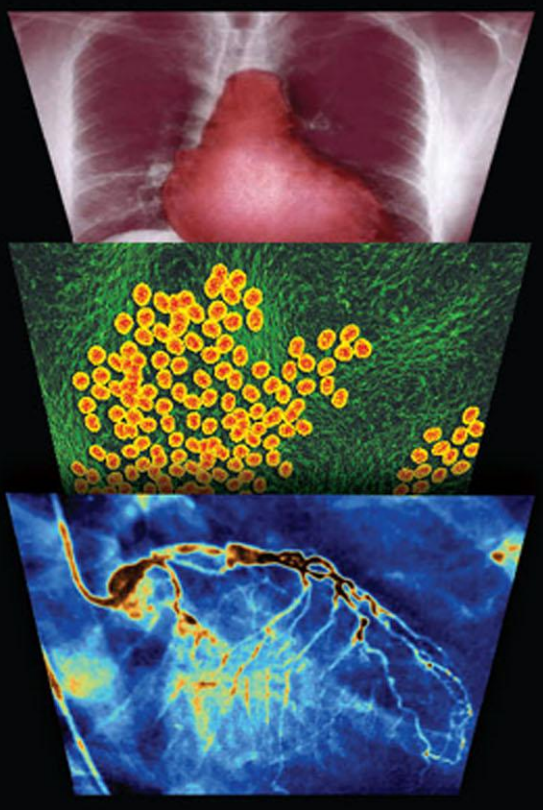
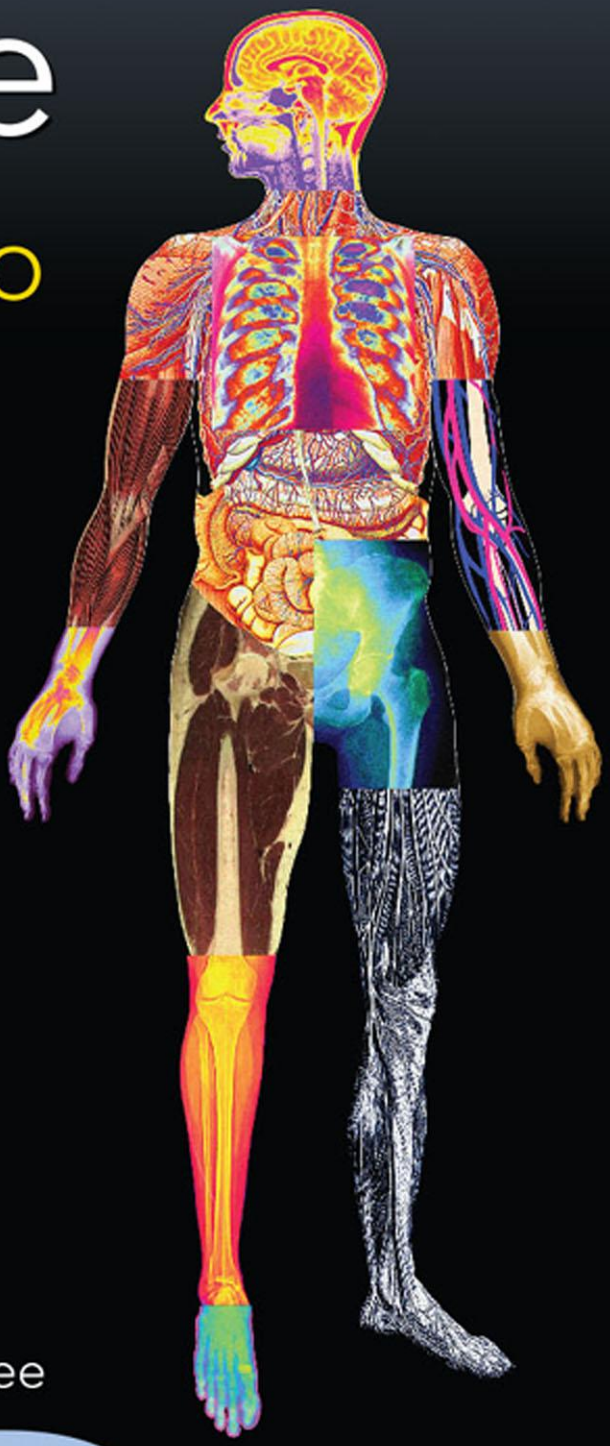
Seventh Edition

Pathophysiology of Disease

An Introduction to Clinical Medicine





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Pathophysiology of Disease:
An Introduction to Clinical Medicine

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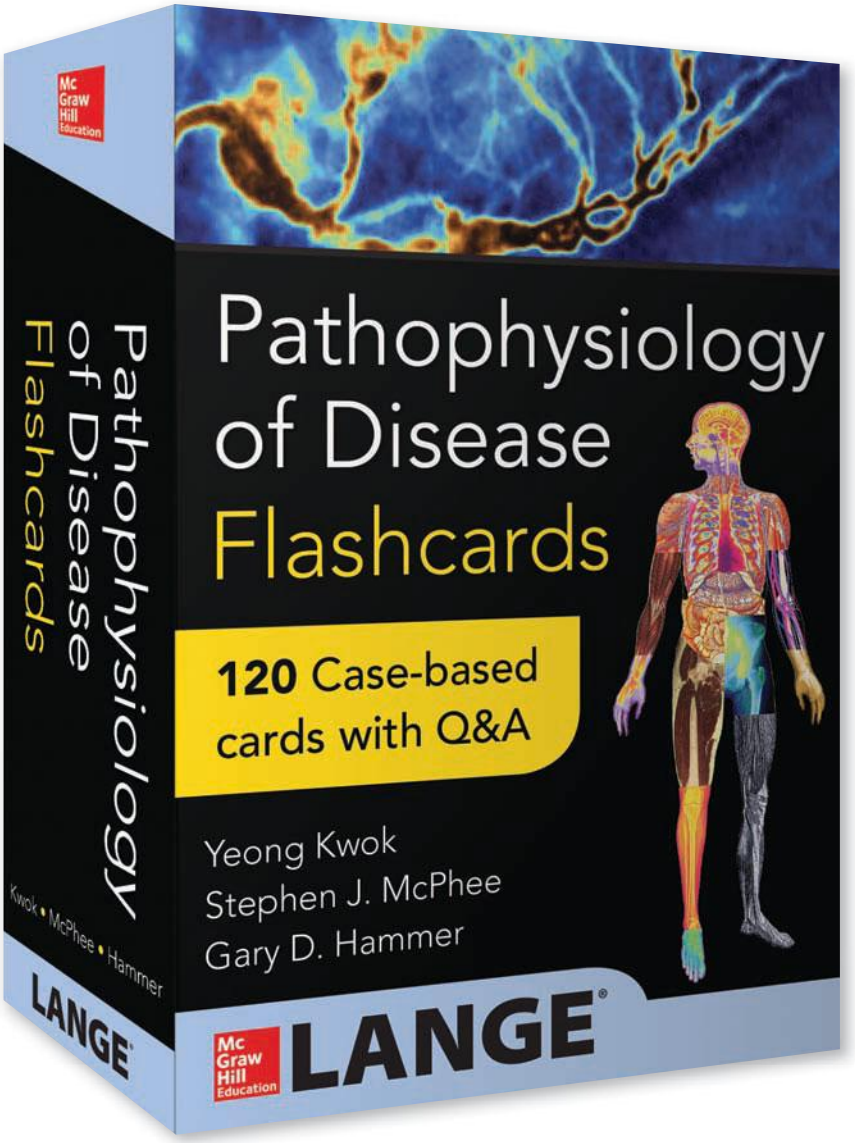

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Key Features of the Seventh Edition of
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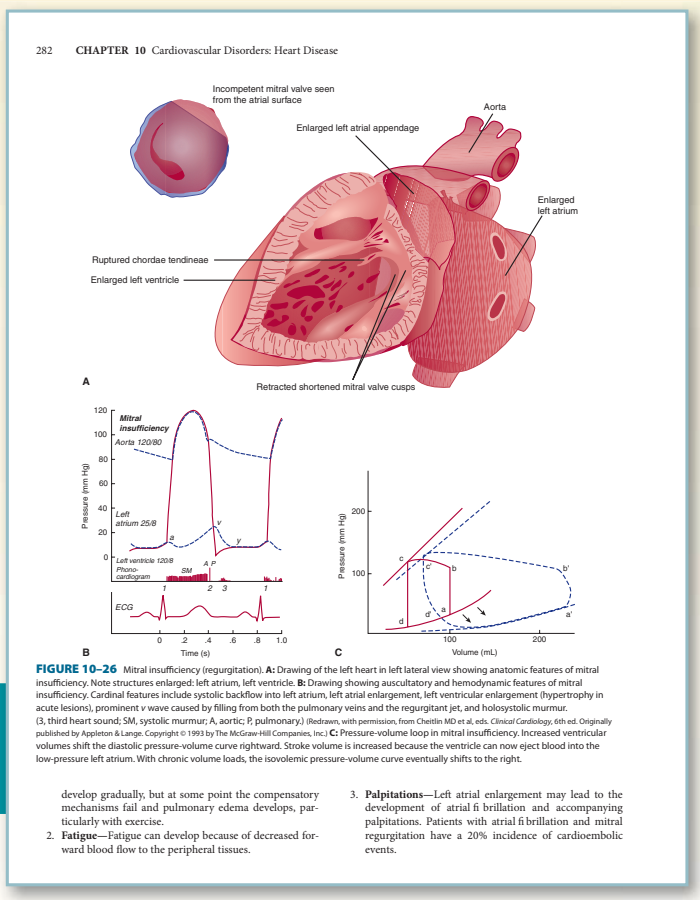

FIGURE 10–26 Mitral insufficiency (regurgitation). **A:** Drawing of the left heart in left lateral view showing anatomic features of mitral insufficiency. Note structures enlarged: left atrium, left ventricle. **B:** Drawing showing auscultatory and hemodynamic features of mitral insufficiency. Cardinal features include systolic backflow into left atrium, left atrial enlargement, left ventricular enlargement (hypertrophy in acute lesions), prominent *v* wave caused by filling from both the pulmonary veins and the regurgitant jet, and holosystolic murmur. (3, third heart sound; SM, systolic murmur; A, aortic; P, pulmonary.) (Redrawn, with permission, from Cheitlin MD et al, eds. *Clinical Cardiology*, 6th ed. Originally published by Appleton & Lange. Copyright © 1993 by The McGraw-Hill Companies, Inc.) **C:** Pressure-volume loop in mitral insufficiency. Increased ventricular volumes shift the diastolic pressure-volume curve rightward. Stroke volume is increased because the ventricle can now eject blood into the low-pressure left atrium. With chronic volume loads, the isovolemic pressure-volume curve eventually shifts to the right.

develop gradually, but at some point the compensatory mechanisms fail and pulmonary edema develops, particularly with exercise.

2. **Fatigue**—Fatigue can develop because of decreased forward blood flow to the peripheral tissues.
3. **Palpitations**—Left atrial enlargement may lead to the development of atrial fibrillation and accompanying palpitations. Patients with atrial fibrillation and mitral regurgitation have a 20% incidence of cardioembolic events.

NEW full-color illustrations enhance the content

Valuable case studies in every chapter

CASE STUDIES

Yeong Kwok, MD

(See Chapter 25, p. 723 for Answers)

CASE 62

A 60-year-old man presents to the clinic with a 3-month history of gradually worsening dysphagia (difficulty swallowing). At first, he noticed the problem when eating solid food such as steak, but now it happens even with drinking water. He has a sensation that whatever he swallows becomes stuck in his chest and does not go into the stomach. He has also developed worsening heartburn, especially upon lying down, and has had to prop himself up at night to lessen the heartburn. He has lost 10 kg as a result of his swallowing difficulties. His physical examination is unremarkable. A barium swallow x-ray reveals a decrease in peristalsis of the body of the esophagus along with dilatation of the lower esophagus and tight closure of the lower esophageal sphincter. There is a beaked appearance of the distal esophagus involving the lower esophageal sphincter. There is very little passage of barium into the stomach.

Questions

A. What is the likely diagnosis in this patient, and what is the underlying pathophysiology of this condition?
B. Botulinum toxin can be used to treat this disorder. How does it help ameliorate the symptoms?
C. What are the possible complications of this disorder, and how do they arise?

CASE 63

A 32-year-old woman presents to her primary care provider complaining of a persistent burning sensation in her chest and upper abdomen. The symptoms are worse at night while she is lying down and after meals. She has tried drinking hot cocoa to help her sleep. She is a smoker and frequently relies on benzodiazepines for insomnia. She notes a sour taste in her mouth every morning. Physical examination is normal.

Questions

A. What is the pathogenetic mechanism of her GI disorder?
B. How may her lifestyle impact her symptoms?
C. What are some complications of chronic esophageal reflux disease?

CASE 64

A 74-year-old man with severe osteoarthritis presents to the emergency department reporting two episodes of melena (black stools) without hematochezia (bright red blood in the stools) or hematemesis (bloody vomitus). He takes 600 mg of ibuprofen three times a day to control his arthritis pain. He denies alcohol use. On examination his blood pressure is 150/70 Hg and his resting pulse is 96/min. His epigastrium is minimally tender to palpation. Rectal examination reveals black tarry stool in the vault, grossly positive for occult blood. Endoscopy demonstrates a 3 cm gastric ulcer. *Helicobacter pylori* is identified on biopsies of the ulcer site.

Questions

A. What are some of the proposed mechanisms for acid-peptic disease and specifically gastric ulcer disease?
B. How may this patient's analgesic use predispose him to acid-peptic disease?
C. What role does *H pylori* infection play in the pathogenesis of ulcer disease? How should this be taken into account when treating this patient?

are greater and more consistent than increases in plasma catecholamines or urinary metanephrines. Administration of clonidine, 0.3 mg orally, can also be used to differentiate patients with pheochromocytoma from those with essential hypertension. Clonidine normally suppresses sympathetic nervous system activity and substantially lowers plasma norepinephrine levels, reducing blood pressure. However, in patients with pheochromocytoma, clonidine has little or no effect on the blood pressure or plasma catecholamine level because these tumors behave autonomously.

C. As a tumor of adrenal medullary tissue, pheochromocytoma produces symptoms of catecholamine excess. Anxiety, headache, and palpitations are direct effects of catecholamine discharge; the weight loss is secondary to one of the metabolic effects of excessive circulating catecholamines. These include an increase in basal metabolic rate and an increase in glycolysis and glycogenolysis, leading to hyperglycemia and glycosuria.

CASE 62

A. This patient likely has achalasia, a condition where the lower esophageal sphincter fails to relax properly. Under normal circumstances, the lower esophageal sphincter is a 3–4 cm ring of smooth muscle that is contracted, under stimulation by vagal cholinergic inputs. When a swallow is initiated, vagal inhibitory fibers allow the sphincter to relax so that the bolus of food can pass into the stomach. In achalasia, there is degeneration of the myenteric plexus and loss of the inhibitory neurons that allow this relaxation. Therefore, the sphincter remains tightly closed. The neural dysfunction can also extend further up the esophagus as well, and effective esophageal peristalsis is also often lost.

B. Injection of botulinum toxin into the lower esophageal sphincter in patients with achalasia diminishes the excitatory pathways responsible for the tonic contraction of the sphincter and allows its partial relaxation.

C. The tight closure of the lower esophageal sphincter in achalasia can result in a dilation of the lower portion of the esophagus and storage of up to 1 L of material there. This material can become infected and aspirated into the lungs. It can also cause esophageal mucosal ulceration and even perforation or rupture.

CASE 63

A. This patient appears to suffer from reflux esophagitis. Normally, the tonically contracted lower esophageal sphincter provides an effective barrier to reflux of acid from the stomach back into the esophagus. Th is is reinforced by secondary esophageal peristaltic waves in response to transient lower esophageal sphincter relaxation. Effectiveness of that barrier can be altered by loss of lower esophageal sphincter tone, increased frequency of transient relaxations, loss of secondary peristalsis after a transient relaxation, increased stomach volume or pressure, or increased production of acid, all of which can make more likely reflux of acidic stomach contents sufficient to cause pain or erosion. Recurrent reflux can damage the mucosa, resulting in inflammation, hence the term "reflux esophagitis." Recurrent reflux itself predisposes to further reflux because the scarring that occurs with healing of the inflamed epithelium renders the lower esophageal sphincter progressively less competent as a barrier.

B. Many factors such as bar food choices (eg, chocolate), medications such as benzodiazepines, and smoking decrease lower esophageal sphincter tone, resulting in reflux of acid-rich gastric contents into the esophageal lumen. This process is exacerbated at night when she lies down to sleep.

C. The most common complication is the development of stricture in the distal esophagus. Progressive obstruction, initially to solid food and later to liquid, presents as dysphagia. Other complications of recurrent reflux include hemorrhage or perforation; hoarseness, coughing, or wheezing; and pneumonia as a result of aspiration of gastric contents into the lungs, particularly during sleep. Epidemiologic studies suggest that cigarette smoking and alcohol abuse associated with recurrent reflux result in a change in the esophageal epithelium from squamous to columnar histology, termed Barrett esophagus. In 2–5% of cases, Barrett esophagus leads to the development of esophageal adenocarcinoma.

CASE 64

A. Excessive acid secretion or diminished mucosal defenses predispose to the development of acid-peptic disease, specifically gastric ulcer. Most gastric ulcers are believed to be related to impaired mucosal defenses, because the acid and pepsin secretory capacity of some affected patients is normal or even below normal. Motility defects have been proposed to contribute to development of gastric ulcer in at least three ways: (1) by a tendency of duodenal contents to reflux back through an incompetent pyloric sphincter (bile acids in the duodenal reflux material act as an irritant and may be an important contributor to a diminished mucosal barrier against acid and pepsin); (2) by delayed emptying of gastric contents, including reflux material, into the duodenum; and (3) by delayed gastric emptying and hence food retention, resulting in increased gastrin secretion and gastric acid production. It is not known whether these motility defects are a cause or a consequence of gastric ulcer formation. Mucosal ischemia may also play a role in the development of a gastric ulcer (see Answer B following). Subsets of gastric ulcer patients with each of these defects have been identified. Thus, the risk factors (NSAID ingestion, smoking, psychologic stress, *H pylori* infection) that have been associated with gastric ulcer probably act by diminishing one or more mucosal defense mechanisms.

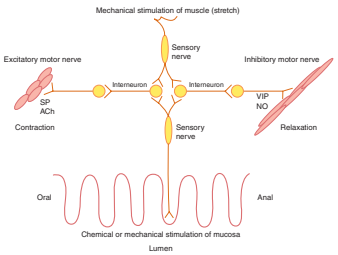

FIGURE 13–16 The peristaltic reflex of the small intestine. Enteric sensory nerves detect chemical or mechanical stimulation of the mucosa or stretch of the muscle layer. Signals are transmitted in an oral or anal direction by interneurons. Excitatory motor nerves release acetylcholine (ACh) and substance P (SP), which cause muscle contraction on the oral side of the stimulus. Inhibitory motor nerves release vasoactive intestinal peptide (VIP) and nitric oxide (NO), which cause muscle relaxation on the anal side of the stimulus.

"Checkpoint" review questions appear in every chapter

CHECKPOINT

31. Describe the hormonal reflex by which fat in the intestine stimulates the secretion of bile.
32. Describe the mechanism by which glucose is absorbed across the apical and basolateral membranes of an enterocyte.
33. What is the mechanism of absorption of tripeptides across an intestinal epithelial cell?
34. What is the role of bile in lipid absorption in the intestine?
35. List three general mechanisms of absorption of Na^+ ions in the small intestine.
36. Describe the mechanism of fluid and electrolyte secretion in the crypts of Lieberkühn.
37. Name two neurotransmitters that are secretagogues.
38. How do certain bacterial toxins stimulate fluid and electrolyte secretion in the crypts of Lieberkühn?
39. Describe the pattern of intestinal motility during fasting and after feeding.
40. Name one hormone that maintains the fasting pattern of motility and one that induces the fed pattern of motility in the small intestine.
41. Name the neurotransmitters that mediate the ascending and descending limbs of the peristaltic reflex.

COLON

Anatomy & Histology

The adult colon is 1.0–1.5 m in length. Its various segments (cecum, ascending, transverse, descending, sigmoid colon, and rectum) are involved in absorption of water and electrolytes, secretion of mucus, and formation, propulsion, and storage of unabsorbed material (feces). The colon is also the home of the majority of the intestinal microbes.

The surface of the colon consists of a columnar epithelium with no villi and few folds except in the distal rectum (Figure 13–13). The epithelial cells include absorptive cells and contain microvilli on their surface as well as mucus-secreting goblet cells. Colonic crypts contain goblet cells, endocrine cells, absorptive cells, and epithelial stem cells. As in the small intestine, the stem cells and their daughter progenitor cells serve to replenish the differentiated cells of the epithelium that continually turnover throughout life.

Digestion & Absorption of the Colon

Digestion in the colon occurs as a consequence of the action of the colonic microbiota. Short-chain fatty acids released by microbial action on dietary fiber are an important source of energy for the colon. More importantly, these short-chain fatty acids promote survival of healthy colonic epithelium while

Figures and tables encapsulate important information

TABLE 7–7 Conditions associated with focal cerebral ischemia.

Vascular disorders
Atherosclerosis
Fibromuscular dysplasia
Vasculitis
Systemic (polyarteritis nodosa, lupus, giant cell, granulomatosis with polyangiitis [formerly Wegner granulomatosis], Takayasu arteritis)
Primary CNS
Meningitis (syphilis, tuberculosis, fungal, bacterial, herpes zoster)
Drug induced (cocaine, amphetamines)
Carotid or vertebral artery dissection
Lacunar infarction
Migraine
Multiple progressive intracranial occlusions (moyamoya syndrome)
Venous or sinus thrombosis
Cardiac disorders
Mural thrombus
Rheumatic heart disease
Arrhythmias
Endocarditis
Mitral valve prolapse
Paradoxic embolus
Atrial myxoma
Prosthetic heart valves
Hematologic disorders
Thrombocytosis
Polycythemia
Sickle cell disease
Leukocytosis
Hypercoagulable states (homocysteinemia, protein S deficiency, antiphospholipid syndrome, sickle cell disease)

young adults. Hemorrhage may be related to spontaneous bleeding from the acute elevation in blood pressure, rupture of an occult vascular abnormality, or drug-induced vasculitis.

Cerebral amyloid angiopathy is a disorder that occurs mainly in the elderly and may be associated with Alzheimer disease. Deposition of amyloid weakens the walls of small cortical vessels and causes lobar hemorrhage, often at several sites.

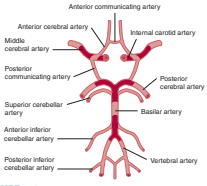

FIGURE 7–35 Sites of predilection (dark red areas) for atherosclerosis in the intracranial arterial circulation. (Redrawn, with permission, from Greenberg DA et al, eds. *Clinical Neurology*, 8th ed. McGraw-Hill, 2012.)

D. Excitotoxicity

Most efforts to intervene in stroke have focused on the vasculature. In ischemic stroke, these efforts include restoring circulation through surgical endarterectomy and reducing thrombosis with anticoagulant, antiplatelet, and thrombolytic drugs. A complementary approach is to attempt to reduce the vulnerability of brain tissue to ischemic damage. This is based on observations that CNS glutamate homeostasis is markedly altered during ischemia, leading to increased and toxic levels of extra-cellular glutamate.

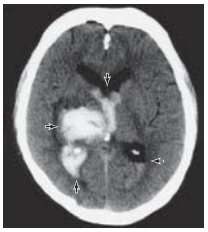

FIGURE 7–36 CT scan in hypertensive intracerebral hemorrhage. Blood is seen as a high-density signal at the site of hemorrhage in the thalamus (left arrow) and its extension into the third ventricle (top arrow) and the occipital horns of the ipsilateral (bottom arrow) and contralateral (right arrow) lateral ventricles. (Reproduced, with permission, from Greenberg DA et al, eds. *Clinical Neurology*, 8th ed. McGraw-Hill, 2012.)

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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, physicians' assistant 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 120 commonly encountered diseases. Nurses, nurse-practitioners, physicians' assistants and other allied health practitioners have found that its concise format and broad scope facilitate their understanding of these basic disease entries.

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 Studies Questions and Answers are also available on the Internet, at www.accessmedicine.com, an online version of McGraw-Hill's many medical textbooks.

New Features for This Edition

In preparation for this seventh edition, the editors and authors reviewed the entire book. There have been many revisions aimed at updating information, improving clarity, and eliminating minor errors. References have also been updated, with emphasis on valuable reviews. "Checkpoints," collections of review questions, which continue to appear throughout the chapters, have been revised.

Examples of New Content Found in This Edition

- Expanded sections on recent advances in whole genome sequencing approaches
- Update on the molecular biology of cells of the immune system and inflammatory mediators
- Update on role of thrombopoietin in thrombopoiesis
- Substantial revision of coagulation factors and the coagulation system, including a new figure summarizing the coagulation cascade
- Update on pathogenesis of immune-mediated and heparin-induced thrombocytopenia
- Revised sections on the pathogenesis of psoriasis, erythema multiforme and bullous pemphigoid
- Revised sections on the pathophysiology of idiopathic pulmonary fibrosis and pulmonary edema
- Updated section on endothelin physiology and pathophysiology
- Revised sections on adaptive and innate immunity of the gastrointestinal tract
- Revised sections on pathophysiology of *Helicobacter pylori*, atrophic gastritis and inflammatory bowel disease
- New detailed section on commensal microbes of the small intestine
- Updated section on pancreatic development and associated congenital disorders
- Revised sections on the pathophysiology of autoimmune, acute and chronic pancreatitis together with associated complications
- Updated section on the pathophysiology and management of pancreatic cancer
- New introduction to the chapter on renal disease
- Revised sections on hormonal control of sodium reabsorption, potassium excretion, and acid/base metabolism
- Updated sections on pathophysiology of renal diseases
- Addition of discussion on role of RANK and RANK-L in bone biology
- Revised section on roles of PTH versus PTHrP in calcium homeostasis
- Updated section on vitamin D physiology
- Revised section on medullary thyroid carcinoma

- Updated roles of glucagon and GLP-1 in the endocrine pancreas
- Updated sections on obesity, insulin resistance and metabolic syndrome
- New information on mutations in various genes shown to predispose to the development of pheochromocytoma and paraganglioma
- Revised information about complications of liver disease such as hepatorenal syndrome, hepatic encephalopathy, and hepatopulmonary syndrome
- Updated section on the mechanism of action of thyroid hormones
- Revised section on the pathophysiology of subclinical thyroid disease
- Revised information on the diagnosis of suspected Cushing syndrome and suspected adrenal insufficiency, on the different forms of genetic primary aldosteronism, and on congenital adrenal hyperplasia
- Updated section on primary ovarian failure
- Updated section on the role of kisspeptins in puberty and the genetics of hypogonadism

Pathophysiology of Disease Flashcards

Another new development with the book's seventh edition is the simultaneous publication of a set of 120 *Pathophysiology of Disease Flashcards,* useful study aids for students and other readers. These *Pathophysiology of Disease Flashcards* were developed by Yeong Kwok, MD, of the University of Michigan, in collaboration with Drs. McPhee and Hammer. The *Flashcards* incorporate clinical "Cases" with several "Questions," each of which is followed by bulleted "Answers." The "Questions" derive from the text's unanswered review "Checkpoints" and the *Flashcards* "Answers" have been drawn from the relevant text material and are printed upside down so as to encourage the user to think through the answers after reading the questions. Note that these questions and answers do not duplicate the Case Studies Questions and Answers already found in the textbook itself.

Changes in Editors and Authors

With this seventh edition, Gary Hammer, MD, PhD at the University of Michigan has assumed the role of "lead" title page editor, and Stephen McPhee, MD at the University of California, San Francisco has moved to "second in command."

With this seventh edition, too, the authorship of several chapters has evolved and transitioned—the editors wish to welcome aboard the following new contributors and thank the following past contributors who are now departing the book:

- Catherine Lomen-Hoerth, MD, PhD, has taken over the current revision of Chapter 7: Nervous System Disorders; we would like to thank Robert O. Messing, MD, for the original development of this chapter and his revisions for the first 5 editions and assistance with the 6th edition
- Melissa M. Meier, MD, has joined Timothy H. McCalmont, MD, (both at the University of California at San Francisco) in producing the revision of Chapter 8: Diseases of the Skin
- Mark Chesnutt, MD, at the University of Oregon has joined Thomas J. Prendergast, MD, as co-author for Chapter 9: Pulmonary Disease; we would like to acknowledge Stephen J. Ruoss, MD, for his role in co-authoring the original chapter with Dr. Prendergast and for his revisions for the next 5 editions; and we thank Eric J. Seeley, MD for his assistance with the 6th edition
- Mandana Khalili, MD, MAS, now working with Blaire Burman, MD, produced the current revision of Chapter 14: Liver Disease; and we thank Tung T. Nguyen, MD, for his work on previous editions, and Charles Liao, MD for his assistance with the 6th edition
- Christopher J. Sonnenday, MD, produced the current revision of Chapter 15: Disorders of the Exocrine Pancreas; and the editors thank Diane M. Simeone, MD, for her assistance with the 6th edition
- Rachel L. Perlman, MD, and Michael Heung, MD, MS, will serve as the new lead co-authors of Chapter 16: Renal Disease with Joachim H. Ix, MD, and they will henceforth take over the chapter from him; we are grateful to Benjamin D. Parker, MD, for his work on the 6th edition
- Erika B. Johnston-MacAnanny, MD, has joined Robert N. Taylor, MD, PhD, (both at Wake Forest University), in revising Chapter 22: Disorders of the Female Reproductive Tract; we thank Karen J. Purcell, MD, PhD, for her work on previous editions

and

- Yeong Kwok, MD, at the University of Michigan, has taken over the revisions and additions of the Case Studies Questions and Answers for each chapter; the editors thank Eva M. Aagaard, MD, and Jonathan D. Fuchs, MD, MPH, for their work on each of the previous editions.

With these transitions, the content of one-third of the book has benefited from new contributors' viewpoint and input.

Case Studies Questions and Answers

As mentioned, each chapter ends with a collection of Case Studies. These clinical problems give students 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 seventh edition, an additional 9 Case Studies with Questions have been added by Yeong Kwok, MD, bringing the total number to 120, or one for each of the clinical entities discussed in the book's 24 chapters. As before, detailed analyses of the cases appear in Chapter 25: Case Study Answers; Dr. Kwok has added Answers to the new Case Studies and updated the existing

answers to reflect the changes made by chapter authors in their revisions.

Finally, the seventh edition of *Pathophysiology of Disease: An Introduction to Clinical Medicine* has more than two dozen new illustrations in its attractive four-color design and layout.

With publication of this seventh 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 electronic mail. The editors' and authors' institutional and e-mail addresses are given in the Authors section.

Gary D. Hammer, MD, PhD
Ann Arbor, Michigan

Stephen J. McPhee, MD
San Francisco, California
March 2014

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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 relation 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 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 relation 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.

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CHAPTER

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 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 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 medical 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**). Although 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**. To show how environmental factors can influence the relationship between genotype and phenotype, I discuss another mendelian condition, **phenylketonuria**. This serves as a paradigm for newborn screening programs and 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 nontraditional 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 mutations can explain the perplexing phenomenon of **genetic anticipation**, where 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 types of human genetic disease 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, I consider how genome sequences and sequencing are improving our understanding of pathophysiology for many diseases. With the completion of the human genome sequence 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

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 mutations 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 mutations 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 mutant genotype affects phenotype, including the tissues that are affected, and the severity of those effects.
Fitness	The effect of a mutant 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, e.g., 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 mutant and nonmutant mitochondrial DNA molecules in a single cell.

(*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 (i.e., heterozygotes) are postulated to have had a higher fitness than homozygous nonmutant 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 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	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 mutations of different genes produce similar or identical phenotypes. Also referred to as genetic heterogeneity.
Mendelian	A form of inheritance that obeys Mendel laws, ie, autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive.
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).
Monosomy	A reduction in zygotic cells from two to one in the number of copies for a particular chromosomal segment or chromosome.
Neomorphic	Refers to a mutation 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 or not 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 pertains when mutations 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 full mutation—which 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 causes 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).
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 mutations; 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.

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 mutation and the affected individual is said to have a "new mutation." In addition, some mutations may arise during early embryogenesis, in which case tissues of the affected individual contain a mixture, or **mosaic**, of mutant and nonmutant cells. Depending on the time of embryogenesis and cell type in which a new mutation arises, an individual may carry the mutation 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 usage 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 measurable trait. 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 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 of them result in a clinically abnormal phenotype.

At the molecular level, variant alleles are usually recognized by DNA sequencing and are referred to as a single nucleotide polymorphism (SNP) if a single base pair change has occurred. As originally coined, the word **polymorphism** referred to an allele present in 1% or more of a population; today, the terminology tends to be less rigid and is often described qualitatively, ie, rare and common variants. At the clinical level, variant alleles are recognized by their effect on a phenotype such as human leukocyte antigen (HLA) type or hair color. For an autosomal gene (those that lie on chromosomes 1–22, carried in two copies 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 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, whereas 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 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 2–1). 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 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 that have a relatively high **fitness** (the extent to which individuals carrying a mutant allele produce offspring relative to individuals who do not carry a mutant allele); Huntington disease and polycystic kidney disease are examples.

When the same mutated gene gives rise to a different spectrum of phenotypes, the situation 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 mutation is penetrant

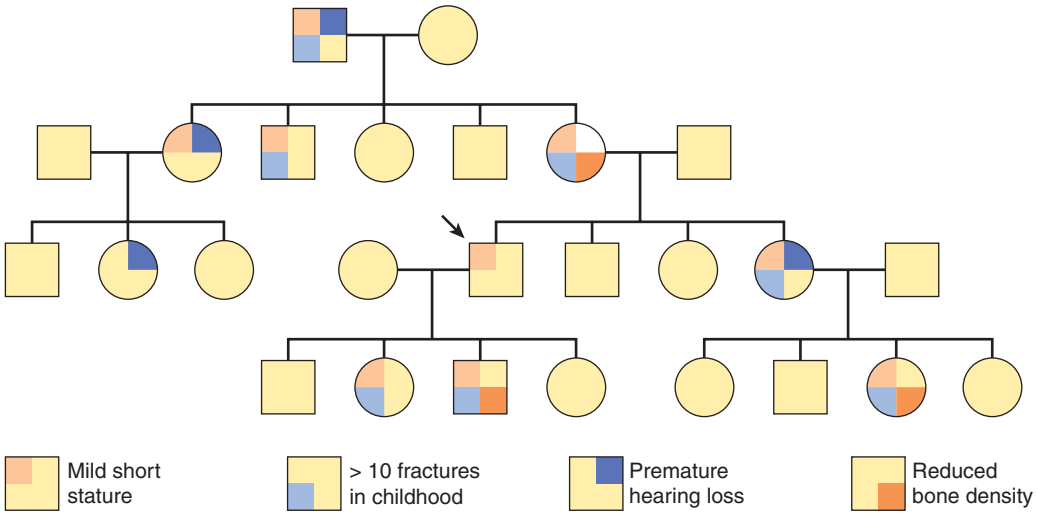

FIGURE 2–1 Penetrance and expressivity in type I osteogenesis imperfecta. In this schematic pedigree of the autosomal dominant condition type I osteogenesis imperfecta, nearly all of the affected individuals exhibit different phenotypic features that vary in severity (variable expressivity). As is shown, type I osteogenesis imperfecta is fully penetrant, because 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.

in both individuals, but its expression is variable. Both reduced penetrance and variable expressivity may occur in individuals who carry the 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—and by their effects on gene activity (ie, no effect [neutral or silent], complete loss of function [amorphic mutation], partial loss of function [hypomorphic mutation], gain of function [hypermorphic mutation], or acquisition of a new property [neomorphic mutation]). 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, 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. 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 a mutant gene causes the disease phenotype (in males and females); X-linked recessive inheritance occurs when two copies of a mutant gene cause the disease phenotype (in females). 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, in X-linked recessive inheritance, one copy of a mutant allele is sufficient to produce a disease phenotype in males, a situation referred to as **hemizygosity**.

RECESSIVE INHERITANCE & LOSS-OF-FUNCTION MUTATIONS

Most recessive mutations are due to loss of function of the gene product, which can occur from a variety of different 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 mutations. First, because expression from the nonmutant allele usually does not change (i.e., there is no **dosage compensation**), gene expression in a heterozygous carrier of a loss-of-function allele is reduced to

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

Disorder	Phenotype	Genetic Mechanism	Incidence
Down 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 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 a 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	Mutation of electron transport chain encoded by mtDNA	≈1:50,000–1:10,000
Myoclonic epilepsy with ragged red fibers	Uncontrolled periodic jerking, muscle weakness	Mutation 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 mutations 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 mutations 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	Mental and growth retardation	Autosomal recessive; caused by multiple loss-of-function mutations in phenylalanine hydroxylase	≈1:10,000

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.

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 produces a dominantly inherited phenotype. Such mutations 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 mutant allele is affected more severely than someone who carries 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; thus, achondroplasia exhibits semidominant inheritance. Huntington disease, a dominantly inherited neurologic disease, is the only known human condition in which the homozygous mutant phenotype is identical to the heterozygous mutant 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 mutant 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 mutations) can result in a dominant negative allele. Type II osteogenesis imperfecta, described later, is an example of a dominant negative mutation.

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

MUTATION RATE & THE PREVALENCE OF GENETIC DISEASE

At the level of DNA sequence, nucleotide mutations (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 mutations per diploid genome. However, only about 5% of the human genome is functional, so most new mutations 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 mutation 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 5000 single-gene disorders have been recognized to cause a human disease. In considering possible explanations for this disparity, it seems likely that deleterious mutations of many single genes are lethal very early in development and thus not clinically apparent, whereas deleterious mutations 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, 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 intellectual and pathophysiologic interest, are not likely to be seen by most practitioners.

Many common conditions such as atherosclerosis and breast cancer that do not show strictly mendelian inheritance patterns have a 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, mutation, heterozygosity, hemizygosity, polymorphism, and phenotype.
2. How is it possible for two individuals with the same mutation to have differences in the severity of an abnormal phenotype?
3. Explain the pathophysiologic difference between mutations 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 fragility of bone. Advances in the last two decades demonstrate two genetically different groups: the "classical" group, in which more than 90% of cases are caused by a mutation 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 mutations in proteins required for proper folding, processing, and secretion of collagen. More than 100 different mutant 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 mutations 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.

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 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 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 one fourth of the cases of type I or type IV osteogenesis imperfecta represent new mutations; in the remainder, the history and examination of other family members reveal findings consistent with autosomal dominant inheritance.

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 mutation 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 mutation in proα1(I) or proα2(I) chain that has mild effect on heterotrimer assembly; quality of collagen is severely abnormal; quantity often reduced also
Type III	**Progressive deforming:** Prenatal fractures, deformities usually present at birth, very short stature, usually nonambulatory, blue scleras, hearing loss	Autosomal dominant[1]	Structural mutation 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 imperfect	Autosomal dominant	Structural mutation 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.

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 mutation, 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 mutations 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 10 additional genes in which mutations can cause autosomal recessive osteogenesis imperfecta and has provided additional insight into the genetic pathophysiology. In general, recessively inherited osteogenesis imperfect is caused by loss-of-function mutations in genes whose protein product is required for proper protein folding, intracellular processing, and trafficking of type I collagen.

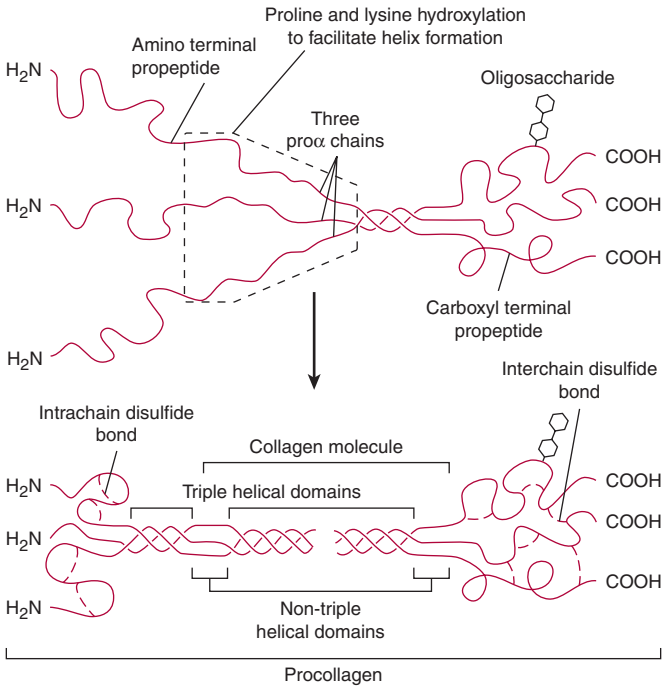

FIGURE 2–2 Molecular assembly of type I pro-collagen. Type I procollagen is assembled in the endoplasmic reticulum from three proα chains that associate with each other beginning at their carboxyl terminals. An important requirement for proper assembly of the triple helix is the presence of a glycine 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*, 3rd ed. Garland Science, 1994.)

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.

The fundamental defect in most individuals with type I osteogenesis imperfecta is reduced synthesis of type I collagen

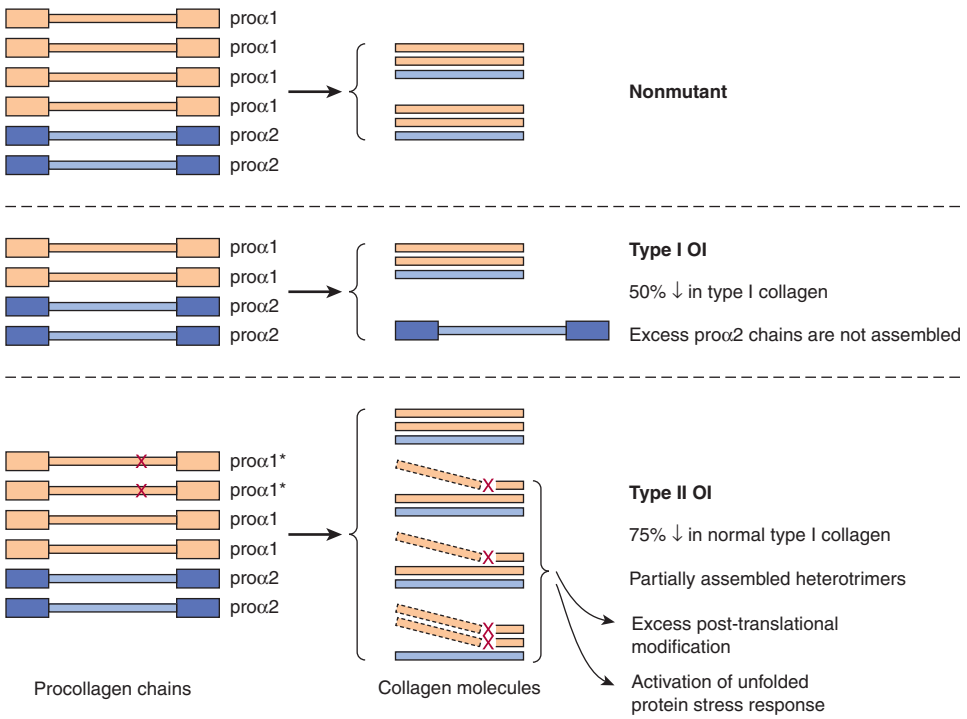

FIGURE 2–3 Molecular pathogenesis of type I and type II osteogenesis imperfecta (OI). The *COL1A1* gene normally produces twice as many proα chains as the *COL1A2* gene. Therefore, in nonmutant cells, the ratio of proα1 to proα2 chains is 2:1, which corresponds to the ratio of α1 and α2 chains in intact collagen molecules. In type I osteogenesis imperfecta, a mutation (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 mutation 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 mutant chain. (Adapted from Thompson MW et al. *Genetics in Medicine,* 5th ed. Saunders, 1991.)

resulting from loss-of-function mutations in *COL1A1*. In most cases, the mutant *COL1A1* allele gives rise to greatly reduced (partial loss-of-function) or no (complete loss-of-function) mRNA. Because the nonmutant *COL1A1* allele continues to produce mRNA at a normal rate (ie, there is no dosage compensation), heterozygosity for a complete loss-of-function mutation results in a 50% reduction in the total rate of proα1(I) mRNA synthesis, whereas heterozygosity for a partial loss-of-function mutation 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).

There are several potential molecular defects responsible for *COL1A1* mutations 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. Mutations 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 mutant peptide chain to bind to normal chains in the initial steps of trimer assembly (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 mutations 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, 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 imperfect 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 mutations in *COL1A1*. However, in approximately one-third of affected individuals, the disease is caused by a new mutation; in addition, there are many ways in which DNA sequence alterations can reduce gene expression. Consequently, there is a wide range of mutant alleles (ie, **allelic heterogeneity**), which represents a challenge for the development of molecular diagnostic tests. In a family in which type I osteogenesis imperfecta is known to occur clinically and a proband seeks a diagnostic test for the purposes of reproductive planning, it is possible in most cases to use linkage analysis at the *COL1A1* locus. In this approach, one distinguishes between chromosomes that carry the mutant and nonmutant *COL1A1* alleles using closely linked DNA-based polymorphisms, even though the causative molecular defect is not known. Once this information is established for a particular family, inheritance of the mutant allele can be predicted in future pregnancies.

For types III and IV osteogenesis imperfecta, mutations 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 mutant genes and different mutant 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 mutant 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 mutant allele among his or her 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 mutations, 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.

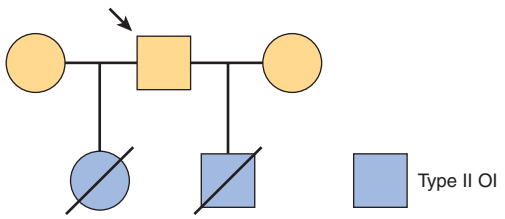

FIGURE 2–4 Gonadal mosaicism for type II osteogenesis imperfecta. In this idealized pedigree, the phenotypically normal father (indicated with the arrow) has had two children by different mates, each of whom is affected with autosomal dominant type II osteogenesis imperfecta (OI). Analysis of the father showed that some of his spermatozoa carried a *COL1A1* mutation, 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.)