicated with the arrow had been considered to be a normal variant, then the condition would have been nonpenetrant in this individual. Thus, in this example, judgments about penetrance or nonpenetrance depend on the criteria for normal and abnormal stature.

ual, while a sibling who carries the identical mutation may be confined to a wheelchair as a result of multiple fractures and deformities. The phenomenon of different phenotypes in these individuals is referred to as **variable expressivity.** Both reduced penetrance and variable expressivity occur in related individuals who carry the exact same mutated allele; therefore, phenotypic differences between these individuals must be due to the effects of other "modifier" genes, to environmental interactions, or to chance.

MECHANISMS OF MUTATION & INHERITANCE PATTERNS

Mutations can be characterized both by their molecular nature—nucleotide deletion, insertion, substitution—or by their effects on the gene product, ie, no effect (neutral), complete loss-of-function (amorphic), partial loss of function (hypomorphic), gain of function (hypermorphic), or acquisition of a new property (neomorphic). Geneticists who study experimental organisms frequently use specific deletions to ensure that a mutated allele causes a loss of function, but human geneticists rely on biochemical or cell culture studies. Amorphic and hypomorphic mutations are probably the most frequent type of mutation in human genetic disease because there are many ways to interfere with a protein's function.

For autosomal genes (those that lie on chromosomes 1–22), the fundamental difference between dominant and recessive inheritance is that with dominant inheritance, the disease state or trait being measured is apparent when one copy of the mutated allele and one copy of the normal allele are present. With recessive inheritance, two copies of the mutated allele must be present for the disease state or trait to be apparent. For genes that lie on the X chromosome, the same definitions apply to females (with two X chromosomes): A phenotype caused by one copy of a mutant gene is X-linked dominant; a phenotype caused by two copies is X-linked recessive. Because most mutations are amorphic or hypomorphic, however, one copy of an X-linked mutant allele in males is not "balanced" with a nonmutant allele, as it would be in females; therefore, one copy of an X-linked recessive gene is sufficient to produce a mutant phenotype in males.

Recessive Inheritance & Loss-of-Function Mutations

As mentioned above, most recessive mutations are due to a loss of function of the gene product, which can occur by a variety of different pathways, including failure of the gene to be transcribed or translated or failure of the translated gene product to function correctly. There are two general principles to keep in mind when considering loss-of-function mutations. First, because expression from the nonmutant allele usually does not change (ie, there is no **dosage com-**

pensation), gene expression in a heterozygous carrier of a loss-of-function allele is reduced to 50% of normal. Second, for most biochemical pathways, a 50% reduction in enzyme concentration is not sufficient to produce a disease state. Thus, most diseases due to enzyme deficiencies such as phenylketonuria (Table 2–2) are inherited in a recessive fashion.

Dominant Inheritance & Loss-of-Function Mutations

If 50% of a particular product is not enough for the cell or tissue to function normally, then a loss-of-function mutation in this gene will produce a dominantly inherited phenotype. Such mutations usually occur in structural proteins; the example we will consider below is type I osteogenesis imperfecta. Most dominantly inherited phenotypes are really **semidominant,** which means that two copies of the mutant allele produce a phenotype more severe than one mutant and one normal copy. However, for most dominantly inherited conditions, homozygous mutant individuals are rarely observed. For example, inheritance of achondroplasia, the most common genetic cause of very short stature, is usually described as autosomal dominant. However, rare matings between two affected individuals have a 25% probability of producing offspring with two copies of the mutant gene. This results in homozygous achondroplasia, a condition that is very severe and usually fatal in the perinatal period. Huntington's disease, a dominantly inherited neurologic disease, is the only known human condition in which the homozygous mutant phenotype is identical with the heterozygous mutant phenotype (sometimes referred to as a "true dominant").

Dominant Negative Mutations

A special kind of mutation referred to as a dominant negative occurs frequently in human diseases that involve polymeric structural proteins. In these disorders, the mutant allele gives rise to a structurally abnormal protein that interferes with the function of the normal allele. The presence of a dominant negative allele can be proved in experimental organisms by showing that one copy of the putative dominant negative allele has an effect similar to two copies of a loss-of-function allele. Such a mutation is said to

Table 2–2. Phenotype, genetic mechanism, and prevalence of selected genetic disorders.

Disorder	Phenotype	Genetic Mechanism	Prevalence
Down's syndrome	Mental and growth retardation, dysmorphic features, internal organ anomalies	Chromosomal imbalance caused by trisomy 21	≈ 1:800; increased risk with advanced maternal age
Fragile X-associated mental retardation	Mental retardation, characteristic facial features, large testes	X-linked; progressive expansion of unstable DNA causes failure to express gene encoding RNA-binding protein	≈ 1:1500 males; can be manifest in females; multistep mechanism
Sickle cell anemia	Recurrent painful crises, increased susceptibility to infections	Autosomal recessive; caused by a single missense mutation in beta globin	≈ 1:400 blacks
Cystic fibrosis	Recurrent pulmonary infections, exocrine pancreatic insufficiency, infertility	Autosomal recessive; caused by multiple loss-of-function mutations in a chloride channel	≈ 1:2000 whites; very rare in Asians
Neurofibromatosis	Multiple café au lait spots, neurofibromas, increased tumor susceptibility	Autosomal dominant; caused by multiple loss-of-function mutations in a signaling molecule	≈ 1:3000; about 50% are new mutations
Duchenne's muscular dystrophy	Muscular weakness and degeneration	X-linked recessive; caused by multiple loss-of-function mutations in a muscle protein	≈ 1:3000 males; about 33% are new mutations
Osteogenesis imperfecta	Increased susceptibility to fractures, connective tissue fragility	Phenotypically and genetically heterogeneous	≈ 1:10,000
Phenylketonuria	Mental and growth retardation	Autosomal recessive; caused by multiple loss-of-function mutations in phenylalanine hydroxylase	≈ 1:10,000