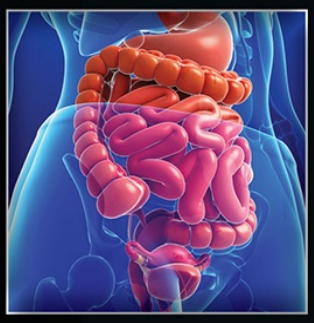
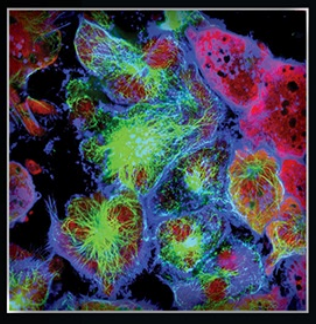
Eighth Edition

Pathophysiology of Disease

AN INTRODUCTION TO CLINICAL MEDICINE





Gary D. Hammer
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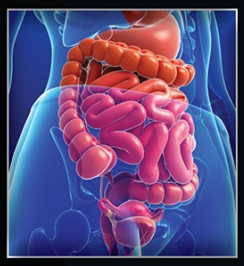

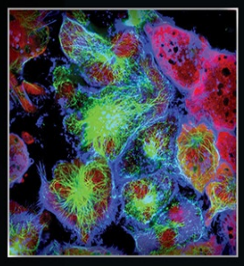

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Pathophysiology of Disease:

An Introduction to Clinical Medicine

Eighth Edition

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ISBN: 978-1-26-002651-1
MHID: 1-26-002651-5

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-002650-4, MHID: 1-26-002650-7.

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Preface

Goal and Audience

The goal of *Pathophysiology of Disease: An Introduction to Clinical Medicine*, as outlined in the introductory chapter (Chapter 1), is to introduce students to clinical medicine by reviewing the pathophysiologic basis of the symptoms and signs of various common diseases.

The book has proved useful as a text for both Pathophysiology and Introduction to Clinical Medicine courses in medical schools, and it has been popular in similar courses in nursing schools, physician assistants' training programs, and other allied health programs. It is valuable to students early in their medical school years by highlighting the clinical relevance of their basic science courses, and in preparation for their USMLE Step 1 examinations. The book is also helpful to students engaged in their internal medicine and surgery clerkships, and to house officers as an up-to-date summary of relevant physiology and a source of key references. Practitioners (both general internists and specialists who provide generalist care) will find it beneficial as a refresher text, designed to update their knowledge of the mechanisms underlying 132 commonly encountered diseases and disorders. Nurses, nurse-practitioners, physician assistants, and other allied health practitioners have found that its concise format and broad scope facilitate their understanding of these basic disease entities.

Pathophysiology of Disease has been widely adopted in the United States, Canada, and the United Kingdom, and it has been translated into Spanish, Italian, Chinese, Japanese, Greek, and Turkish. Both the text and its Case Study Questions and Answers are also available online at accessmedicine.mhmedical.com, the online version of McGraw-Hill's many medical textbooks (search under "Books, Library, Basic Science" for "Pathophysiology," listed alphabetically).

New Features for This Edition

In preparation for this eighth edition, the editors and authors reviewed the entire book. There have been many text revisions aimed at updating information, improving clarity, and eliminating minor errors. With emphasis on recent pertinent reviews, references have been entirely updated, as have figures and tables. “Checkpoints,” collections of review questions, continue to appear throughout the chapters and have been revised.

Examples of Substantive New Content Found in This Eighth Edition

- Update on components and physiology of normal immunity
- Most recent surveillance case definition for HIV infection
- Explication of the concepts of innate immunity and pathogen-associated molecular patterns
- Totally revised chapter on neoplasia, including 19 new figures and 4 new tables
- New figure illustrating iron transport and regulation in the duodenal enterocyte
- New chapter section on urticaria (perivascular dermatitis)
- New chapter section on various forms of spinocerebellar ataxia
- Clarification in text and figures of regional alterations in the overall distribution of ventilation and perfusion referred to as $\dot{V}/\dot{Q}$ mismatch, including concepts of anatomic versus alveolar (wasted ventilation) dead space and right-to-left shunt
- Update on genetic factors implicated in asthma risk, as well as allergic versus nonallergic asthma
- Newly rewritten section on idiopathic pulmonary fibrosis as a prototypic restrictive (interstitial) lung disease
- Extensive revision of sections on pulmonary edema, adult respiratory distress syndrome (ARDS), and pulmonary venous thromboembolism
- Expanded material on paragangliomas
- New figures on mechanisms leading to nonalcoholic fatty liver disease and to hepatic steatosis
- New table summarizing adverse prognostic signs in acute pancreatitis derived from the Acute Pancreatitis Classification Working Group’s 2012 classification, a revision of the Atlanta international consensus classification and definitions of acute pancreatitis
- New table summarizing genetic syndromes associated with pancreatic cancer

- New table summarizing the prevalence of various causes of end-stage renal disease for U.S. Medicare recipients in the 2016 U.S. Renal Data System
- Revised flowchart summarizing the pathogenesis of bone diseases in chronic kidney disease
- Updated information on familial hypocalcuric hypercalcemia, malignant hypercalcemia, autosomal dominant hypocalcemia, and the autoimmune polyendocrine failure syndromes
- The American Diabetes Association's new diagnosis and etiologic classification of diabetes mellitus
- New figure illustrating the amino acid sequence and covalent structure of human proinsulin
- New schematic diagram of glucose-stimulated insulin release from the pancreatic β cell
- New figure showing how pancreatic islet cell secretions of glucagon (from α cells) and insulin (from β cells), which are reciprocally regulated by glucose, play key roles in maintaining glucose homeostasis
- Diagram demonstrating stages in the development of type 1 diabetes mellitus with the appearance of β-cell autoantibodies, followed by dysglycemia, insulinopenia, and then frank hyperglycemia
- Review of mechanisms of the newest classes of pharmacologic agents approved for type 2 diabetes mellitus
- New figure illustrating modifiable cardiovascular risk factors in individuals with diabetes
- New figure illustrating the control of energy homeostasis by arcuate nucleus neurons, both stimulatory and inhibitory neurons with regard to food intake
- Updated information on fine-needle aspiration biopsy of thyroid nodules
- Update on thyroid disorders in pregnancy
- New schematic drawing of the sequence of changes that occur in the alveolar secretory units and duct system of the female breast before, during, and after pregnancy and lactation
- Update of indicators of mild to moderate versus severe preeclampsia-eclampsia
- Incorporation of new International Federation of Gynecology and Obstetrics classification system for pathogenesis of abnormal uterine bleeding
- Update to pathogenesis and pathophysiology of inflammatory myopathies and rheumatoid arthritis
- New chapter section on spondyloarthropathies, including ankylosing spondylitis, reactive arthritis, inflammatory bowel disease–associated arthritis, and psoriatic arthritis

- Updated references throughout the text, including articles mainly from 2015, 2016, and 2017
- Revised and updated figure citations throughout the text

Case Study Questions and Answers

Each chapter ends with a collection of Case Studies. These clinical problems give readers an opportunity to test their understanding of the pathophysiology of each clinical entity discussed and to apply their knowledge to exemplar clinical situations. In this eighth edition, Yeong S. Kwok, MD, of the University of Michigan, has added an additional 12 Case Studies with questions, bringing the total number to 132, or one for each of the clinical entities discussed in the book's 24 chapters. New Case Study topics include:

- Down syndrome as a result of a balanced robertsonian translocation
- Chronic granulomatous disease
- Malignant hypercalcemia
- Cerebellar ataxia
- Urticaria
- Ulcerative colitis
- Type 1 diabetes mellitus
- Subclinical hypothyroidism
- Subclinical hyperthyroidism
- Amenorrhea caused by polycystic ovary syndrome
- Abnormal vaginal bleeding as a result of endometrial cancer
- Spondyloarthropathy as a result of ankylosing spondylitis

As before, detailed analyses of the Cases appear in Chapter 25: Case Study Answers. There, Dr. Kwok has updated the Answers to the existing 120 Case Study Questions to reflect the changes made by chapter authors in their revisions, and he has added Answers to the Questions for the 12 new Case Studies.

Changes in Authors

With this eighth edition, the authorship of many chapters has evolved and transitioned—this should not be surprising given the book's multiple editions since it was first published in 1992 and given the transition in location of the book's lead editor from the University of California, San Francisco (Stephen J. McPhee, MD), to the University of Michigan (Gary Hammer, MD, PhD). The

editors wish to welcome aboard the following new contributors who are joining the book's authors and to thank the following past contributors who are now departing the book:

- Shane C. Quinonez, MD, of the University of Michigan, has taken over the current revision of Chapter 2, *Genetic Disease*, from Greg Barsh, MD, PhD, of Stanford University; Dr. Barsh, who has been this chapter's author since the book's first edition, will continue as a coauthor for this eighth edition only
- Jennifer J. Chang, MD, and Suzanne M. Donovan, MD, MPH, joined Jeffrey L. Kishiyama, MD, in revising Chapter 3, *Disorders of the Immune System*. Sadly, Dr. Kishiyama died during the final production process for this edition; please see the **In Memoriam** below
- Christina T. Fiske, MD, MPH, of Vanderbilt University, has joined Karen C. Bloch, MD, MPH, in revising Chapter 4, *Infectious Diseases*
- Weiyun Z. Ai, PhD, MD, of UCSF, has assisted chapter author Mark M. Moasser, MD, by revising the hematologic disorders section of Chapter 5, *Neoplasia*
- J. Ben Davoren, MD, PhD, of UCSF, has replaced Sunny Wang, MD, with Gerald Hsu, MD, PhD, as coauthor of Chapter 6, *Blood Disorders*; we would like to thank Dr. Wang for her revisions for the sixth and seventh editions
- Vikram G. Shakkottai, MD, PhD, of the University of Michigan, has taken over the current revision of Chapter 7, *Nervous System Disorders*, from Catherine Lomen-Hoerth, MD, PhD, of UCSF; Dr. Lomen-Hoerth will continue only once more as coauthor for this eighth edition
- Laura B. Pincus, MD, of UCSF, has replaced Melissa M. Meier, MD, as the coauthor, with Timothy H. McCalmont, MD, of Chapter 8, *Diseases of the Skin*; we would like to thank Dr. Meier for her revisions for the seventh edition
- Thomas H. Sisson, MD, and Dru Claar, MD, of the University of Michigan, have taken over the current revision of Chapter 9, *Pulmonary Disease*, from Mark S. Chesnutt, MD, and Thomas J. Prendergast, MD, of Oregon Health and Sciences University; Drs. Chesnutt and Prendergast will continue as coauthors for this eighth edition only. We would like to acknowledge Dr. Prendergast for his role in coauthoring the original chapter in the book's first edition and for his revisions for the next seven editions, and Dr. Chesnutt for his assistance with the seventh and eighth editions
- Lauren Fishbein, MD, PhD, of the University of Colorado, is now coauthor of Chapter 12, *Disorders of the Adrenal Medulla*, with Tobias Else, MD, of the University of Michigan; after the sixth and seventh editions, Gary Hammer,

MD, PhD, has now “retired” from coauthorship of this chapter

- Matthew A. Ciorba, MD, of the Washington University at St. Louis, has now joined his colleague Jason C. Mills, MD, PhD, as coauthor of Chapter 13, *Gastrointestinal Disease*; we are thankful for the past contributions of Thaddeus S. Stappenbeck, MD, PhD, to its revision for the sixth and seventh editions
- Mandana Khalili, MD, MAS, of UCSF, is now working with Nizar A. Mukhtar, MD, of Seattle’s Swedish Medical Center in producing the current revision of Chapter 14, *Liver Disease*; we are grateful to Blaire Burman, MD, of UCSF for assistance with the seventh edition revision
- Timothy L. Frankel, MD, has now joined his University of Michigan colleague Christopher J. Sonnenday, MD, MHS, in producing the current revision of Chapter 15, *Disorders of the Exocrine Pancreas*
- Joachim H. Ix, MD, has now “retired” from coauthorship of Chapter 16, *Renal Disease*, which is now coauthored by Rachel Leah Pearlman, MD, and Michael Heung, MD, MS; we thank Dr. Ix for his revisions in the fifth, sixth, and seventh editions
- Deborah E. Sellmeyer, MD, has now “retired” from coauthorship with Dolores M. Shoback, MD, of Chapter 17, *Disorders of the Parathyroids & Calcium and Phosphorus Metabolism*; we thank Dr. Sellmeyer for her contributions to the fifth, sixth, and seventh editions
- Nazanene H. Esfandiari, MD, of the University of Michigan, has replaced Douglas C. Bauer, MD, of UCSF, as the coauthor, with Stephen J. McPhee, MD, of Chapter 20, *Thyroid Disease*; we thank Dr. Bauer for his revisions for the second through seventh editions and note that Dr. McPhee, who has been this chapter’s author or coauthor for the prior seven editions, will continue as coauthor for this eighth edition only
- Bansari G. Patel, MD, at Wake Forest University, now joins Erika B. Johnston-MacAnanny, MD, now in Richmond, VA, and Robert N. Taylor, MD, PhD, now at the University of Utah, as a coauthor of Chapter 22: *Disorders of the Female Reproductive Tract*
- Mikkel Fode, MD, PhD, and Jens Sønksen, MD, PhD, of Herlev & Gentofte Hospital of the University of Copenhagen in Herlev, Denmark, and Dana A. Ohl, MD, of the University of Michigan, have assumed authorship of Chapter 23, *Disorders of the Male Reproductive Tract*; after seven editions, Stephen J. McPhee, MD, has now “retired” from authorship or coauthorship of this chapter
- Allan C. Gelber, MD, MPH, PhD, and Stuart M. Levine, MD, have been joined by a new coauthor, Erika Darrah, PhD, of Johns Hopkins University,

for Chapter 24, *Inflammatory Rheumatic Diseases*; the chapter authors and textbook editors gratefully acknowledge the intellectual contributions of Antony Rosen, MB, ChB, BSc (Hons), to the content of this chapter in the book's third through seventh editions

With these transitions, the content of more than two-thirds of this eighth edition has greatly benefited from the new contributors' viewpoints and inputs (for instance, by including 36 new illustrations in the book's attractive four-color design and layout).

In Memoriam: Jeffrey L. Kishiyama, MD

We are saddened to report that, following submission of the revision of Chapter 3, *Disorders of the Immune System*, for the eighth edition of *Pathophysiology of Disease*, its lead author, Jeffrey L. Kishiyama, MD, died.

A graduate of Stanford University with a degree in biology and economics, Dr. Kishiyama received his MD from Creighton University School of Medicine. He did his internal medicine residency at Northwestern University, after which he completed a fellowship in allergy and immunology at the University of California, San Francisco (UCSF). Thereafter, Dr. Kishiyama spent many years on the faculties of both UCSF and Stanford University, where he served in a variety of positions, including director of the UCSF Clinical Immunology Laboratory and director of the UCSF Stanford Allergy and Immunology training program. In addition to his academic positions, Dr. Kishiyama maintained an active clinical practice, treating patients at Allergy Asthma Associates of Northern California.

Jeff first joined the authors of *Pathophysiology of Disease* as a coauthor with Richard Shames, MD, for its third and fourth editions, published in 2000 and 2003. Thereafter, Jeff continued as a solo author for the fifth edition in 2006, the sixth edition in 2010, and the seventh edition in 2014. For the eighth edition, he recruited coauthors Jennifer J. Chang, MD, Fellow in HIV Medicine, and Suzanne M. Donovan, MD, MPH, Clinical Professor of Medicine, Division of Infectious Diseases, of the UCLA School of Medicine.

Jeff was a superb contributor to *Pathophysiology*, helping to make understandable the increasingly complex field of immunology. Through the years, our readers, particularly our student readers, have been most grateful for his gift in this regard. As one small example, Jeff more than tripled the size of the introductory table of acronyms and abbreviations used throughout both Chapter 3 and the entire book.

We will greatly miss having Jeff as an outstanding (and timely!) contributor to our wonderful book.

With the publication of this eighth edition, the editors want to extend special thanks, not only to the contributors old and new, but also to the students and colleagues who have offered helpful comments and criticisms for each of the previous editions. The authors and editors continue to welcome comments and recommendations for future editions, in writing or via email. The editors' and authors' institutional and email addresses are given in the Authors section.

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CHAPTER

1

Introduction

Gary D. Hammer, MD, PhD, & Stephen J. McPhee, MD

A man cannot become a competent surgeon without the full knowledge of human anatomy and physiology, and the physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.

Sir William Osler (1849–1919)

Osler expresses particularly well the relationship between the basic sciences and clinical medicine in the aphorism cited above. Indeed, ever since the Middle Ages, wise physicians and others concerned with the sick and their care have realized that most human disease may be understood in a real sense as disordered physiology (pathophysiology). Something (eg, a mutation [pathogenic variant] in a gene or invasion by a bacterial organism) triggers an illness, and the body reacts with molecular, cellular, and systemic responses that are the symptoms and signs of the disease. Therefore, with proper knowledge of the body's normal structure and function, and the ways in which these can become disordered, comes the ability to understand disease and to design rational and effective treatment. In addition, of course, the relationship between pathophysiology and disease is a two-way street. Diseases may be viewed as "experiments of nature" that may uncover previously unknown or unappreciated physiologic mechanisms, and the investigation of these physiologic mechanisms in normal individuals advances our fundamental biomedical knowledge. Therefore, it is important that students understand normal structure and function, and how they can become disordered, and apply this knowledge to disease.

The aim of this book is to provide students with an introduction to clinical medicine through the study of diseases as manifestations of pathophysiology.

The authors (all experts in their respective fields) have provided a brief review of the relevant normal structure and function of each system in the body, followed by a description of the underlying pathophysiologic mechanisms that underlie several common diseases related to that system. With this approach comes an explication of the symptoms and signs of each disease state and an essential framework for the student's later mastery of treatment strategies. Several subject areas that are not restricted to a single body system are also covered (eg, neoplasia and infectious disease), but the same approach is used in these instances as well. For the most part, diagnosis and treatment are not covered here but are left for later, more detailed study and textbooks such as the annually updated *Current Medical Diagnosis & Treatment*. No attempt is made here to be comprehensive or complete; the pathophysiology section of each chapter discusses one to five relevant clinical entities, based either on their frequency (eg, coronary artery disease and hypertension) or on their importance to understanding how physiologic systems may become disordered (eg, fragile X mental retardation or pheochromocytoma). The aim is to introduce students to diseases as manifestations of disordered function and to start them thinking about the related symptoms and signs in terms of their pathophysiologic basis.

This is the eighth edition of this basic science textbook, first published in 1992. It has grown from 20 to 25 chapters, with the number of clinical entities discussed increasing and the number of case study problems increasing gradually from 38 when debuted in the third edition, to 89 in the fourth and fifth editions, to 111 in the sixth, to 120 in the seventh, and now to 132 in this eighth edition. In addition, the authorship of chapters has gradually transitioned, with 18 new authors or co-authors in this eighth edition alone (compared to the seventh edition). Finally, with the rapid expansion in our understanding of the genetic and genomic origin of many pathophysiologic entities, the amount of content devoted to this particular disease mechanism has greatly increased. In this new edition, for example, a revised Table 15–9 gives a much longer listing of the genetic syndromes associated with pancreatic cancer. And a newly rewritten Chapter 5 provides a detailed explanation of the genetic and genomic origins of neoplastic disorders—including several types of epithelial neoplasms (carcinomas); mesenchymal, neuroendocrine, and germ cell neoplasms (neuroendocrine tumors, testicular germ cell cancers, and sarcomas); and hematologic neoplasms (lymphomas and acute and chronic leukemias).

CHAPTER

2

Genetic Disease

Shane C. Quinonez, MD, & 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 resulting from decreased bone density in osteoporosis heals in much the same way 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 low-density lipoprotein (LDL) receptor. Thus, the pathophysiologic principles that distinguish genetic disease focus not so much on the affected organ system as on the mechanisms of genetic and genomic changes, 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 medical genetics. Important terms and key words used throughout the chapter are defined in Table 2–1.

TABLE 2–1 Glossary of terms and keywords.

Term	Definition
Acrocentric	Refers to the terminal location of the centromere on chromosomes 13, 14, 15, 21, and 22.
Allelic heterogeneity	The situation in which multiple alleles at a single locus can produce one or more disease phenotypes.
Amorphic	Refers to pathogenic variants that cause a complete loss of function for the respective gene and therefore yield the same phenotype as a complete gene deletion.
Aneuploidy	A general term used to denote any unbalanced chromosome complement.
Antimorphic	Refers to pathogenic variants that, when present in heterozygous form opposite a nonmutant allele, will result in a phenotype similar to homozygosity for loss-of-function alleles.
Ascertainment bias	The situation in which 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	A type of pathophysiologic mechanism that occurs when a mutant allele interferes with the normal function of the nonmutant gene product.
Dosage compensation	Mechanism by which a difference in gene dosage between two cells is equalized. For XX cells in mammals, decreased expression from one of the two X chromosomes results in a concentration of gene product similar to 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 is heritable, through somatic cell division and/or across organismal generations, but that does not depend on variation in DNA sequence. Instead, epigenetic inheritance is associated with alterations in chromatin structure such as DNA methylation or histone modification that can be transmitted during cell division.
Expressivity	The extent to which a variant genotype affects phenotype, including the tissues that are affected, and the severity of those effects.
Fitness	The effect of a variant allele on an individual's ability to produce offspring.
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 in which 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.
Haplotype	A set of closely linked DNA sequence variants on a single chromosome.
Hemizygous	A term referring to the presence of only one allele at a locus, either because the other allele is deleted or because it is normally not present; eg, X-linked genes in males.
Heterochromatin	One of two alternative forms of chromosomal material (the other is euchromatin) in which chromosomal DNA is highly condensed and, usually, devoid of genes that are actively transcribed.
Heteroplasmy	The mixture of abnormal and normal mitochondrial DNA molecules in a single cell.

Heterozygote advantage	One way to explain an unexpectedly high frequency of a recessively inherited pathogenic variant in a particular population. During recent evolution, carriers (ie, heterozygotes) are postulated to have had a higher fitness than homozygous wild-type individuals.
Heterozygous	Having two alleles at the same locus that are different.
Homozygous	Having two alleles at the same locus that are the same.
Hypermorphic	Refers to a variant that has an effect similar to increasing the number of normal gene copies per cell.
Hypomorphic	Refers to a variant that reduces but does not eliminate the activity of a particular gene product.
Imprinting	Most commonly, the process whereby expression of a gene depends on whether it was inherited from the mother or the father.
Linkage disequilibrium	A condition in which certain combinations of closely linked alleles, or haplotypes, are present in a population at frequencies not predicted by their individual allele frequencies.
Locus heterogeneity	A situation in which pathogenic variants of different genes produce similar or identical phenotypes. Also referred to as genetic heterogeneity.
Mendelian	A form of inheritance that obeys the "laws" or principles of heredity postulated by Gregor Mendel, ie, segregation, independent assortment and dominance; clinically, these are commonly expressed as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive.
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 of the cells of a single individual. In germline or gonadal mosaicism, the alteration is present in germ cells but not 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 variant that imparts a novel function to its gene product and consequently 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 refers to whether the variant genotype can be inferred based on defined phenotypic criteria. In a population, reduced penetrance refers to the rate at which individuals of a variant genotype cannot be recognized according to specific phenotypic criteria.
Phenotypic heterogeneity	The situation that occurs when pathogenic variants of a single gene produce multiple different phenotypes.
Postzygotic	A mutational event that occurs after fertilization and that commonly gives rise to mosaicism.
Premutation	A genetic change that does not result in a phenotype itself but has a high probability of developing a second alteration—a fully pathogenic variant/full mutation—that does cause a phenotype.
Primordial germ cell	The group of 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 harboring a pathogenic variant causes a phenotype only in the absence of a normal allele. Thus, for autosomal conditions, the variant or disease phenotype is manifest when two copies of the allele harboring a pathogenic variant are present. For X-linked conditions, the variant or disease phenotype is manifest in cells, tissues, or individuals in which the normal allele is either inactivated (a heterozygous female) or not present (a hemizygous male).
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.
SNP	Single nucleotide polymorphism—one of the most common types of genetic variation. There are approximately 1 million common SNPs in the human genome (those that exist at a frequency >1%), and billions of rare single-nucleotide variants (at a frequency >0.001%). Most do not affect protein structure, but the common SNPs may serve as valuable markers for determining the effect of genetic variation on complex and common diseases and disorders such as diabetes, heart disease, hypertension, and obesity.
Structural variant	A deletion, insertion, or more complex rearrangement, usually caused by recombination between repetitive elements. Also referred to as "copy number variant" (CNV) and the most common type of genomic variation. Most structural variants involve deletions or insertions that are relatively small (<10 kb) and do not cause any clinical phenotype. Larger structural variants (>100 kb) are increasingly likely to have clinical effects.

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 pathogenic variants; in addition, alteration 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.
Variant	A genetic sequence alteration. A variant can be classified further using modifiers such as "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign." Use of this nomenclature has replaced the previously used terms "polymorphism" and "mutation."

Next, a group of disorders caused by pathogenic variants (formerly termed "mutations") in collagen genes is discussed (ie, **osteogenesis imperfecta**). Although osteogenesis imperfecta is often considered a single entity, different pathogenic variants and different genes subject to alteration 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**. To show how environmental factors can influence the relationship between genotype and phenotype, another mendelian condition, **phenylketonuria**, is discussed. This serves as a paradigm for newborn screening programs and for treatment of genetic disease. 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 non-autosomal inheritance, **fragile X–associated mental retardation syndrome** is discussed. This syndrome not only is the most common inherited cause of mental retardation but also illustrates how different types of pathogenic variants can explain the perplexing phenomenon of **genetic anticipation**, in which the severity of a mendelian syndrome appears to progress with every generation of inheritance. Another group of disorders that depend on the phenotype and sex of the parent consists of those that affect the mitochondrial genome. As examples, **Leber hereditary optic neuropathy** (**LHON**) and **myoclonic epilepsy with ragged red fibers** (**MERRF**) are considered. These illustrate the principles of mitochondrial inheritance and its pathophysiology. **Aneuploidy** is discussed as one of the most common causes of human genetic disorders that does not affect DNA structure but instead alters the normal chromosome content per cell. The example that is considered, **Down 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, this chapter considers how genome sequences and sequencing are improving our understanding of pathophysiology for many diseases. With the completion of the annotation of the human genome and technological advances that allow

individual genomes to be sequenced rapidly and inexpensively, prospects are at hand to identify genetic components of any human phenotype and to provide medical care that is truly personalized.

UNIQUE PATHOPHYSIOLOGIC ASPECTS OF GENETIC DISEASES

Although the phenotypes of genetic diseases are diverse, their causes are not. The primary cause of any genetic disease is a change in the sequence or cellular content of DNA that ultimately deranges gene expression. 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 by (1) structural rearrangements that result in deletion or duplication of a group of closely linked genes or (2) abnormalities 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 cell (**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 variant, and the affected individual is said to have a "de novo variant." In addition, some variants may arise during early embryogenesis, in which case tissues of the affected individual contain a mixture, or **mosaic**, of abnormal and normal cells. Depending on the time of embryogenesis and cell type in which a new variant arises, an individual may carry the alteration in some but not all of their germ cells (**germline mosaicism**), some but not all of their somatic cells (**somatic mosaicism**), or both.

It is helpful to begin with a brief review of terms that are commonly used in discussing genetic disease with patients and their families. Although genes were recognized and studied long before the structure of DNA was known, it has become common to regard a **gene** as a short stretch of DNA, usually but not always <100,000 base pairs (bp) in length, that encodes a product (usually protein) responsible for a function within the cell. DNA length is typically measured in base pairs, kilobase pairs (kb), or megabase pairs (Mb); chromosomes vary in length from about 46 Mb to 245 Mb. The **locus** is where a particular gene lies on its chromosome. A gene's DNA sequence nearly always has slight differences when compared across many unrelated individuals within a population. These variant versions of a gene are referred to as different **alleles** of that gene. A genetic variant arises via a biochemical event such as a nucleotide

change, deletion, or insertion that has produced a new allele. The historic terms “polymorphism” and “mutation” are rarely used in current scientific and clinic discourse. A “polymorphism” was defined as a benign variant when it exhibited a population frequency greater than 1% in DNA sequence and did not contribute to disease manifestation. A “mutation” was defined as a pathogenic change in DNA sequence that did contribute to disease manifestation. The term “variant” is now the recommended term to define a change in DNA sequence from the population norm and is used with the following modifiers: “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign.” 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 variants result in a biochemical or molecular biologic phenotype (ie, a change in DNA), only some of them result in a clinically abnormal phenotype.

At the molecular level, variant sequences are usually detected through laboratory evaluation (DNA sequencing) and are referred to as a single nucleotide variant (SNV) if a single base pair change has occurred. At the clinical level, variant alleles are recognized by their effect on a phenotype such as human leukocyte antigen (HLA) type or hair color. Two copies or alleles of each autosomal gene (ie, genes on chromosomes 1–22) are present per cell. Individuals carrying identical copies are **homozygous**, whereas individuals whose two copies differ from each other are **heterozygous**. These terms —“homozygous” and “heterozygous”—can apply to the DNA sequence, the protein product, or the clinical phenotype. In other words, an individual may be heterozygous for a single nucleotide polymorphism (SNP) that does not alter the protein product, heterozygous for a deletion that causes a genetic disease, or heterozygous for a DNA sequence alteration that causes a change in protein structure but does not cause disease.

This discussion helps to illustrate the use of the word **phenotype**, which refers simply to any characteristic that can be measured, with the type of measurement depending on the characteristic. Hair color and height are phenotypes readily apparent to a casual observer that are not obviously associated with disease; diabetes and coronary artery disease are disease phenotypes that typically require clinical investigation to be recognized; and restriction fragment length polymorphisms (RFLPs), simple sequence length polymorphisms (SSLPs), and SNPs are molecular biologic phenotypes that can be detected only with a laboratory test.

PENETRANCE & EXPRESSIVITY

One of the most important principles of human genetics is that two individuals with the same mutated gene may have different phenotypes. For example, in the genetic condition of type I osteogenesis imperfecta, pedigrees may occur in which there are both a phenotypically affected grandparent and an affected grandchild even though the obligate carrier parent of the grandchild with the identical genetic variant is asymptomatic (Figure 2–1). Given a set of defined criteria, phenotypic expression of the condition in individuals known to carry the pathogenic variant gene is described as **penetrance**. In other words, if 7 of 10 individuals older than 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 (see below) that often have a relatively high **fitness** (the extent to which individuals carrying an altered allele produce offspring relative to individuals who carry a normal allele); Huntington disease and polycystic kidney disease are examples of disorders with low **fitness**. Genetic conditions that result in a high degree of embryonic lethality have low **fitness**.

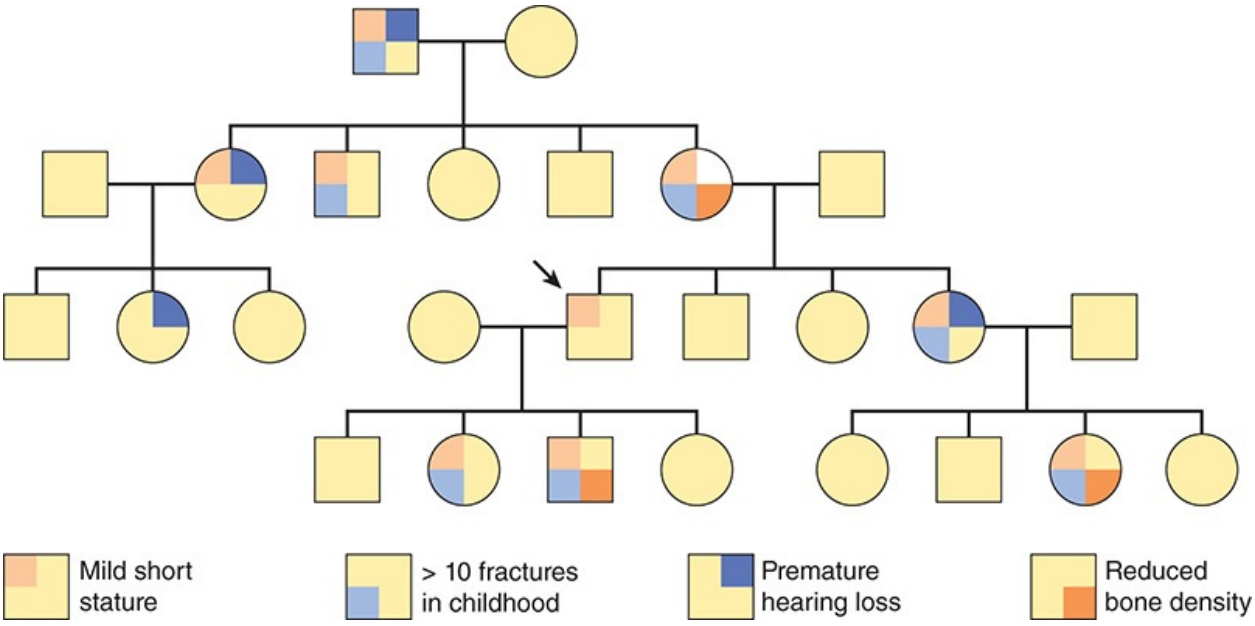

FIGURE 2–1 Penetrance and expressivity in type I osteogenesis imperfecta. In this schematic

pedigree of the autosomal dominant condition of type I osteogenesis imperfecta, nearly all affected individuals exhibit different phenotypic features that vary in severity (variable expressivity). As is shown, type I osteogenesis imperfecta is fully penetrant, because every individual who transmits the pathogenic variant 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.

The same altered gene giving rise to a spectrum of different phenotypes is referred to as **variable expressivity**. For example, blue scleras and short stature may be the only manifestations of type I osteogenesis imperfecta in a particular individual, whereas a sibling who carries the identical mutation may be confined to a wheelchair as a result of multiple fractures and deformities. The pathogenic variant is penetrant in both individuals, but its expression is variable. Both reduced penetrance and variable expressivity may occur in individuals who carry the same altered 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

Genetic variants can be characterized both by their molecular nature—nucleotide deletion, insertion, substitution—and by their effects on gene activity (ie, no effect [neutral or silent], complete loss of function [amorphic variant], partial loss of function [hypomorphic variant], gain of function [hypermorphic variant], or acquisition of a new property [neomorphic variant]). Geneticists who study experimental organisms frequently use specific deletions to ensure that an altered allele causes a loss of function, but human geneticists rely on biochemical or cell culture studies to assess both losses and gains of function. Amorphic and hypomorphic variants are probably the most frequent types of pathogenic variant in human genetic disease because there are many ways to interfere with a protein’s function.

For autosomal genes, the fundamental difference between dominant and recessive inheritance is that, with dominant inheritance, the disease state or phenotypic trait being measured is apparent when one copy of the altered allele and one copy of the normal allele are present. With recessive inheritance, two copies of the altered allele must be present for the disease state or trait to be apparent. However, for genes that lie on the X chromosome, the situation is

slightly different because females have two X chromosomes and males have only one. X-linked dominant inheritance occurs when one copy of an abnormal gene causes the disease phenotype (in males and females); X-linked recessive inheritance occurs when two copies of an abnormal gene cause the disease phenotype (in females). Because most pathogenic variants are amorphic or hypomorphic, however, one copy of an X-linked abnormal allele in males is not "balanced" with a normal allele, as it would be in females; therefore, in X-linked recessive inheritance, one copy of an abnormal allele is sufficient to produce a disease phenotype in males, a situation referred to as **hemizygosity**.

RECESSIVE INHERITANCE & LOSS-OF-FUNCTION PATHOGENIC VARIANTS

Most recessive pathogenic variants are due to loss of function of the gene product, which can occur from a variety of causes, including failure of the gene to be transcribed or translated and failure of the translated gene product to function correctly. There are two general principles to keep in mind when considering loss-of-function variants. First, because expression from the normal allele usually does not change (ie, there is no **dosage compensation**), 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 resulting from enzyme deficiencies such as phenylketonuria (Table 2–2) are inherited in a recessive fashion.

TABLE 2–2 Phenotype, inheritance, and prevalence of selected genetic disorders.

Disorder	Phenotype	Genetic Mechanism	Incidence
Down syndrome	Intellectual disability and growth deficiencies, dysmorphic features, internal organ anomalies	Chromosomal imbalance; caused by trisomy 21	≈1:700; increased risk with advanced maternal age
Fragile X–associated mental retardation syndrome	Intellectual disability, 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 manifested 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
Leber hereditary optic neuropathy	Acute or subacute blindness, occasional myopathy or neurodegeneration	Pathogenic variant of electron transport chain encoded by mtDNA	≈1:50,000–1:10,000
Myoclonic epilepsy with ragged red fibers	Uncontrolled periodic jerking, muscle weakness	Pathogenic variant of mitochondrial tRNA in mtDNA	≈1:100,000–1:50,000
Neurofibromatosis	Multiple café-au-lait spots, neurofibromas, increased tumor susceptibility	Autosomal dominant; caused by multiple loss-of-function variants in a signaling molecule	≈1:3000; ≈50% are new mutations
Duchenne muscular dystrophy	Muscular weakness and degeneration	X-linked recessive; caused by multiple loss-of-function variants in muscle protein	≈1:3000 males; ≈33% are new mutations
Osteogenesis imperfecta	Increased susceptibility to fractures, connective tissue fragility, blue scleras	Phenotypically and genetically heterogeneous	≈1:10,000
Phenylketonuria	Intellectual disability and growth deficiencies	Autosomal recessive; caused by multiple loss-of-function variants in phenylalanine hydroxylase	≈1:10,000

DOMINANT INHERITANCE & LOSS-OF-FUNCTION PATHOGENIC VARIANTS

If 50% of a particular product is not enough for the cell or tissue to function normally, then a loss-of-function variant in this gene produces a dominantly inherited phenotype. Such pathogenic variants often occur in structural proteins; an example is type I osteogenesis imperfecta, which is considered in detail later. Most dominantly inherited phenotypes are actually **semidominant**, which means that an individual who carries two copies of the abnormal allele is affected more severely than someone who carries one abnormal and one normal copy. However, for most dominantly inherited conditions, individuals homozygous for two pathogenic variants 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 abnormal gene. This results in homozygous achondroplasia, a condition that is very severe and usually fatal in the perinatal period; thus, achondroplasia exhibits semidominant inheritance. Huntington disease, a dominantly inherited neurologic disease, is the only known human condition in which the homozygous abnormal phenotype is identical to the heterozygous abnormal phenotype (sometimes referred to as a “true dominant”).

DOMINANT NEGATIVE GENE ACTION

A special kind of pathophysiologic mechanism, referred to as dominant negative, occurs frequently in human genetic diseases that involve proteins that form oligomeric or polymeric complexes. In these disorders, the abnormal allele gives rise to a structurally abnormal protein that interferes with the function of the normal allele. Note that any molecular lesion (ie, deletion, nonsense, missense, or splicing) can produce a loss-of-function allele. However, only molecular lesions that yield a protein product (ie, splicing, missense, or nonsense variants) can result in a dominant negative allele. Type II osteogenesis imperfecta, described later, is an example of a dominant negative pathogenic variant.

Although the terms “dominant” and “recessive” are occasionally used to describe specific pathogenic variants, a DNA sequence alteration itself cannot, strictly speaking, be dominant or recessive. The terms are instead appropriate to the effect of a pathogenic variant on a particular trait. Therefore, in characterizing a particular pathogenic variant as “recessive,” one is referring to the effect of the variant on the trait being studied.

MUTATION RATE & THE PREVALENCE OF GENETIC DISEASE

At the level of DNA sequence, nucleotide variants (substitutions, small insertions, or small deletions) in humans occur at a rate of approximately 2×10^{-8} per nucleotide per human generation, or 150 new variants per diploid genome. However, only about 5% of the human genome is protein coding, so most new variants have no effect. Still, with approximately 23,000 genes in the human

genome and an estimated deleterious “per locus” mutation rate of 10^{-5} per generation, the chance of a new deleterious variant occurring in any one individual is about 20%. Furthermore, assuming 10 billion new births in the last millennium, every gene in the human genome has probably been mutated (in a deleterious manner) about 100,000 different times. However, from a clinical perspective, only about 6000 single-gene disorders have been recognized to cause a human disease. In considering possible explanations for this disparity, it seems likely that deleterious variants of many single genes are lethal very early in development and thus not clinically apparent, whereas deleterious variants in other genes do not cause an easily recognizable phenotype. The overall frequency of disease attributable to defects in single genes (ie, mendelian disorders) is approximately 1% of the general population.

Table 2–2 lists the major symptoms and signs (phenotypes), genetic mechanisms, and prevalence of the diseases considered in this chapter as well as of several others. The most common conditions, such as neurofibromatosis, cystic fibrosis, and fragile X–associated mental retardation syndrome, will be encountered at some time by most health care professionals regardless of their field of interest. Other conditions, such as Huntington disease and adenosine deaminase deficiency, although of academic and pathophysiologic interest, are not likely to be seen by most practitioners.

Many common conditions such as atherosclerosis and breast cancer, while in a minority of cases are caused by a single-gene disorder, usually do not show strictly mendelian inheritance patterns but have some genetic component evident from familial aggregation or twin studies. These conditions are usually described as **multifactorial**, which means that the effects of one or more mutated genes and environmental differences all contribute to the likelihood that a given individual will manifest the phenotype.

ISSUES IN CLINICAL GENETICS

Most patients with genetic disease present during early childhood with symptoms that ultimately give rise to a diagnosis such as fragile X–associated mental retardation or Down syndrome. The major clinical issues at presentation are arriving at the correct diagnosis and counseling the patient and family regarding the natural history and prognosis of the condition. It is important to assess the likelihood that the same condition will occur again in the family and determine whether it can be diagnosed prenatally. These issues are the subject

matter of genetic counseling by medical geneticists and genetic counselors.

Understanding the pathophysiology of genetic diseases that interfere with specific metabolic pathways—so-called inborn errors of metabolism—has led to effective treatments for selected conditions such as phenylketonuria, maple syrup urine disease, and homocystinuria. Many of these diseases are rare, but efforts are underway to develop treatments for common single-gene disorders such as Duchenne muscular dystrophy, cystic fibrosis, and hemophilia. Some forms of therapy are directed at replacing the mutant protein, whereas others are directed at ameliorating its effects.

CHECKPOINT

1. Define gene, locus, allele, variant, heterozygosity, hemizygosity, and phenotype.
2. How is it possible for two individuals with the same pathogenic variant to experience differences in the severity of an abnormal phenotype?
3. Explain the pathophysiologic difference between variants that act via loss of function and those that act via dominant negative gene action.

PATHOPHYSIOLOGY OF SELECTED GENETIC DISEASES

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is a condition inherited in mendelian fashion that illustrates many principles of human genetics. It is a heterogeneous and pleiotropic group of disorders characterized by a tendency toward bone fragility. Advances in the last two decades demonstrate two genetically different groups: the “classical” group, in which more than 90% of cases are caused by pathogenic variants of the *COL1A1* or *COL1A2* genes, which encode the subunits of type I collagen, proα1(I) and proα2(I), respectively, and a newer group, caused by loss-of-function pathogenic variants in other proteins required for proper folding, processing, and collagen secretion. More than 100 different abnormal alleles have been described for osteogenesis imperfecta; the relationships between

different DNA sequence alterations and the type of disease (genotype–phenotype correlations) illustrate several pathophysiologic principles in human genetics.

Clinical Manifestations

The clinical and genetic characteristics of osteogenesis imperfecta are summarized in Table 2–3, in which the timing and severity of fractures, radiologic findings, and presence of additional clinical features help to distinguish four different subtypes. This classification was presented more than 30 years ago. Over the past decade, it has become clear that there are more than a dozen different genes in which pathogenic variants can cause osteogenesis imperfecta, and that the utility of alternative or more extended nosologic approaches depends on whether the condition is being considered from the perspective of patients, caregivers, or molecular geneticists.

TABLE 2–3 Subtypes of dominant osteogenesis imperfecta.

Type	Phenotype	Genetics	Molecular Pathophysiology
Type I	**Mild:** Short stature, postnatal fractures, little or no deformity, blue scleras, premature hearing loss	Autosomal dominant	Loss-of-function variant in proα1(I) chain resulting in decreased amount of mRNA; quality of collagen is normal; quantity is reduced twofold
Type II	**Perinatal lethal:** Severe prenatal fractures, abnormal bone formation, severe deformities, blue scleras, connective tissue fragility	Sporadic (autosomal dominant)	Structural variant in proα1(I) or proα2(I) chain that has mild effect on heterotrimer assembly; quality of collagen is severely abnormal; quantity also often reduced
Type III	**Progressive deforming:** Prenatal fractures, deformities usually present at birth, very short stature, usually nonambulatory, blue scleras, hearing loss	Autosomal dominant[1]	Structural variant in proα1(I) or proα2(I) chain that has mild effect on heterotrimer assembly; quality of collagen is severely abnormal; quantity can be normal
Type IV	**Deforming with normal scleras:** Postnatal fractures, mild to moderate deformities, premature hearing loss, normal or gray scleras, dental abnormalities	Autosomal dominant	Structural variant in the proα2(I), or, less frequently, proα1(I) chain that has little or no effect on heterotrimer assembly; quality of collagen is usually abnormal; quantity can be normal

[1]Autosomal recessive in rare cases.

All forms of osteogenesis imperfecta are characterized by increased susceptibility to fractures (“brittle bones”), but there is considerable phenotypic heterogeneity, even within individual subtypes. Individuals with type I or type IV osteogenesis imperfecta present in early childhood with one or a few fractures of long bones in response to minimal or no trauma; x-ray films may reveal mild osteopenia, little or no bony deformity, and often evidence of earlier subclinical fractures. However, most individuals with type I or type IV osteogenesis imperfecta do not have fractures in utero. Type I and type IV

osteogenesis imperfecta are distinguished by the severity (less in type I than in type IV) and by scleral hue, which indicates the thickness of this tissue and the deposition of type I collagen. Individuals with type I osteogenesis imperfecta typically have blue scleras, whereas the scleras of those with type IV are normal or slightly gray. In type I, the typical number of fractures during childhood is 10–20; fracture incidence decreases after puberty, and the main features in adult life are mild short stature, a tendency toward conductive hearing loss, and occasionally dentinogenesis imperfecta. Individuals with type IV osteogenesis imperfecta generally experience more fractures than those with type I and have significant short stature caused by a combination of long bone and spinal deformities, but they often are able to walk independently. Approximately 60% of the cases of type I and type IV osteogenesis imperfecta represent de novo previously undescribed pathogenic variants; in the remainder, the history and examination of other family members reveal findings consistent with autosomal dominant inheritance. In most cases, identified pathogenic variants are unique to an individual or family.

Type II osteogenesis imperfecta presents at or before birth (diagnosed by prenatal imaging) with multiple fractures, bony deformities, increased fragility of nonbony connective tissue, and blue scleras, and usually results in death in infancy. Two typical radiologic findings are the presence of isolated “islands” of mineralization in the skull (wormian bones) and a beaded appearance to the ribs. Nearly all cases of type II osteogenesis imperfecta represent a new dominant pathogenic variant, and there is no family history. Death usually results from respiratory difficulties.

Type III osteogenesis imperfecta presents at birth or in infancy with progressive bony deformities, multiple fractures, and blue scleras. It is intermediate in severity between types II and IV; most affected individuals will require multiple corrective surgeries and lose the ability to ambulate by early adulthood. Unlike other forms of osteogenesis imperfecta, which are nearly always due to variants that act dominantly, type III may be inherited, very rarely, in a recessive manner.

Although different subtypes of osteogenesis imperfecta can often be distinguished biochemically, the classification presented in Table 2–3 is primarily clinical rather than molecular, and the disease phenotypes for each subtype show a spectrum of severities that overlap one another. For example, a few individuals diagnosed with type II osteogenesis imperfecta based on the presence of severe bony deformities in utero will survive for many years and thus overlap the type III subtype. Similarly, some individuals with type IV

osteogenesis imperfecta have fractures in utero and develop deformities that lead to loss of ambulation. Distinguishing this presentation from type III osteogenesis imperfecta may be possible only if other affected family members exhibit a milder course.

Additional subtypes of osteogenesis imperfecta have been suggested for individuals that do not match types I–IV, and there are additional disorders associated with congenital fractures that are usually not considered to be "classic" osteogenesis imperfecta. In particular, work over the past several years has identified 11 additional genes in which pathogenic variants can cause autosomal recessive osteogenesis imperfecta and has provided additional insight into the genetic pathophysiology. In general, recessively inherited osteogenesis imperfecta is caused by loss-of-function variants in genes whose protein product is required for proper protein folding, intracellular processing, and trafficking of type I collagen.

Pathophysiology

Osteogenesis imperfecta is a disease of type I collagen, which constitutes the major extracellular protein in the body. It is the major collagen in the dermis, the connective tissue capsules of most organs, and the vascular and gastrointestinal (GI) adventitia and is the only collagen in bone. A mature type I collagen fibril is a rigid structure that contains multiple type I collagen molecules packed in a staggered array and stabilized by intermolecular covalent cross-links. Each mature type I collagen molecule contains two α1 chains and one α2 chain, encoded by the *COL1A1* and *COL1A2* genes, respectively (Figure 2–2). The α1 and α2 chains are synthesized as larger precursors with amino and carboxyl terminal "propeptide" extensions, assemble with each other inside the cell, and are ultimately secreted as a heterotrimeric type I procollagen molecule. During intracellular assembly, the three chains wind around each other in a triple helix that is stabilized by interchain interactions between hydroxylated proline and adjacent carbonyl residues. There is a dynamic relationship between the post-translational action of prolyl hydroxylase and assembly of the triple helix, which begins at the carboxyl terminal end of the molecule. Increased levels of hydroxylation result in a more stable helix, but helix formation prevents further prolyl hydroxylation. The nature of the triple helix causes the side chain of every third amino acid to point inward, and steric constraints allow only a proton in this position. Thus, the amino acid sequence of virtually all collagen chains in the triple-helical portion is $(Gly\text{-}X\text{-}Y)_n$, where Y is proline about one-third of the time.

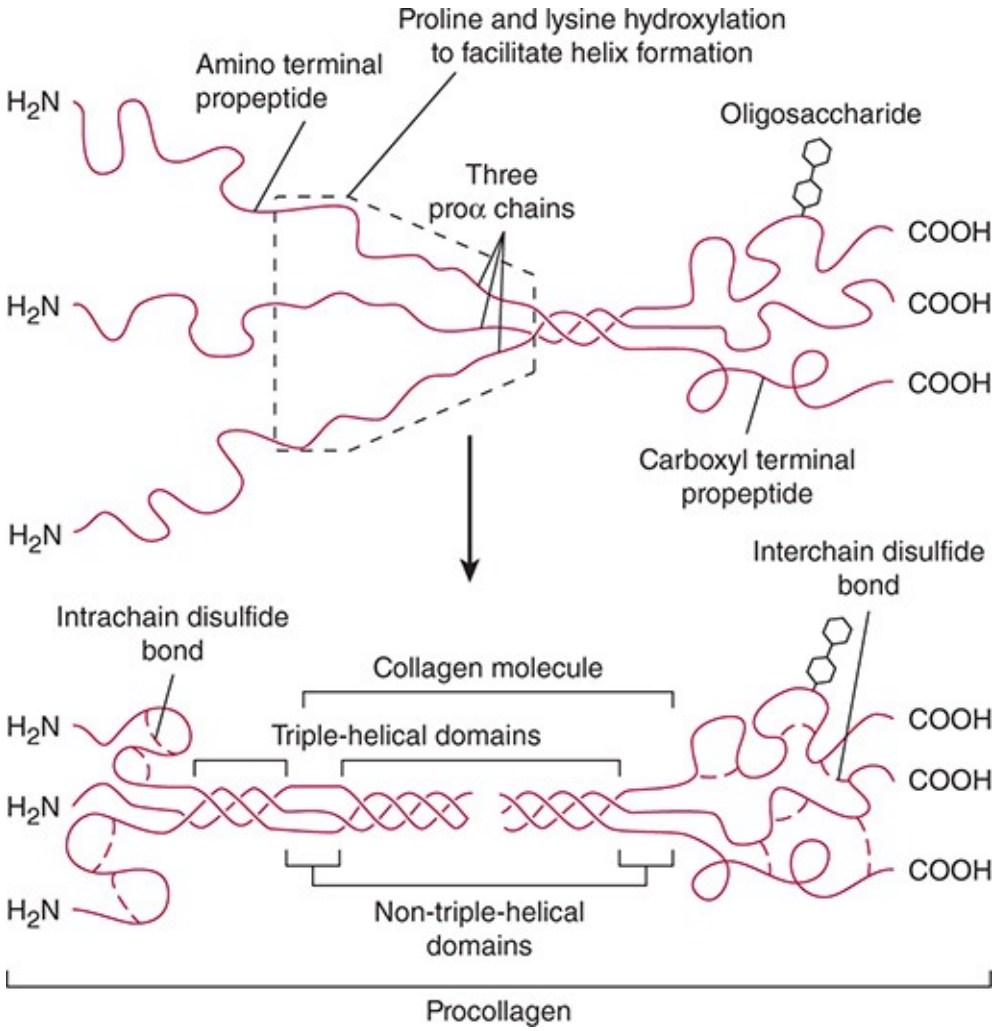

FIGURE 2–2 Molecular assembly of type I procollagen. Type I procollagen is assembled in the endoplasmic reticulum from three proα chains that associate with each other beginning at their carboxyl terminals. An important requirement for proper assembly of the triple helix is the presence of a glycine residue at every third position in each of the proα chains. After secretion, the amino and carboxyl terminal propeptides are proteolytically cleaved, leaving a rigid triple helical collagen molecule with very short non–triple-helical domains at both ends. (Modified and reproduced, with permission, from Alberts BA. *Molecular Biology of the Cell*, 4th ed. Garland Science, 2002. [Fig. 19-47].)

The fundamental defect in most individuals with type I osteogenesis imperfecta is reduced synthesis of type I collagen resulting from loss-of-function variants in *COL1A1*. In most cases, the abnormal *COL1A1* allele gives rise to greatly reduced (partial loss-of-function) or no (complete loss-of-function) mRNA. Because the normal *COL1A1* allele continues to produce mRNA at a normal rate (ie, there is no dosage compensation), heterozygosity for a complete loss-of-function variant results in a 50% reduction in the total rate of proα1(I) mRNA synthesis, whereas heterozygosity for a partial loss-of-function variant results in a less severe reduction. A reduced concentration of proα1(I) chains

limits the production of type I procollagen, leading to (1) a reduced amount of structurally normal type I collagen and (2) an excess of unassembled proα2(I) chains, which are degraded inside the cell (Figure 2–3).

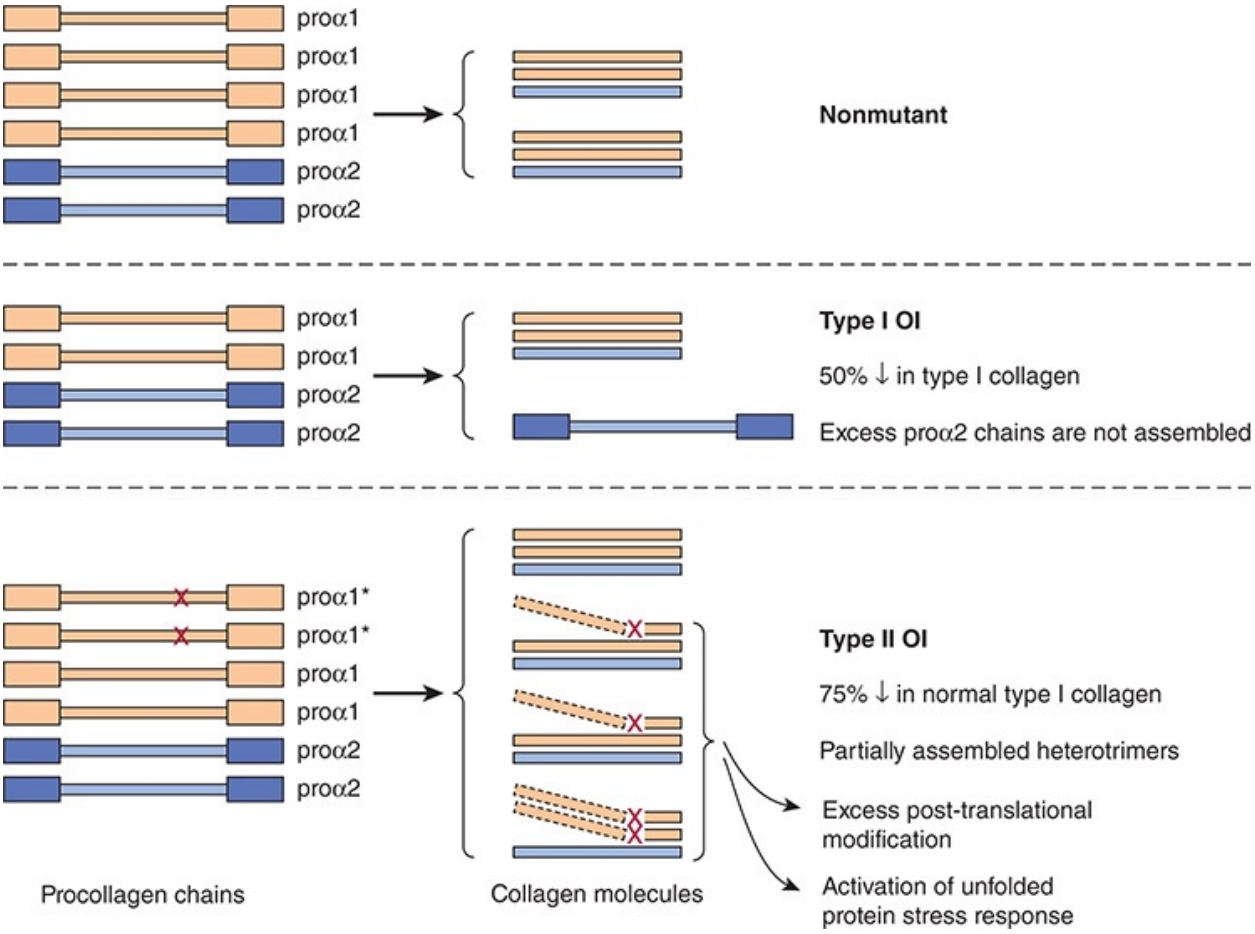

FIGURE 2–3 Molecular pathogenesis of type I and type II osteogenesis imperfecta (OI). The *COL1A1* gene normally produces twice as many proα chains as the *COL1A2* gene. Therefore, in normal cells, the ratio of proα1 to proα2 chains is 2:1, which corresponds to the ratio of α1 and α2 chains in intact collagen molecules. In type I osteogenesis imperfecta, a variant (X) in one of the *COL1A1* alleles (*) results in failure to produce proα1 chains, leading to a 50% reduction in the total number of proα1 chains, a 50% reduction in the production of intact type I collagen molecules, and an excess of unassembled proα2 chains, which are degraded inside the cell. In type II osteogenesis imperfecta, a pathogenic variant in one of the *COL1A1* alleles results in a structural alteration that blocks triple-helix formation and secretion of partially assembled collagen molecules containing the abnormal chain. (Adapted from Nussbaum RL et al. *Thompson & Thompson Genetics in Medicine*, 7th ed. Saunders Elsevier, 2007.)

There are several potential molecular defects responsible for *COL1A1* pathogenic variants in type I osteogenesis imperfecta, including alterations in a regulatory region leading to reduced transcription, splicing abnormalities leading to reduced steady-state levels of RNA, and deletion of the entire *COL1A1* gene. However, in many cases, the underlying defect is a single base pair change that

creates a premature stop codon (also known as a **“nonsense mutation”**) in an internal exon. In a process referred to as nonsense-mediated decay, partially synthesized mRNA precursors that carry the nonsense codon are recognized and degraded by the cell. With collagen and many other genes, production of a truncated protein (as might be predicted from a nonsense mutation) would be more damaging to the cell than production of no protein at all. Thus, nonsense-mediated decay, which has been observed to occur for mutations in many different multiexon genes, serves as a protective phenomenon and is an important component of the genetic pathophysiology.

An example of these principles is apparent from considering type II osteogenesis imperfecta, which is caused by structurally abnormal forms of type I collagen and is more severe than type I osteogenesis imperfecta. Pathogenic variants in type II osteogenesis imperfecta can be caused by defects in either *COL1A1* or *COL1A2* and usually are missense alterations of a glycine residue that allow the abnormal peptide chain to bind to normal chains in the initial steps of trimer assembly (see Figure 2–3). However, triple-helix formation is ineffective, often because amino acids with large side chains are substituted for glycine. Ineffective triple-helix formation leads to increased post-translational modification by prolyl hydroxylase, a reduced rate of secretion, and activation of the unfolded protein stress response. These appear to be critical events in the cellular pathogenesis of type II osteogenesis imperfecta, because glycine substitutions toward the carboxyl terminal end of the molecule are generally more severe than those at the amino terminal end.

These considerations help to explain why type II osteogenesis imperfecta is more severe than type I and exemplify the principle of dominant negative gene action. The effects of an amino acid substitution in a proα1(I) peptide chain are amplified at the levels of both triple-helix assembly and fibril formation. Because every type I procollagen molecule has two proα1(I) chains, only 25% of type I procollagen molecules will contain two normal proα1(I) chains, even though only one of the two *COL1A1* alleles is mutated. Furthermore, activation of the unfolded protein stress response appears to be a key event in the pathophysiology of the disease, as discussed further below. Finally, because each molecule in a fibril interacts with several others, incorporation of an abnormal molecule can have disproportionately large effects on fibril structure and integrity.

Collagen pathogenic variants that cause type III and type IV osteogenesis imperfecta are diverse and include glycine substitutions in the amino terminal portion of the collagen triple helix, a few internal deletions of *COL1A1* and

COL1A2 that do not significantly disturb triple helix formation, and some unusual alterations in the non–triple-helical extensions at the amino and carboxyl terminals of proα chains.

Recessively inherited osteogenesis imperfect can be caused by loss of function for a key prolyl hydroxylase encoded by the *PLOD2* gene, one of three genes—*CRTAP, LEPRE1*, and *PPIB*—that encode members of a protein complex that resides within the rough endoplasmic reticulum and facilitates the folding and processing of type I collagen, as well as several additional genes whose protein products are required for intracellular trafficking and secretion of type I collagen. A common pathway for all types of osteogenesis imperfecta involves a combination of reduced production of type I collagen in the extracellular matrix and/or dysfunctional intracellular collagen processing and maturation.

Genetic Principles

As already described, most cases of type I osteogenesis imperfecta are caused by partial or complete loss-of-function variants in *COL1A1*. Moreover, in approximately 60% of affected individuals, the disease is caused by a de novo previously unidentified pathogenic variant. In addition, there are many ways in which DNA sequence alterations can reduce gene expression. Consequently, there is a wide range of abnormal alleles (ie, **allelic heterogeneity**), which represents a challenge for the development of molecular diagnostic tests. Using current sequencing strategies, the pathogenic variant is identifiable in almost all patients affected with types I–IV osteogenesis imperfecta. Identifying the pathogenic variant or variants in a patient and their family allows for precise recurrence risk estimates and for prenatal testing, if desired.

For types III and IV osteogenesis imperfecta, pathogenic variants can occur in *COL1A1* or *COL1A2* (ie, **locus heterogeneity**), and in this situation, linkage analysis is more difficult because one cannot be sure which locus is abnormal.

For both type I and type IV osteogenesis imperfecta, the most important question in the clinical setting often relates to the natural history of the illness. For example, reproductive decision making in families at risk for osteogenesis imperfecta is influenced greatly by the relative likelihood of producing a child who will never walk and will require multiple orthopedic operations versus a child whose major problems will be a few long bone fractures and an increased risk of mixed sensorineural and conductive hearing loss in childhood and adulthood. As evident from the prior discussion, different abnormal genes and different abnormal alleles, as well as other genes that modify the osteogenesis

imperfecta phenotype, can contribute to this **phenotypic heterogeneity**.

In type II osteogenesis imperfecta, a single copy of the abnormal allele causes the abnormal phenotype and, therefore, has a dominant mechanism of action. Although the type II phenotype itself is never inherited, there are rare situations in which a phenotypically normal individual harbors a *COL1A1* pathogenic variant allele among their germ cells. These individuals with so-called **gonadal mosaicism** can produce multiple offspring with type II osteogenesis imperfecta (Figure 2–4), a pattern of segregation that can be confused with recessive inheritance. In fact, many other pathogenic variants, including Duchenne muscular dystrophy, which is X linked, and type 1 neurofibromatosis, which is autosomal dominant, also occasionally show unusual inheritance patterns explained by gonadal mosaicism.

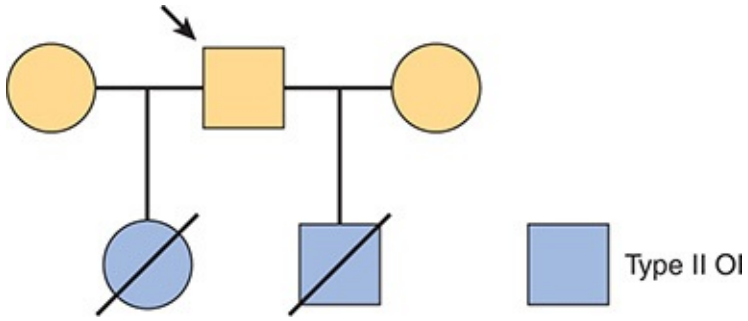

FIGURE 2–4 Gonadal mosaicism for type II osteogenesis imperfecta. In this idealized pedigree, the phenotypically normal father (indicated with the arrow) has had two children by different mates, each of whom is affected with autosomal dominant type II osteogenesis imperfecta (OI). Analysis of the father showed that some of his spermatozoa carried a *COL1A1* pathogenic variant, indicating that the explanation for this unusual pedigree is germline mosaicism. (Adapted from Cohn DH et al. Recurrence of lethal osteogenesis imperfecta due to parental mosaicism for a dominant mutation in a human type I collagen gene [*COL1A1*]. Am J Hum Genet. 1990;46:591.)

CHECKPOINT

4. When and how does type II osteogenesis imperfecta present? To what do these individuals succumb?
5. What are two typical radiologic findings in type II osteo-genesis imperfecta?
6. Explain how nonsense-mediated decay can help pro-tect individuals affected by a genetic disease.

PHENYLKETONURIA

Phenylketonuria represents one of the most dramatic examples of how the relationship between genotype and phenotype can depend on environmental variables. Phenylketonuria was first recognized as an inherited cause of intellectual disability in 1934, and systematic attempts to treat the condition were initiated in the 1950s. The term “phenylketonuria” denotes elevated levels of urinary phenylpyruvate and phenylacetate, which occur when circulating phenylalanine levels, normally between 0.06 and 0.1 mmol/L, rise above 1.2 mmol/L. Thus, the primary defect in phenylketonuria is **hyperphenylalaninemia**, which itself has a number of distinct genetic causes.

The pathophysiology of phenylketonuria illustrates several important principles in human genetics. Hyperphenylalaninemia itself is caused by **substrate accumulation**, which occurs when a normal intermediary metabolite fails to be eliminated properly and its concentrations become elevated to toxic levels. The most common cause of hyperphenylalaninemia is deficiency of the enzyme phenylalanine hydroxylase, which catalyzes the conversion of phenylalanine to tyrosine. Individuals with pathogenic variants in phenylalanine hydroxylase usually do not suffer from the absence of tyrosine because this amino acid can be supplied to the body by mechanisms independent of phenylalanine hydroxylase. In other forms of phenylketonuria, however, additional disease manifestations occur as a result of **end-product deficiency**, which occurs when the downstream product of a particular enzyme is required for a key physiologic process.

A discussion of phenylketonuria also helps to illustrate the rationale for, and application of, population-based screening programs for genetic disease. More than 10 million newborn infants per year are tested for phenylketonuria, and the focus today in treatment has shifted in several respects. First, “successful” treatment of phenylketonuria by dietary restriction of phenylalanine is, in general, accompanied by subtle neuropsychologic defects that have been recognized only in the last decade. Thus, current investigations focus on alternative treatment strategies such as somatic gene therapy, as well as on the social and psychologic factors that affect compliance with dietary management. Second, a generation of females treated for phenylketonuria are now bearing children, and the phenomenon of **maternal phenylketonuria** has been recognized in which in utero exposure to maternal hyperphenylalaninemia results in congenital abnormalities regardless of fetal genotype. The number of pregnancies at risk has risen in proportion to the successful treatment of

phenylketonuria and represents a challenge to public health officials, physicians, dieticians, and geneticists in the future.

Clinical Manifestations

The incidence of hyperphenylalaninemia varies among populations. In African Americans, it is about 1:50,000; in Yemenite Jews, about 1:5000; and in most Northern European populations, about 1:10,000. Post-natal growth restriction, moderate-to-severe intellectual disability, recurrent seizures, hypopigmentation, and eczematous skin rashes constitute the major phenotypic features of untreated phenylketonuria. However, with the advent of widespread newborn screening programs for hyperphenylalaninemia, the major phenotypic manifestations of phenylketonuria today occur when treatment is partial or when it is terminated prematurely during late childhood or adolescence. In these cases, there is a variety of neurocognitive deficits and psychiatric problems that can develop, including deficits in executive functioning and anxiety, depression, and phobias.

Newborn screening for phenylketonuria is performed on a small amount of dried blood obtained at 24–72 hours of age. From the initial screen, there is about a 1% incidence of positive or indeterminate screening results, and in such cases, a more quantitative measurement of plasma phenylalanine is then performed, ideally before 2 weeks of age. In neonates who undergo this confirmatory testing, the diagnosis of phenylketonuria is ultimately validated in about 1%, providing an estimated phenylketonuria prevalence of 1:10,000, although there is great geographic and ethnic variation (see prior discussion).

Infants in whom a diagnosis of phenylketonuria is confirmed are usually placed on a dietary regimen in which a semisynthetic formula low in phenylalanine can be combined with regular breast feeding. This regimen is adjusted empirically to maintain a plasma phenylalanine concentration at or below 1 mmol/L, which is still several times greater than normal but similar to levels observed in so-called **benign hyperphenylalaninemia** (see later discussion), a biochemical diagnosis which is not associated with phenylketonuria and has no clinical consequences. Phenylalanine is an essential amino acid, and even individuals with phenylketonuria must consume small amounts to avoid protein starvation and a catabolic state. Most children require between 25–50 mg/kg/d of phenylalanine, and these requirements are met by combining natural foods with commercial products designed for phenylketonuria treatment. When dietary treatment programs were first implemented, it was hoped that the risk of neurologic damage from the hyperphenylalaninemia of phenylketonuria would have a limited window and that treatment could be