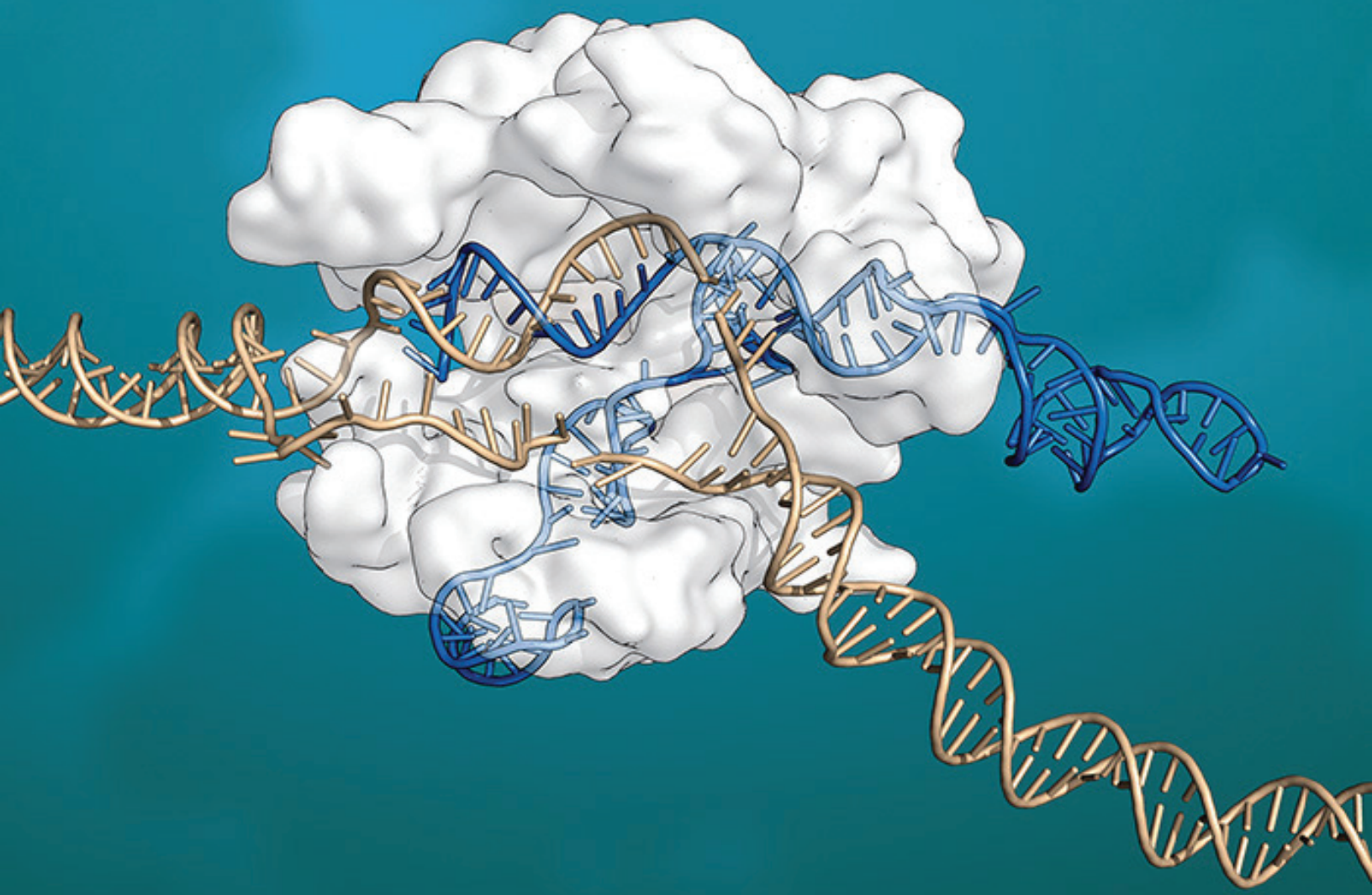
CONCEPTS OF GENETICS

TWELFTH EDITION



Klug | Cummings | Spencer
Palladino | Killian

Brief Contents

Nobel Prizes Awarded for Research in Genetics or Genetics-Related Areas

Year	Recipients	Nobel Prize	Discovery/Research Topic
2017	J. C. Hall M. Rosbash M. W. Young	Physiology or Medicine	Identification of the genes and molecular mechanisms that regulate circadian rhythms
2015	T. Lindahl P. Modrich A. Sancar	Chemistry	Mechanistic studies of DNA repair
2012	J. B. Gurdon S. Yamanaka	Physiology or Medicine	Differentiated cells can be reprogrammed to become pluripotent
2009	V. Ramakrishnan T. A. Steitz A. E. Yonath	Chemistry	Structure and function of the ribosome
2009	E. H. Blackburn C. W. Greider J. W. Szostak	Physiology or Medicine	The nature and replication of the DNA of telomeres, and the discovery of the telomere-replenishing ribonucleoprotein enzyme telomerase
2008	O. Shimomura M. Chalfie R. Y. Tsien	Chemistry	Discovery and development of a genetically encoded fluorescent protein as an *in vivo* marker of gene expression
2007	M. R. Capecchi M. J. Evans O. Smithies	Physiology or Medicine	Gene-targeting technology essential to the creation of knockout mice serving as animal models of human disease
2006	R. D. Kornberg	Chemistry	Molecular basis of eukaryotic transcription
2006	A. Z. Fire C. C. Mello	Physiology or Medicine	Gene silencing using RNA interference (RNAi)
2004	A. Ciechanover A. Hershko I. Rose	Chemistry	Regulation of protein degradation by the proteasome
2002	S. Brenner H. R. Horvitz J. E. Sulston	Physiology or Medicine	Genetic regulation of organ development and programmed cell death (apoptosis)
2001	L. H. Hartwell T. Hunt P. M. Nurse	Physiology or Medicine	Genes and regulatory molecules controlling the cell cycle
1999	G. Blobel	Physiology or Medicine	Genetically encoded amino acid sequences in proteins that guide their cellular transport
1997	S. B. Prusiner	Physiology or Medicine	Prions—a new biological principle of infection
1995	E. B. Lewis C. Nüsslein-Volhard E. Wieschaus	Physiology or Medicine	Genetic control of early development in *Drosophila*
1993	R. J. Roberts P. A. Sharp	Physiology or Medicine	RNA processing of split genes
	K. B. Mullis M. Smith	Chemistry	Development of polymerase chain reaction (PCR) and site-directed mutagenesis (SDM)
1989	J. M. Bishop H. E. Varmus	Physiology or Medicine	Role of retroviruses and oncogenes in cancer
	T. R. Cech S. Altman	Chemistry	Ribozyme function during RNA splicing
1987	S. Tonegawa	Physiology or Medicine	Genetic basis of antibody diversity

Year	Recipients	Nobel Prize	Discovery/Research Topic
1985	M. S. Brown J. L. Goldstein	Physiology or Medicine	Genetic regulation of cholesterol metabolism
1983	B. McClintock	Physiology or Medicine	Mobile genetic elements in maize
1982	A. Klug	Chemistry	Crystalline structure analysis of significant complexes, including tRNA and nucleosomes
1980	P. Berg W. Gilbert F. Sanger	Chemistry	Development of recombinant DNA and DNA sequencing technology
1978	W. Arber D. Nathans H. O. Smith	Physiology or Medicine	Recombinant DNA technology using restriction endonuclease technology
1976	B. S. Blumberg D. C. Gajdusek	Physiology or Medicine	Elucidation of the human prion-based diseases, kuru and Creutzfeldt-Jakob disease
1975	D. Baltimore R. Dulbecco H. M. Temin	Physiology or Medicine	Molecular genetics of tumor viruses
1972	G. M. Edelman R. R. Porter	Physiology or Medicine	Chemical structure of immunoglobulins
	C. B. Anfinsen	Chemistry	Relationship between primary and tertiary structure of proteins
1970	N. Borlaug	Peace Prize	Genetic improvement of Mexican wheat
1969	M. Delbrück A. D. Hershey S. E. Luria	Physiology or Medicine	Replication mechanisms and genetic structure of bacteriophages
1968	H. G. Khorana M. W. Nirenberg R. W. Holley	Physiology or Medicine	For their interpretation of the genetic code and its function during protein synthesis
1966	P. F. Rous	Physiology or Medicine	Viral induction of cancer in chickens
1965	F. Jacob A. M. Lwoff J. L. Monod	Physiology or Medicine	Genetic regulation of enzyme synthesis in bacteria
1962	F. H. C. Crick J. D. Watson M. H. F. Wilkins	Physiology or Medicine	Double helical model of DNA
	J. C. Kendrew M. F. Perutz	Chemistry	Three-dimensional structure of globular proteins
1959	A. Kornberg S. Ochoa	Physiology or Medicine	Biological synthesis of DNA and RNA
1958	G. W. Beadle E. L. Tatum	Physiology or Medicine	Genetic control of biochemical processes
	J. Lederberg	Physiology or Medicine	Genetic recombination in bacteria
	F. Sanger	Chemistry	Primary structure of proteins
1954	L. C. Pauling	Chemistry	Alpha helical structure of proteins
1946	H. J. Müller	Physiology or Medicine	X-ray induction of mutations in *Drosophila*
1933	T. H. Morgan	Physiology or Medicine	Chromosomal theory of inheritance
1930	K. Landsteiner	Physiology or Medicine	Discovery of human blood groups

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TWELFTH EDITION

William S. Klug
THE COLLEGE OF NEW JERSEY

Michael R. Cummings
ILLINOIS INSTITUTE OF TECHNOLOGY

Charlotte A. Spencer
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Library of Congress Cataloging-in-Publication Data
Names: Klug, William S., author. | Cummings, Michael R., author. | Spencer,
Charlotte A., author. | Palladino, Michael A., author. | Killian, Darrell J., author.
Title: Concepts of genetics / William S. Klug (The College of New Jersey),
Michael R. Cummings (Illinois Institute of Technology), Charlotte A. Spencer, Michael A. Palladino (Monmouth University), Darrell J. Killian (Colorado College).
Description: Twelfth edition. | Hoboken, New Jersey : Pearson Education, Inc., 2018. | Includes index.
Identifiers: LCCN 2017047484 | ISBN 9780134604718
Subjects: LCSH: Genetics—Textbooks.
Classification: LCC QH430 .K574 2018 | DDC 572.8—dc23
LC record available at https://lccn.loc.gov/2017047484

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Photo Researcher: Eric Schrader
Manufacturing Buyer: Stacey J. Weinberger

Cover Illustration: H. Adam Steinberg, artforscience.com

ISBN 10: 0-134-60471-7; ISBN 13: 978-0-134-60471-8 (Student edition)
ISBN 10: 0-134-81892-X; ISBN 13: 978-0-134-81892-4 (Books à la Carte edition)
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About the Authors

William S. Klug is an Emeritus Professor of Biology at The College of New Jersey (formerly Trenton State College) in Ewing, New Jersey, where he served as Chair of the Biology Department for 17 years. He received his B.A. degree in Biology from Wabash College in Crawfordsville, Indiana, and his Ph.D. from Northwestern University in Evanston, Illinois. Prior to coming to The College of New Jersey, he was on the faculty of Wabash College, where he first taught genetics, as well as general biology and electron microscopy. His research interests have involved ultrastructural and molecular genetic studies of development, utilizing oogenesis in *Drosophila* as a model system. He has taught the genetics course as well as the senior capstone seminar course in Human and Molecular Genetics to undergraduate biology majors for over four decades. He was the recipient in 2001 of the first annual teaching award given at The College of New Jersey, granted to the faculty member who "most challenges students to achieve high standards." He also received the 2004 Outstanding Professor Award from Sigma Pi International, and in the same year, he was nominated as the Educator of the Year, an award given by the Research and Development Council of New Jersey. When not revising one of his textbooks, immersed in the literature of genetics, or trying to avoid double bogies, Dr. Klug can sometimes be found paddling in the Gulf of Mexico or in Maine's Penobscot Bay.

Michael R. Cummings is a Research Professor in the Department of Biological, Chemical, and Physical Sciences at Illinois Institute of Technology, Chicago, Illinois. For more than 25 years, he was a faculty member in the Department of Biological Sciences and in the Department of Molecular Genetics at the University of Illinois at Chicago. He has also served on the faculties of Northwestern University and Florida State University. He received his B.A. from St. Mary's College in Winona, Minnesota, and his M.S. and Ph.D. from Northwestern University in Evanston, Illinois. In addition to this text, he has written textbooks in human genetics and general biology. His research interests center on the molecular organization and physical mapping of the heterochromatic regions of human acrocentric chromosomes. At the undergraduate level, he teaches courses in molecular genetics, human genetics, and general biology, and has received numerous awards for teaching excellence given by university faculty, student organizations, and graduating seniors. When not teaching or writing, Dr. Cummings can often be found far offshore fishing for the one that got away.

Charlotte A. Spencer is a retired Associate Professor from the Department of Oncology at the University of Alberta in Edmonton, Alberta, Canada. She has also served as a faculty member in the Department of Biochemistry at the University of Alberta. She received her B.Sc. in Microbiology from the University of British Columbia and her Ph.D. in Genetics from the University of Alberta, followed by postdoctoral training at the Fred Hutchinson Cancer Research Center in Seattle, Washington. Her research interests involve the regulation of RNA polymerase II transcription in cancer cells, cells infected with DNA viruses, and cells traversing the mitotic phase of the cell cycle. She has taught undergraduate and graduate courses in biochemistry, genetics, molecular biology, and oncology. She has also written booklets in the Prentice Hall Exploring Biology series. When not writing and editing contributions to genetics textbooks, Dr. Spencer works on her hazelnut farm and enjoys the peace and quiet of a remote Island off the west coast of British Columbia.

Michael A. Palladino is Vice Provost for Graduate Studies, former Dean of the School of Science, and Professor of Biology at Monmouth University in West Long Branch, New Jersey. He received his B.S. degree in Biology from The College of New Jersey and his Ph.D. in Anatomy and Cell Biology from the University of Virginia. For more than 15 years he directed a laboratory of undergraduate student researchers supported by external funding from the National Institutes of Health, biopharma companies, and other agencies. He and his undergraduates studied molecular mechanisms involved in innate immunity of mammalian male reproductive organs and genes involved in oxygen homeostasis and ischemic injury of the testis. He has taught a wide range of courses including genetics, biotechnology, endocrinology, and cell and molecular biology. He has received several awards for research and teaching, including the 2009 Young Andrologist Award of the American Society of Andrology, the 2005 Distinguished Teacher Award from Monmouth University, and the 2005 Caring Heart Award from the New Jersey Association for Biomedical Research. He is co-author of the undergraduate textbook *Introduction to Biotechnology*. He was Series Editor for the Benjamin Cummings *Special Topics in Biology* booklet series, and author of the first booklet in the series, *Understanding the Human Genome Project.* When away from the university or authoring textbooks, Dr. Palladino can often be found watching or playing soccer or attempting to catch most any species of fish in freshwater or saltwater.

Darrell J. Killian is an Associate Professor and current Chair of the Department of Molecular Biology at Colorado College in Colorado Springs, Colorado. He received his B.A. degree in Molecular Biology and Biochemistry from Wesleyan University in Middletown, Connecticut, prior to working as a Research Technician in Molecular Genetics at Rockefeller University in New York, New York. He earned his Ph.D. in Developmental Genetics from New York University in New York, New York, and received his postdoctoral training at the University of Colorado—Boulder in the Department of Molecular, Cellular, and Developmental Biology. Prior to joining Colorado College, he was an Assistant Professor of Biology at the College of New Jersey in Ewing, New Jersey. His research focuses on the genetic regulation of animal development, and he has received funding from the National Institutes of Health and the National Science Foundation. Currently, he and his undergraduate research assistants are investigating the molecular genetic regulation of nervous system development using *C. elegans* and *Drosophila* as model systems. He teaches undergraduate courses in genetics, molecular and cellular biology, stem cell biology, and developmental neurobiology. When away from the classroom and research lab, Dr. Killian can often be found on two wheels exploring trails in the Pike and San Isabel National Forests.

Dedication

We dedicate this edition to our long-time colleague and friend Harry Nickla, who sadly passed away in 2017. With decades of experience teaching Genetics to students at Creighton University, Harry's contribution to our texts included authorship of the *Student Handbook and Solutions Manual* and the test bank, as well as devising most of the Extra Spicy problems at the end of each chapter. He was also a source of advice during the planning session for each new edition, and during our many revisions. We always appreciated his professional insights, friendship, and conviviality. We were lucky to have him as part of our team, and we miss him greatly.

WSK, MRC, CAS, MAP, and DJK

Brief Contents

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Explore Cutting-Edge Topics

Concepts of Genetics **emphasizes the fundamental ideas of genetics, while exploring modern techniques and applications of genetic analysis. This best-selling text continues to provide understandable explanations of complex, analytical topics and recognizes the importance of teaching students how to become effective problem solvers.**

Six **Special Topics in Modern Genetics** mini-chapters concisely explore cutting-edge, engaging, and relevant topics.

- **NEW!** CRISPR-Cas and Genome Editing
- DNA Forensics
- Genomics and Precision Medicine
- Genetically Modified Foods
- Gene Therapy
- **NEW!** Advances in Neurogenetics: The Study of Huntington Disease

Special Topic chapters include Review and Discussion questions, which are also assignable in Mastering Genetics.

CRISPR-Cas and Genome Editing

Genetic research is often a slow incremental process that may extend our understanding of a concept or improve the efficiency of a genetic technology. More rarely, discoveries advance the field in sudden and profound ways. For example, studies in the early 1980s led to the discovery of catalytic RNAs, which transformed how geneticists think about RNA. Around the same time, the development of the polymerase chain reaction (PCR) provided a revolutionary tool for geneticists and other scientists. Rapid and targeted DNA amplification is now indispensable to genetic research and medical science. Given this context, one can appreciate how rare and significant a discovery would be that both illuminates a novel genetic concept as well as yields a new technology for genetics research and application. CRISPR-Cas is exactly that.

For over a century, scientists have studied the biological warfare between bacteria and the viruses that infect them. However, in 2007, experiments confirmed that bacteria have a completely novel defense mechanism against viruses known as CRISPR-Cas. This discovery completely changed the scope of our understanding of how bacteria and viruses combat one another, and coevolve. Moreover, the CRISPR-Cas system has now been adapted as an incredibly powerful tool for genome editing.

The ability to specifically and efficiently edit a genome has broad implications for research, biotechnology, and medicine. For decades, geneticists have used various strategies for genome editing with many successes, but also with limited efficiency and a significant investment of time and resources. CRISPR-Cas has been developed into an efficient, cost-effective molecular tool that can introduce precise and specific edits to a genome. It is not without its limitations, but it represents a technological leap, which we have not seen, arguably, since the innovation of PCR.

"CRISPR-Cas has been developed into an efficient, cost-effective molecular tool that can introduce precise and specific edits to a genome."

The discovery of CRISPR-Cas has impacted genetics and other related fields at an unprecedented pace (Figure ST 1.1). CRISPR-Cas is the focus of numerous patent applications and disputes, has been approved for use in clinical trials to treat disease, has been used to edit the genome of human embryos as a proof of concept for future medical applications, has instigated international discussions on its ethical use, and is most deserving of its own chapter in a genetics textbook.

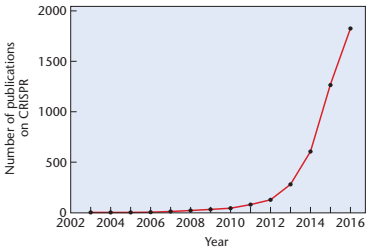

FIGURE ST 1.1 The number of publications returned in a search for "CRISPR" in PubMed by year.

ST 1.1 CRISPR-Cas Is an Adaptive Immune System in Prokaryotes

Bacteria and viruses (bacteriophages or phages) engage in constant biological warfare. Consequently, bacteria exhibit a diverse suite of defense mechanisms. For example, bacteria express endonucleases (restriction enzymes), which cleave specific DNA sequences. Such restriction enzymes destroy foreign bacteriophage DNA, while the bacterium protects its own DNA by methylating it. As you know (from Chapter 20), restriction enzymes have been adopted by molecular biologists for use in recombinant DNA technology. Bacteria can also defend against phage attack by blocking phage adsorption, blocking phage DNA insertion, and inducing suicide in infected cells to prevent the spread of infection to other cells. All of these defense mechanisms are considered **innate immunity** because they are not tailored to a specific pathogen.

Explore the Latest Updates

The 12th edition has been heavily updated throughout, including a reorganization and expansion of coverage of gene regulation in eukaryotes. This expansion reflects our growing knowledge of the critical roles RNA and epigenetics play in regulating gene activity.

NEW! Gene regulation in eukaryotes has been expanded into three chapters: transcriptional regulation (Ch. 17), posttranscriptional regulation (Ch. 18), and epigenetic regulation (Ch. 19).

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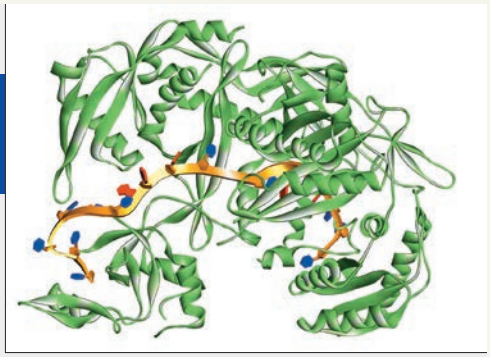

Posttranscriptional Regulation in Eukaryotes

Crystal structure of human Argonaute2 protein interacting with "guide" RNA. Argonaute2 plays an important role in mediating a posttranscriptional RNA-induced silencing pathway.

CHAPTER CONCEPTS

- Following transcription, there are several mechanisms that regulate gene expression, referred to as posttranscriptional regulation.
- Alternative splicing allows for a single gene to encode different protein isoforms with different functions.
- The interaction between *cis*-acting mRNA sequence elements and *trans*-acting RNA-binding proteins regulates mRNA stability, degradation, localization, and translation.
- Noncoding RNAs may regulate gene expression by targeting mRNAs for destruction or translational inhibition.
- Posttranslational modification of proteins can alter their activity or promote their degradation.

and the synthesis of a 3′ poly-A tail. Each of these steps can be regulated to control gene expression. After mature mRNAs are exported to the cytoplasm, they follow different paths: They may be localized to specific regions of the cell; they may be stabilized or degraded; or they may be translated robustly or stored for translation at a later time. Even after translation, protein activity, localization, and stability can be altered through covalent protein modifications. These and other eukaryotic posttranscriptional regulatory mechanisms are summarized in Figure 18.1.

Whereas the regulation of transcription depends on transcription factors and DNA regulatory elements (see Chapter 17), many posttranscriptional mechanisms involve RNA-level regulation. Moreover, posttranscriptional regulation is not only centered *on* RNA, but, in some cases, is regulated *by* RNA. Noncoding RNAs play important roles in the regulation of eukaryotic gene expression.

In this chapter, we will explore several important mechanisms and themes of eukaryotic posttranscriptional regulation. As you read on, keep in mind that while scientists have learned a great deal about how genes are regulated at the posttranscriptional level, there are still many unanswered questions for the curious student to ponder.

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Epigenetic Regulation of Gene Expression

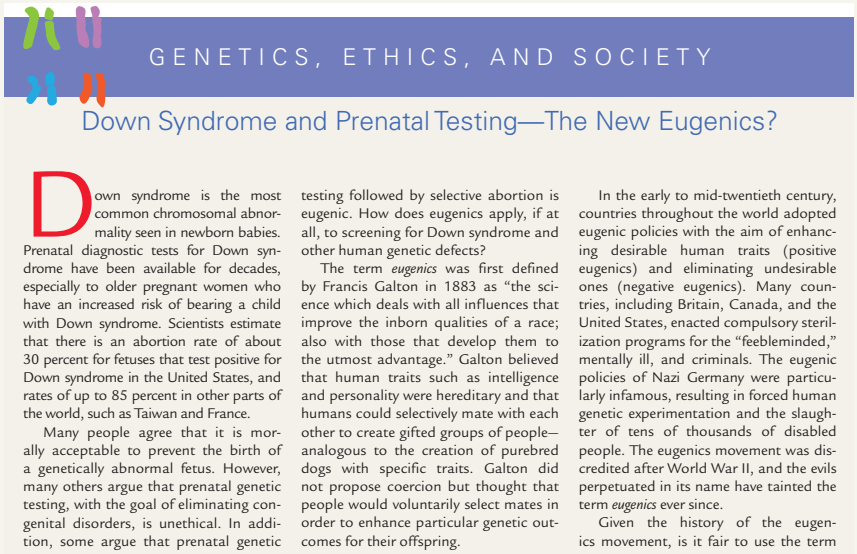
In toadflax, the shape of individual flowers changes from bilateral symmetry (photo on the left) to radial symmetry (photo on the right) in a naturally occurring, heritable gene silencing epimutation associated with the methylation of a single gene. There is no alteration of the DNA sequence at this locus.

CHAPTER CONCEPTS

NEW! A new chapter focuses on epigenetics, updating and expanding coverage that used to be in a Special Topics chapter.

and Ethical Considerations

With the rapid growth of our understanding of genetics and the ongoing introduction of powerful tools that can edit genes and genomes, it's important to encourage students to confront ethical issues and consider questions that arise in the study of genetics.



GENETICS, ETHICS, AND SOCIETY

Down Syndrome and Prenatal Testing—The New Eugenics?

Down syndrome is the most common chromosomal abnormality seen in newborn babies. Prenatal diagnostic tests for Down syndrome have been available for decades, especially to older pregnant women who have an increased risk of bearing a child with Down syndrome. Scientists estimate that there is an abortion rate of about 30 percent for fetuses that test positive for Down syndrome in the United States, and rates of up to 85 percent in other parts of the world, such as Taiwan and France.

Many people agree that it is morally acceptable to prevent the birth of a genetically abnormal fetus. However, many others argue that prenatal genetic testing, with the goal of eliminating congenital disorders, is unethical. In addition, some argue that prenatal genetic testing followed by selective abortion is eugenic. How does eugenics apply, if at all, to screening for Down syndrome and other human genetic defects?

The term *eugenics* was first defined by Francis Galton in 1883 as "the science which deals with all influences that improve the inborn qualities of a race; also with those that develop them to the utmost advantage." Galton believed that human traits such as intelligence and personality were hereditary and that humans could selectively mate with each other to create gifted groups of people—analogous to the creation of purebred dogs with specific traits. Galton did not propose coercion but thought that people would voluntarily select mates in order to enhance particular genetic outcomes for their offspring.

In the early to mid-twentieth century, countries throughout the world adopted eugenic policies with the aim of enhancing desirable human traits (positive eugenics) and eliminating undesirable ones (negative eugenics). Many countries, including Britain, Canada, and the United States, enacted compulsory sterilization programs for the "feebleminded," mentally ill, and criminals. The eugenic policies of Nazi Germany were particularly infamous, resulting in forced human genetic experimentation and the slaughter of tens of thousands of disabled people. The eugenics movement was discredited after World War II, and the evils perpetuated in its name have tainted the term *eugenics* ever since.

Given the history of the eugenics movement, is it fair to use the term

NEW! Genetics, Ethics, and Society essays appear in many chapters. Each one provides a synopsis of an ethical issue, related to chapter content, that impacts society today. Each includes a section called Your Turn, directing students to resources to help them explore the issue and answer questions.

NEW and REVISED! Case Studies conclude each chapter, introducing a short vignette of an everyday genetics-related situation and posing several discussion questions, including one focusing on ethics.

CASE STUDY Fish tales

Controlling the overgrowth of invasive aquatic vegetation is a significant problem in the waterways of most U.S. states. Originally, herbicides and dredging were used for control, but in 1963, diploid Asian carp were introduced in Alabama and Arkansas. Unfortunately, through escapes and illegal introductions, the carp spread rapidly and became serious threats to aquatic ecosystems in 45 states. Beginning in 1983, many states began using triploid, sterile grass carp as an alternative, because of their inability to reproduce, their longevity, and their voracious appetite. On the other hand, this genetically modified exotic species, if not used properly, can reduce or eliminate desirable plants and outcompete native fish, causing more damage than good. The use of one exotic species to control other exotic species has had a problematic history across the globe, generating controversy and criticism. Newer methods for genetic modification of organisms to achieve specific outcomes will certainly become more common in the future and raise several interesting questions.

1. Why would the creation and use of a tetraploid carp species be unacceptable in the above situation?
2. If you were a state official in charge of a particular waterway, what questions would you ask before approving the use of a laboratory-produced, triploid species in this waterway?
3. What ethical responsibilities accompany the ecological and economic risks and benefits of releasing exotic species into the environment? Who pays the costs if ecosystems and food supplies are damaged?

See Seastedt, T. R. (2015). Biological control of invasive plant species: A reassessment for the Anthropocene. *New Phytologist* 205:490–502.

Learn Genetics Concepts and Problem Solving

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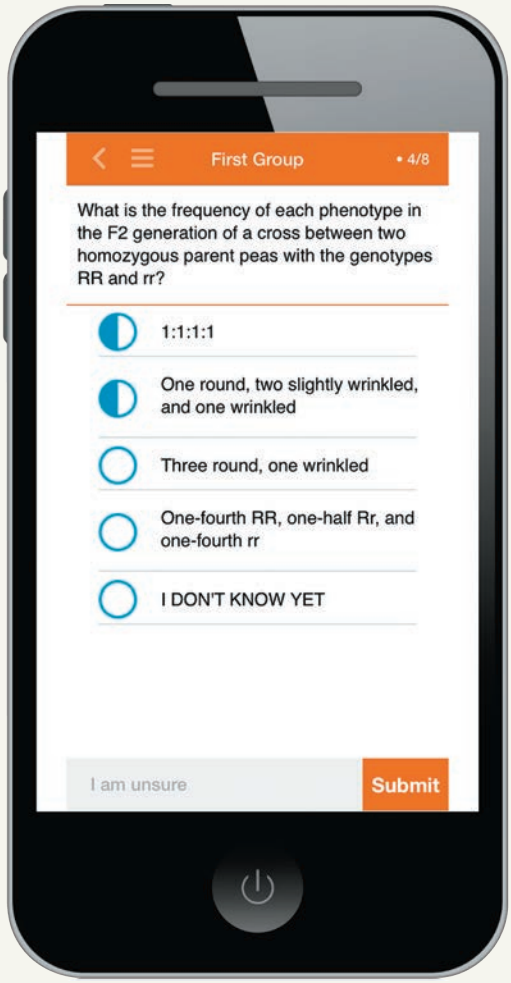

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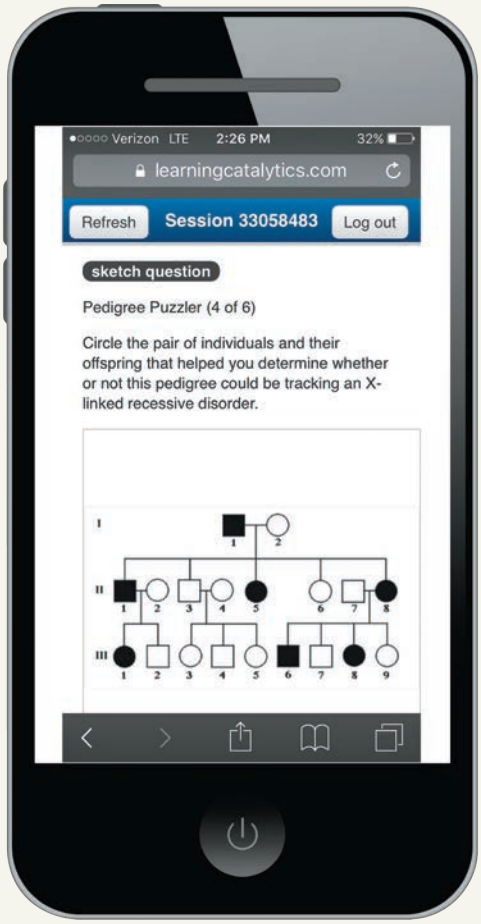
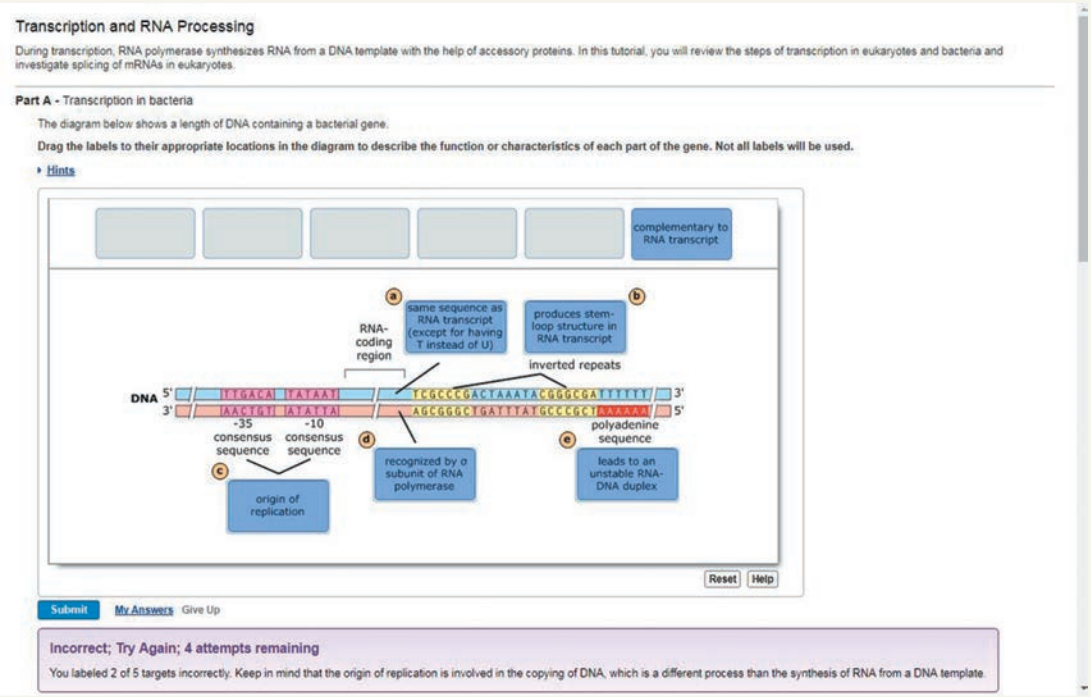


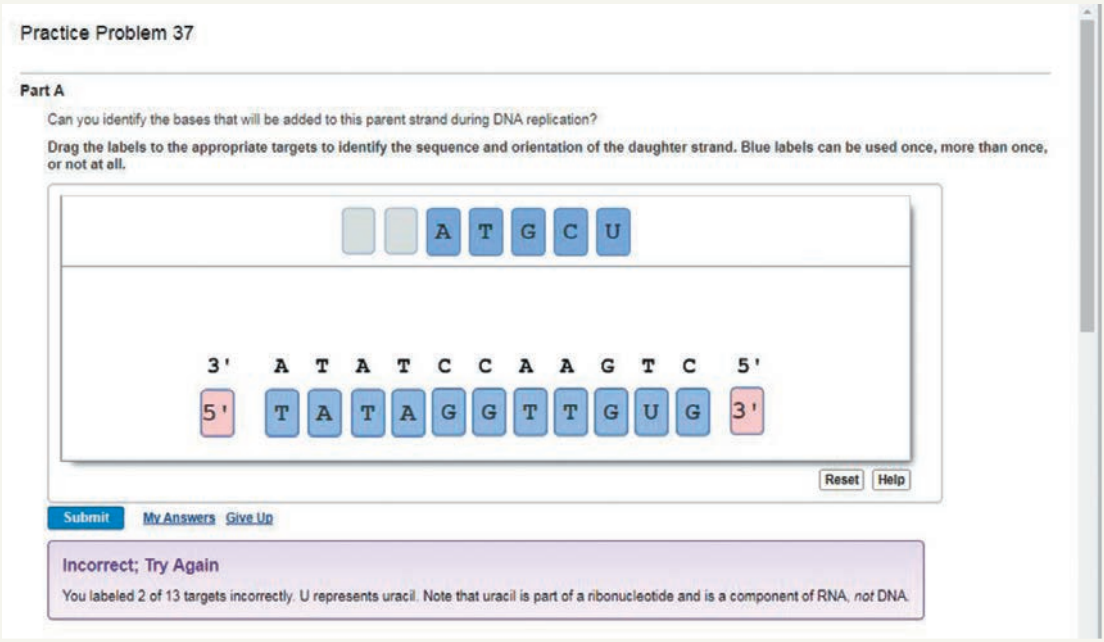
Learning Catalytics is a "bring your own device" (smartphone, tablet, or laptop) assessment and active classroom system that helps engage students. Instructors can create their own questions, draw from community content, or access Pearson's library of question clusters.

with Mastering Genetics



Tutorials and activities feature personalized wrong-answer feedback and hints that emulate the office-hour experience to guide student learning. New tutorials include coverage of topics like CRISPR-Cas.

100 Practice Problems offer more opportunities to develop problem-solving skills. These questions appear only in Mastering Genetics and include targeted wrong-answer feedback to help students learn.



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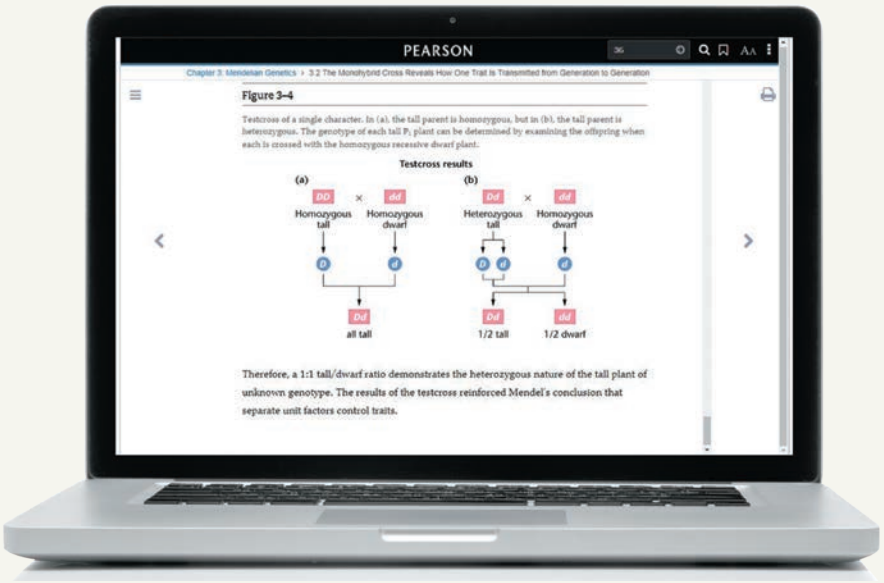

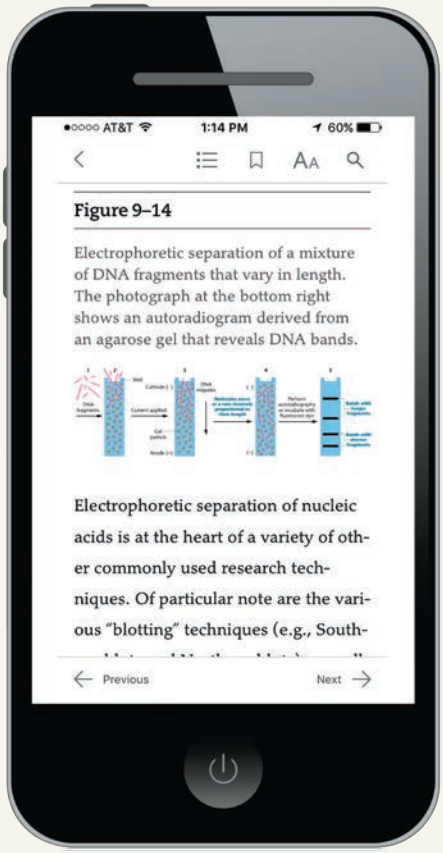

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Preface

It is essential that textbook authors step back and look with fresh eyes as each edition of their work is planned. In doing so, two main questions must be posed: (1) How has the body of information in their field—in this case, Genetics—grown and shifted since the last edition? (2) Which pedagogic innovations that are currently incorporated into the text should be maintained, modified, or deleted? The preparation of the 12th edition of *Concepts of Genetics*, a text well into its fourth decade of providing support for students studying in this field, has occasioned still another fresh look. And what we focused on in this new edition, in addition to the normal updating that is inevitably required, were three things:

1. **The importance of continuing to provide comprehensive coverage of important, emerging topics.**

   In this regard, we continue to include a unique approach in genetics textbooks that offers readers a set of abbreviated, highly focused chapters that we label **Special Topics in Modern Genetics**. In this edition, these provide unique, cohesive coverage of six important topics: *CRISPR-Cas and Genomic Editing*, *DNA Forensics*, *Genomics and Precision Medicine*, *Genetically Modified Foods*, *Gene Therapy*, and *Advances in Neurogenetics: The Study of Huntington Disease*. The initial and final chapters in this series are both new to this edition.

2. **The recognition of the vastly increased knowledge resulting from the study of gene regulation in eukaryotes.**

   To that end, the single chapter on this topic in previous editions has been expanded to three chapters: "Transcriptional Regulation in Eukaryotes" (Chapter 17), "Posttranscriptional Regulation in Eukaryotes" (Chapter 18), and "Epigenetic Regulation of Gene Expression" (Chapter 19). This extended coverage reflects many recent discoveries that reveal that RNA in many forms other than those that are essential to the process of transcription and translation (mRNA, tRNA, and rRNA) play critical roles in the regulation of eukaryotic gene activity. As well, it is now clear based on molecular studies related to epigenetics that this topic is best taught as an integral part of eukaryotic gene regulation. This new material provides the student exposure to modern coverage of a significant research topic.

3. **The importance of providing an increased emphasis on ethical considerations that genetics is bringing into everyday life.**

   Regarding this point, we have converted the essay feature *Genetics, Technology, and Society* to one with added emphasis on ethics and renamed it *Genetics, Ethics, and Society*. Approximately half the chapters have new or revised essays. In addition, the feature called *Case Study*, which appears near the end of all chapters, has been recast with an increased focus on ethics. Both of these features increase the opportunities for active and cooperative learning.

Goals

In the 12th edition of *Concepts of Genetics*, as in all past editions, we have five major overarching goals. Specifically, we have sought to:

- Emphasize the basic concepts of genetics.
- Write clearly and directly to students, providing understandable explanations of complex, analytical topics.
- Maintain our strong emphasis on and provide multiple approaches to problem solving.
- Propagate the rich history of genetics, which so beautifully illustrates how information is acquired during scientific investigation.
- Create inviting, engaging, and pedagogically useful full-color figures enhanced by equally helpful photographs to support concept development.

These goals collectively serve as the cornerstone of *Concepts of Genetics*. This pedagogic foundation allows the book to be used in courses with many different approaches and lecture formats.

Writing a textbook that achieves these goals and having the opportunity to continually improve on each new edition has been a labor of love for all of us. The creation of each of the twelve editions is a reflection not only of our passion for teaching genetics, but also of the constructive feedback and encouragement provided by adopters, reviewers, and our students over the past four decades.

New to This Edition

New to this edition are four chapters. Two are Special Topics in Modern Genetics entries entitled "CRISPR-Cas and Genome Editing" and "Advances in Neurogenetics: The Study of Huntington Disease." Both cover cutting-edge information and represent very recent breakthroughs in genetics. CRISPR, a genome-editing tool, is a straightforward technique that allows specific, highly accurate modification of DNA sequences within genes and is thus a powerful tool in the world of genetic research and gene therapy. In addition to this chapter, we call your attention to the introduction to Chapter 1 for an introduction to CRISPR and to also note that we have chosen this gene-editing system as the subject matter illustrated on the cover. Special Topics Chapter 6 illustrates the many of advances that have been made in the study of human neurogenetics. Huntington disease, a monogenic human disorder, has been subjected to analysis for over 40 years using every major approach and technique developed to study molecular genetics, and as such, exemplifies the growing body of information that has accrued regarding its causes, symptoms, and future treatment.

Additional new chapters arise from a major reorganization and expansion of our coverage of regulation of gene expression in eukaryotes, where we have split our previous coverage into three parts: transcriptional regulation (Chapter 17), posttranscriptional regulation (Chapter 18), and epigenetic regulation (Chapter 19). Chapter 18 includes much of the content previously contained in the Special Topics chapter *Emerging Roles of RNA* in the previous edition. Chapter 19, focused on epigenetics, is an expansion of the content previously contained in the *Epigenetics* Special Topics chapter from the previous edition.

Collectively, the addition of these four new chapters provides students and instructors with a much clearer, up-to-date presentation to these important aspects of genetics.

Continuing Pedagogic Features

We continue to include features that are distinct from, and go beyond, the text coverage, which encourage active and cooperative learning between students and the instructor.

- **Modern Approaches to Understanding Gene Function** This feature highlights how advances in genetic technology have led to our modern understanding of gene function. Appearing in many chapters, this feature prompts students to apply their analytical thinking skills, linking the experimental technology to the findings that enhance our understanding of gene function.
- **Genetics, Ethics, and Society** This feature provides a synopsis of an ethical issue related to a current finding in genetics that impacts directly on society today. It includes a section called *Your Turn*, which directs students to related resources of short readings and Web sites to support deeper investigation and discussion of the main topic of each essay.
- **Case Study** This feature, at the end of each chapter, introduces a short vignette of an everyday genetics-related situation, followed by several discussion questions. Use of the Case Study should prompt students to relate their newly acquired information in genetics to ethical issues that they may encounter away from the course.
- **Evolving Concept of the Gene** This short feature, integrated in appropriate chapters, highlights how scientists' understanding of the gene has changed over time. Since we cannot see genes, we must infer just what this unit of heredity is, based on experimental findings. By highlighting how scientists' conceptualization of the gene has advanced over time, we aim to help students appreciate the process of discovery that has led to an ever more sophisticated understanding of hereditary information.
- **How Do We Know Question** Found as the initial question in the *Problems and Discussion Questions* at the end of each chapter, this feature emphasizes the pedagogic value of studying how information is acquired in science. Students are asked to review numerous findings discussed in the chapter and to summarize the process of discovery that was involved.
- **Concept Question** This feature, found as the second question in the *Problems and Discussion Questions* at the end of each chapter, asks the student to review and comment on common aspects of the Chapter Concepts, listed at the beginning of each chapter. This feature places added emphasis on our pedagogic approach of conceptual learning.
- **Mastering Genetics** This robust online homework and assessment program guides students through complex topics in genetics, using in-depth tutorials that coach students to correct answers with hints and feedback specific to their misconceptions. New content for the 12th edition of *Concepts of Genetics* includes tutorials on emerging topics such as CRISPR-Cas, and Dyanamic Study Modules, interactive flash cards that help students master basic content so they can be more prepared for class and for solving genetics problems.

New and Updated Topics

We have revised each chapter in the text to present the most current, relevant findings in genetics. Here is a list of some of the most significant new and updated topics covered in this edition.

Chapter 1: Introduction to Genetics
- New introductory vignette that discusses the discovery and applications of the genome-editing CRISPR-Cas system
- Updated section "We Live in the Age of Genetics"

Chapter 7: Sex Determination and Sex Chromosomes
- Updated content on the XIST gene product as a long noncoding RNA
- New insights about a novel gene involved in temperature-sensitive differentiation of snapping turtles and lizards, as well as the impact of climate change on sex, sex reversal, and sex ratios

Chapter 9: Extranuclear Inheritance
- Updated information on mtDNA disorders and nuclear DNA mismatches

Chapter 11: DNA Replication and Recombination
- New coverage of the role of telomeres in disease, aging, and cancer
- New and expanded coverage of telomeres and chromosome stability, explaining how telomeres protect chromosome ends

Chapter 13: The Genetic Code and Transcription
- New coverage on transcription termination in bacteria
- New section entitled "Why Do Introns Exist?"
- Updated coverage on RNA editing

Chapter 14: Translation and Proteins
- New coverage of eukaryotic closed-loop translation, including a new figure
- Revised coverage of Beadle and Tatum's classic experiments
- Expanded coverage on the posttranslational modifications of proteins
- New coverage of the insights gleaned from the crystal structure of the human 80*S* ribosome

Chapter 15: Gene Mutation, DNA Repair, and Transposons
- New and revised coverage on transposons, focusing on the mechanisms of transposition by both retrotransposons and DNA transposons, as well as a discussion of how transposition creates mutations. Two new tables and five new figures are included
- Reorganization of the mutation classification section with table summaries
- New and expanded coverage of human germ-line and somatic mutation rates

Chapter 17: Transcriptional Regulation in Eukaryotes
- Revised chapter organization focuses specifically on transcriptional regulation
- Revised coverage of regulation of the *GAL* gene system in yeast with an updated figure
- New coverage on genetic boundary elements called insulators

Chapter 18: Posttranscriptional Regulation in Eukaryotes
- New chapter that greatly expands upon the previous coverage of posttranscriptional gene regulation in eukaryotes
- Revised and expanded coverage of alternative splicing and its relevance to human disease
- Expanded coverage on RNA stability and decay with a new figure
- Updated coverage of noncoding RNAs that regulate gene expression with a new figure
- Enriched coverage of ubiquitin-mediated protein degradation with a new figure

Chapter 19: Epigenetic Regulation of Gene Expression
- New chapter emphasizing the role of epigenetics in regulating gene expression, including coverage of cancer, transmission of epigenetic traits across generations, and epigenetics and behavior
- New coverage on the recently discovered phenomenon of monoallelic expression of autosomal genes
- Updated coverage of epigenome projects

Chapter 20: Recombinant DNA Technology
- Increased emphasis on the importance of whole-genome sequencing approaches
- New coverage of CRISPR-Cas as a gene editing approach, including a new figure
- Updated content on next-generation and third-generation sequencing

Chapter 21: Genomic Analysis
- Increased emphasis on the integration of genomic, bioinformatic, and proteomic approaches to analyzing genomes and understanding genome function

- A new section entitled "Genomic Analysis Before Modern Sequencing Methods," which briefly summarizes approaches to mapping and identifying genes prior to modern sequencing
- Reorganized and revised content on the Human Genome Project. Updated content on personal genome projects and new content on diploid genomes and mosaicism and the pangenome to emphasize human genetic variations
- New coverage of the Human Microbiome Project including a new figure displaying microbiome results of patients with different human disease conditions
- New coverage of *in situ* RNA sequencing

Chapter 22: Applications of Genetic Engineering and Biotechnology

- Updated content on biopharmaceutical products including newly approved recombinant proteins, DNA vaccine trials to immunize against Zika virus, genetically modified organisms, and gene drive in mosquitos to control the spread of Zika
- New coverage of genes essential for life and how synthetic genomics is being applied to elucidate them. Clarification of prognostic and diagnostic genetics tests and the relative value of each for genetic analysis
- New content on DNA and RNA sequencing
- New section entitled "Screening the Genome for Genes or Mutations You Want," which discusses how scientists can look at genetic variation that confers beneficial phenotypes
- New section entitled "Genetic Analysis by Personal Genomics Can Include Sequencing of DNA and RNA" that expands coverage of personal genome projects and new approaches for single-cell genetic analysis of DNA and RNA

Chapter 23: Developmental Genetics

- New section entitled "Epigenetic Regulation of Development"
- New coverage of DNA methylation and progressive restriction of developmental potential
- Expanded coverage of binary switch genes and regulatory networks

Chapter 24: Cancer Genetics

- Extended coverage of environmental agents that contribute to human cancers, including more information about both natural and human-made carcinogens
- New section entitled "Tobacco Smoke and Cancer" explaining how a well-studied carcinogen induces a wide range of genetic effects that may lead to mutations and cancer
- New section entitled "Cancer Therapies and Cancer Cell Biology," describing the mechanisms of chemotherapies and radiotherapies as they relate to cancer cell proliferation, DNA repair, and apoptosis

Chapter 25: Quantitative Genetics and Multifactorial Traits

- Updated coverage on quantitative trait loci (QTLs)
- Revised and expanded section entitled "eQTLs and Gene Expression"

Chapter 26: Population and Evolutionary Genetics

- New coverage on vertebrate evolution
- New coverage of phylogenetic trees
- Updated coverage on the origins of the human genome
- New section entitled "Genotype and Allele Frequency Changes"
- New coverage on pre- and post-zygotic isolating mechanisms

Special Topic Chapter 1: CRISPR-Cas and Genome Editing

- New chapter on a powerful genome editing tool called CRISPR-Cas
- Up-to-date coverage on CRISPR-Cas applications, the patenting of this technology, and the ethical concerns of human genome editing

Special Topic Chapter 2: DNA Forensics

- New section on the still controversial DNA phenotyping method, including new explanations of how law-enforcement agencies currently use this technology

Special Topic Chapter 3: Genomics and Precision Medicine

- New section entitled "Precision Oncology," including descriptions of two targeted cancer immunotherapies: adoptive cell transfer and engineered T-cell therapies
- Updated pharmacogenomics coverage, including a description of new trends in preemptive gene screening for pharmacogenomic variants as well as the pGEN4Kids program, a preemptive gene screening program that integrates DNA analysis data into patient electronic health records

Special Topic Chapter 4: Genetically Modified (GM) Foods

- New section entitled "Gene Editing and GM Foods" describing how scientists are using the new techniques of gene editing (including ZFN, TALENS, and CRISPR-Cas) to create GM food plants and animals,

and how these methods are changing the way in which GM foods are being regulated
- A new box entitled "The New CRISPR Mushroom" describing the development and regulatory approval of the first CRISPR-created GM food to be approved for human consumption

Special Topic Chapter 5: Gene Therapy
- Updated coverage of gene therapy trials currently underway
- Reordered chapter content to highlight emergence of CRISPR-Cas in a new section entitled "Gene Editing"
- Substantially expanded content on CRISPR-Cas including a brief summary of some of the most promising trials in humans and animals to date
- Incorporation of antisense RNA and RNA interference into a new section entitled "RNA-based Therapeutics," including updated trials involving spinal muscular atrophy
- Updated content on roles for stem cells in gene therapy
- New content on combining gene editing with immunotherapy
- New ethical discussions on CRISPR-Cas and germline and embryo editing

Special Topic Chapter 6: Advances in Neurogenetics: The Study of Huntington Disease (HD)
- New chapter that surveys the study of HD commencing around 1970 up to the current time
- Coverage of the genetic basis and expression of HD, the mapping and isolation of the gene responsible for the disorder, the mutant gene product, molecular and cellular alterations caused by the mutation, transgenic animal models of HD, cellular and molecular approaches to therapy, and a comparison of HD to other inherited neurodegenerative disorders

Strengths of This Edition

- **Organization** —We have continued to attend to the organization of material by arranging chapters within major sections to reflect changing trends in genetics. Of particular note is the expansion of our coverage of the regulation of gene expression in eukaryotes, now reorganized into three chapters at the end of Part Three. Additionally, Part Four continues to provide organized coverage of genomics into three carefully integrated chapters.
- **Active Learning** —A continuing goal of this book is to provide features within each chapter that small groups of students can use either in the classroom or as assignments outside of class. Pedagogic research continues to support the value and effectiveness of such active and cooperative learning experiences. To this end, there are four features that greatly strengthen this edition: *Case Study*; *Genetics, Ethics, and Society*; *Exploring Genomics*; and *Modern Approaches to Understanding Gene Function*. Whether instructors use these activities as active learning in the classroom or as assigned interactions outside of the classroom, the above features will stimulate the use of current pedagogic approaches during student' learning. The activities help engage students, and the content of each feature ensures that they will become knowledgeable about cutting-edge topics in genetics.

Emphasis on Concepts

The title of our textbook—*Concepts of Genetics*—was purposefully chosen, reflecting our fundamental pedagogic approach to teaching and writing about genetics. However, the word "concept" is not as easy to define as one might think. Most simply put, we consider a concept to be *a cognitive unit of meaning—an abstract representation that encompasses a related set of scientifically derived findings and ideas*. Thus, a concept provides a broad mental image that, for example, might reflect a straightforward snapshot in your mind's eye of what constitutes a chromosome; a dynamic vision of the detailed processes of replication, transcription, and translation of genetic information; or just an abstract perception of varying modes of inheritance.

We think that creating such mental imagery is the very best way to teach science, in this case, genetics. Details that might be memorized, but soon forgotten, are instead subsumed within a conceptual framework that is easily retained and nearly impossible to forget. Such a framework may be expanded in content as new information is acquired and may interface with other concepts, providing a useful mechanism to integrate and better understand related processes and ideas. An extensive set of concepts may be devised and conveyed to eventually encompass and represent an entire discipline—and this is our goal in this genetics textbook.

To aid students in identifying the conceptual aspects of a major topic, each chapter begins with a section called *Chapter Concepts*, which identifies the most important topics about to be presented. Each chapter ends with a section called *Summary Points*, which enumerates the five to ten key points that have been discussed. And in the *How Do We Know*? question that starts each chapter's problem set, students are asked to connect concepts to experimental findings. This question is then followed by a *Concept Question*, which asks the student to review and comment on common aspects of the Chapter Concepts. Collectively, these features help to ensure that students engage in, become aware of, and understand the major conceptual issues as they confront the extensive vocabulary and the many important details of genetics. Carefully designed figures also support our conceptual approach throughout the book.

Emphasis on Problem Solving

As authors and teachers, we have always recognized the importance of enhancing students' problem-solving skills. Students need guidance and practice if they are to develop into strong analytical thinkers. To that end, we present a suite of features in every chapter to optimize opportunities for student growth in the important areas of problem solving and analytical thinking.

- **Now Solve This** Found several times within the text of each chapter, each entry provides a problem similar to ones found at the end of the chapter that is closely related to the current text discussion. In each case, a pedagogic hint is provided to offer insight and to aid in solving the problem.
- **Insights and Solutions** As an aid to the student in learning to solve problems, the *Problems and Discussion Questions* section of each chapter is preceded by what has become an extremely popular and successful section. *Insights and Solutions* poses problems or questions and provides detailed solutions and analytical insights as answers are provided. The questions and their solutions are designed to stress problem solving, quantitative analysis, analytical thinking, and experimental rationale. Collectively, these constitute the cornerstone of scientific inquiry and discovery.
- **Problems and Discussion Questions** Each chapter ends with an extensive collection of *Problems and Discussion Questions*. These include several levels of difficulty, with the most challenging (*Extra-Spicy Problems*) located at the end of each section. Often, Extra-Spicy Problems are derived from the literature of genetic research, with citations. Brief answers to all even-numbered problems are presented in Appendix B. The *Student Handbook and Solutions Manual* answers every problem and is available to students whenever faculty decide that it is appropriate.
- **How Do We Know?** Appearing as the first entry in the *Problems and Discussion Questions* section, this question asks the student to identify and examine the experimental basis underlying important concepts and conclusions that have been presented in the chapter. Addressing these questions will aid the student in more fully understanding, rather than memorizing, the endpoint of each body of research. This feature is an extension of the learning approach in biology first formally described by John A. Moore in his 1999 book *Science as a Way of Knowing—The Foundation of Modern Biology*.
- **Mastering Genetics** Tutorials in Mastering Genetics help students strengthen their problem-solving skills while exploring challenging activities about key genetics content. In addition, end-of-chapter problems are also available for instructors to assign as online homework. Students will also be able to access materials in the Study Area that help them assess their understanding and prepare for exams.

For the Instructor

Mastering Genetics—http://www.masteringgenetics.com

Mastering Genetics engages and motivates students to learn and allows you to easily assign automatically graded activities. Tutorials provide students with personalized coaching and feedback. Using the gradebook, you can quickly monitor and display student results. Mastering Genetics easily captures data to demonstrate assessment outcomes. Resources include:

- New Dynamic Study Modules, which are interactive flashcards, provide students with multiple sets of questions with extensive feedback so they can test, learn, and retest until they achieve mastery of the textbook material. These can be assigned for credit or used for self-study, and they are powerful preclass activities that help prepare students for more involved content coverage or problem solving in class.
- New tutorials on topics like CRISPR-Cas will help students master important, challenging concepts.
- In-depth tutorials that coach students with hints and feedback specific to their misconceptions
- An item library of thousands of assignable questions including end-of-chapter problems, reading quizzes, and test bank items. You can use publisher-created prebuilt assignments to get started quickly. Each question can be easily edited to match the precise language you use.
- Over 100 Practice Problems are like end-of-chapter questions in scope and level of difficulty and are found only in Mastering Genetics. Solutions are not available in the Student Solutions Manual, and the bank of questions extends your options for assigning challenging problems. Each problem includes specific wrong answer feedback to help students learn from their mistakes and to guide them toward the correct answer.
- eText 2.0 provides a dynamic digital version of the textbook, including embedded videos. The text adapts to the size of the screen being used, and features include student and instructor note-taking, highlighting, bookmarking, search, and hot-linked glossary.
- A gradebook that provides you with quick results and easy-to-interpret insights into student performance.

Downloadable Instructor Resources

The Instructor Resources for the 12th edition offers adopters of the text convenient access to a comprehensive and innovative set of lecture presentation and teaching tools. Developed to meet the needs of veteran and newer instructors alike, these resources include:

- The JPEG files of all text line drawings with labels individually enhanced for optimal projection results (as well as unlabeled versions) and all text tables.
- Most of the text photos, including all photos with pedagogical significance, as JPEG files.
- The JPEG files of line drawings, photos, and tables preloaded into comprehensive PowerPoint® presentations for each chapter.
- A second set of PowerPoint® presentations consisting of a thorough lecture outline for each chapter augmented by key text illustrations.
- PowerPoint® presentations containing a comprehensive set of in-class clicker questions for each chapter.
- An impressive series of concise instructor animations adding depth and visual clarity to the most important topics and dynamic processes described in the text.
- In Word and PDF files, a complete set of the assessment materials and study questions and answers from the testbank. Files are also available in TestGen format.

TestGen EQ Computerized Testing Software

(013483223X / 9780134832234) Test questions are available as part of the TestGen EQ Testing Software, a text-specific testing program that is networkable for administering tests. It also allows instructors to view and edit questions, export the questions as tests, and print them out in a variety of formats.

For the Student

Student Handbook and Solutions Manual

(0134870085 / 9780134870083) Authored by Michelle Gaudette (*Tufts University*) and Harry Nickla (*Creighton University*-Emeritus). This valuable handbook provides a detailed step-by-step solution or lengthy discussion for every problem in the text. The handbook also features additional study aids, including extra study problems, chapter outlines, vocabulary exercises, and an overview of how to study genetics.

Mastering Genetics—http://www.masteringgenetics.com

Used by over one million science students, the Mastering platform is the most effective and widely used online tutorial, homework, and assessment system for the sciences; it helps students perform better on homework and exams. As an instructor-assigned homework system, Mastering Genetics is designed to provide students with a variety of assessment tools to help them understand key topics and concepts and to build problem-solving skills. Mastering Genetics tutorials guide students through the toughest topics in genetics with self-paced tutorials that provide individualized coaching with hints and feedback specific to a student's individual misconceptions. Students can also explore the Mastering Genetics Study Area, which includes animations, the eText, *Exploring Genomics* exercises, and other study aids. The interactive eText 2.0 allows students to highlight text, add study notes, review instructor's notes, and search throughout the text.

Acknowledgments

Contributors

We begin with special acknowledgments to those who have made direct contributions to this text. First of all, we are pleased to acknowledge the work of Michelle Gaudette, who has assumed responsibility for writing the *Student Handbook and Solutions Manual* and the answers in Appendix B. We much appreciate this important contribution. We also thank Jutta Heller of the University of Washington—Tacoma, Christopher Halweg of North Carolina State University, Pamela Osenkowski of Loyola University—Chicago, and John Osterman of the University of Nebraska—Lincoln for their work on the media program. Steven Gorsich of Central Michigan University, Virginia McDonough of Hope College, Cindy Malone of California State University—Northridge, Pamela Marshall of Arizona State University West, and Brad Mehrtens of University of Illinois all made important contributions to the instructor resources program. We are grateful to all of these contributors not only for sharing their genetic expertise, but for their dedication to this project as well as the pleasant interactions they provided.

Proofreaders and Accuracy Checking

Reading the manuscript of an 800+ page textbook deserves more thanks than words can offer. Our utmost appreciation is extended to Ann Blakey, *Ball State University*, Jutta Heller, *University of Washington—Tacoma*, and Valerie Oke, *University of Pittsburgh*, who provided accuracy checking of many chapters, and to Kay Brimeyer, who proofread the entire manuscript. They confronted this task with patience and diligence, contributing greatly to the quality of this text.

Reviewers

All comprehensive texts are dependent on the valuable input provided by many reviewers. While we take full responsibility for any errors in this book, we gratefully acknowledge

the help provided by those individuals who reviewed the content and pedagogy of this edition:

Kyle Belozerov, York University
Ann Blakey, Ball State University
Michelle Boissiere, Xavier University of Louisiana
Gregory Booton, The Ohio State University
Mary Bryk, Texas A&M University
Soochin Cho, Creighton University
Claire Cronmiller, University of Virginia
Johnny El-Rady, University of South Florida
Christy Fillman, University of Colorado—Boulder
Edison Fowlks, Hampton University
Shaghayegh Harbi, New York University
Christopher Harendza, Montgomery County Community College
Benjamin Harrison, University of Alaska—Anchorage
Steven Karpowicz, University of Central Oklahoma
David Kass, Eastern Michigan University
Oliver Kerscher, The College of William and Mary
Kirkwood Land, University of the Pacific
Howard Laten, Loyola University Chicago
Haiying Liang, Clemson University
Te-Wen Lo, Ithaca College
Kari Loomis, University of Massachusetts—Amherst
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Matthew Marcello, Pace University
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Virginia McDonough, Hope College
Craig Miller, University of California—Berkeley
Anna Newman, University of Houston
Pamela Osenkowski, Loyola University Chicago
Stephen Page, Community College of Baltimore County
Dennis Ray, The University of Arizona
Jennifer Schisa, Central Michigan University
Randall Small, The University of Tennessee—Knoxville
Paul Small, Eureka College
Doug Thrower, University of California—Santa Barbara
Harald Vaessin, The Ohio State University
Meena Vijayaraghavan, Tulane University

As these acknowledgments make clear, a text such as this is a collective enterprise. All of the individuals above deserve to share in the success this text enjoys. We want them to know that our gratitude is equaled only by the extreme dedication evident in their efforts. Many, many thanks to them all.

Editorial and Production Input

At Pearson, we express appreciation and high praise for the editorial guidance of Michael Gillespie, whose ideas and efforts have helped to shape and refine the features of this edition of the text. Brett Coker, our Content Producer, has worked tirelessly to keep the project on schedule and to maintain our standards of high quality. Sonia DiVittorio provided detailed feedback in her role as developmental editor. In addition, our editorial team—Ginnie Simione Jutson, Director of Content Development; Barbara Price, Senior Development Editor; Margot Otway, Senior Development Editor; Sarah Jensen, Senior Content Developer for Mastering Genetics; and Chloe Veylit, Rich Media Producer—have provided valuable input into the current edition. They have worked creatively to ensure that the pedagogy and design of the book and media package are at the cutting edge of a rapidly changing discipline. Summer Giles, Editorial Assistant, helped manage and edit the instructor resources. Shaghayegh Harbi authored engaging, insightful tutorials for Mastering Genetics. Michelle Gardner supervised all the production intricacies with great attention to detail and perseverance. Outstanding copyediting was performed by Lucy Mullins, for which we are most grateful. Kelly Galli and Christa Pelaez have professionally and enthusiastically managed the marketing of the text. Finally, the beauty and consistent presentation of the artwork are the product of Imagineering of Toronto. Without the work ethic and dedication of the above individuals, the text would never have come to fruition.

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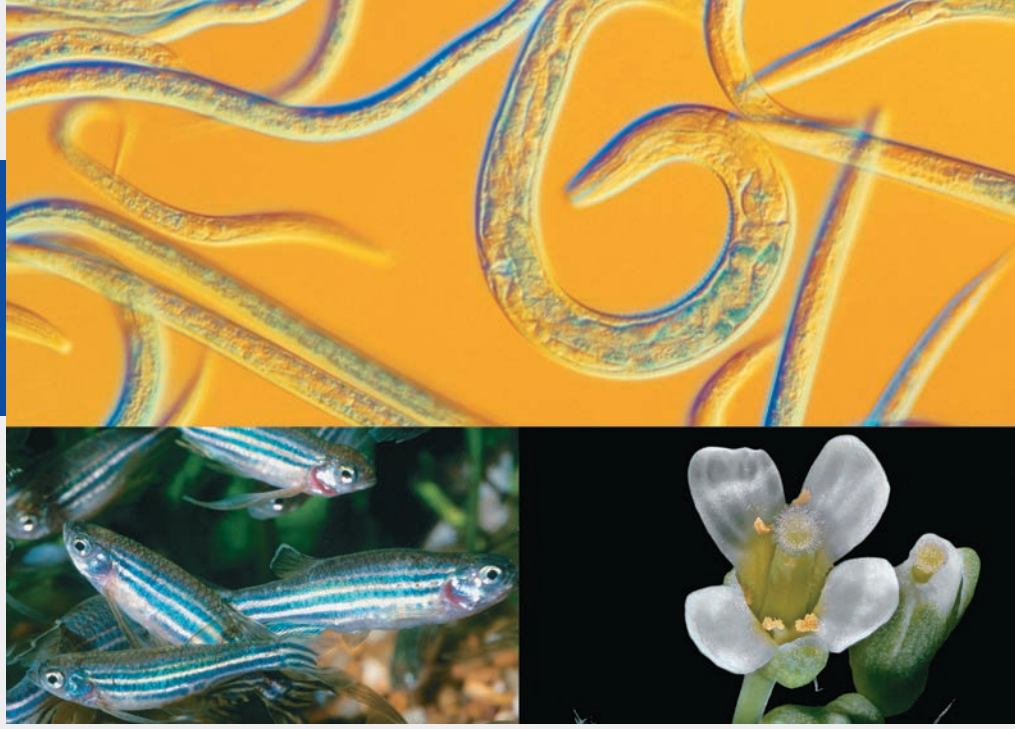

Introduction to Genetics

Newer model organisms in genetics include the roundworm, *Caenorhabditis elegans*; the zebrafish, *Danio rerio*; and the mustard plant, *Arabidopsis thaliana*.

CHAPTER CONCEPTS

- Genetics in the twenty-first century is built on a rich tradition of discovery and experimentation stretching from the ancient world through the nineteenth century to the present day.
- Transmission genetics is the general process by which traits controlled by genes are transmitted through gametes from generation to generation.
- Mutant strains can be used in genetic crosses to map the location and distance between genes on chromosomes.
- The Watson–Crick model of DNA structure explains how genetic information is stored and expressed. This discovery is the foundation of molecular genetics.
- Recombinant DNA technology revolutionized genetics, was the foundation for the Human Genome Project, and has generated new fields that combine genetics with information technology.
- Biotechnology provides genetically modified organisms and their products that are used across a wide range of fields including agriculture, medicine, and industry.
- Model organisms used in genetics research are now utilized in combination with recombinant DNA technology and genomics to study human diseases.
- Genetic technology is developing faster than the policies, laws, and conventions that govern its use.

One of the small pleasures of writing a genetics textbook is being able to occasionally introduce in the very first paragraph of the initial chapter a truly significant breakthrough in the discipline that hopefully will soon have a major, diverse impact on human lives. In this edition, we are fortunate to be able to discuss the discovery of **CRISPR-Cas**, a molecular complex found in bacteria that has the potential to revolutionize our ability to rewrite the DNA sequence of genes from any organism. As such, it represents the ultimate tool in genetic technology, whereby the genome of organisms, including humans, may be precisely edited. Such gene modification represents the ultimate application of the many advances in biotechnology made in the last 35 years, including the sequencing of the human genome.

Other systems have been developed, including **zinc-finger nucleases (ZFNs)** and **transcription activator-like effector nucleases (TALENs)**, that are now undergoing clinical trials for the treatment of human diseases, and which we will discuss later in the text. However, the CRISPR-Cas system is the most powerful and far-reaching method and is now the preferred approach in gene modification. This system allows researchers to edit genomes with greater accuracy, is easier to use, and is more versatile than the ZFN or TALEN systems. CRISPR-Cas molecules were initially discovered as a molecular complex that protects bacterial cells

from invasion by viruses. CRISPR (clustered regularly interspersed short palindromic repeats) designates an RNA molecule, which in the laboratory can be synthesized to match any DNA sequence of choice. CRISPR RNA has two ends: one recognizes and binds to a matching DNA sequence in the gene of interest, and the other binds to a CRISPR-associated (Cas) nuclease, or DNA-cutting enzyme. The most commonly used Cas nuclease is Cas9, but there are many other Cas nucleases, each of which has slightly different properties, contributing to the system's versatility. In laboratory experiments, CRISPR-Cas systems have already been used to repair mutations in cells derived from individuals with several genetic disorders, including cystic fibrosis, Huntington disease, beta-thalassemia, sickle cell disease, muscular dystrophy, and X-linked retinitis pigmentosa, which results in progressive vision loss. In the United States a clinical trial using CRISPR-Cas9 for genome editing in cancer therapy has been approved, and a second proposal for treating a genetic form of blindness is in preparation. A clinical trial using CRISPR-Cas9 for cancer therapy is already under way in China.

The application of this remarkable system goes far beyond research involving human genetic disorders. In organisms of all kinds, wherever genetic modification may improve on nature to the benefit of human existence and of our planet, the use of CRISPR-Cas will find many targets. For example, one research group was able to use this system to spread genes that prevent mosquitoes from carrying the parasite that causes malaria. Other researchers have proposed using CRISPR-Cas9 to engineer laboratory-grown human blood vessels and organs that do not express proteins that cause rejection of transplanted tissues and organs. The method has also been used to create disease-resistant strains of wheat and rice.

The power of this system, like any major technological advance, has already raised ethical concerns. For example, genetic modification of human germ cells or embryos would change the genetic information carried by future generations. These modifications may have unintended and significant negative consequences for our species. An international summit on human gene editing in December 2015 concluded that a global forum to address concerns about heritable modifications should be convened to formulate regulations that apply to all countries involved in CRISPR research.

CRISPR-Cas may turn out to be one of the most exciting genetic advances in decades. We will return later in the text to an extended discussion of its discovery, describe how it works, its many applications, and the ethical considerations that it raises (see Special Topic Chapter 1—CRISPR and Genomic Editing).

For now, we hope that this short introduction has stimulated your curiosity, interest, and enthusiasm for the study of genetics. The remainder of this chapter provides an overview of major concepts of genetics and a survey of the major turning points in the history of the discipline. Along the way, enjoy your studies, but take your responsibilities as a novice geneticist most seriously.

1.1 Genetics Has a Rich and Interesting History

We don't know when people first recognized the hereditary nature of certain traits, but archaeological evidence (e.g., pictorial representations, preserved bones and skulls, and dried seeds) documents the successful domestication of animals and the cultivation of plants thousands of years ago by the artificial selection of genetic variants from wild populations. Between 8000 and 1000 B.C., horses, camels, oxen, and wolves were domesticated, and selective breeding of these species soon followed. Cultivation of many plants, including maize, wheat, rice, and the date palm, began around 5000 B.C. Such evidence documents our ancestors' successful attempts to manipulate the genetic composition of species.

During the Golden Age of Greek culture, the writings of the Hippocratic School of Medicine (500–400 B.C.) and of the philosopher and naturalist Aristotle (384–322 B.C.) discussed heredity as it relates to humans. The Hippocratic treatise *On the Seed* argued that active "humors" in various parts of the body served as the bearers of hereditary traits. Drawn from various parts of the male body to the semen and passed on to offspring, these humors could be healthy or diseased, with the diseased humors accounting for the appearance of newborns with congenital disorders or deformities. It was also believed that these humors could be altered in individuals before they were passed on to offspring, explaining how newborns could "inherit" traits that their parents had "acquired" in response to their environment.

Aristotle extended Hippocrates' thinking and proposed that the male semen contained a "vital heat" with the capacity to produce offspring of the same "form" (i.e., basic structure and capacities) as the parent. Aristotle believed that this heat cooked and shaped the menstrual blood produced by the female, which was the "physical substance" that gave rise to an offspring. The embryo developed not because it already contained the parts of an adult in miniature form (as some Hippocratics had thought) but because of the shaping power of the vital heat. Although the ideas of Hippocrates and Aristotle sound primitive and naive today, we should recall that prior to the 1800s neither sperm nor eggs had been observed in mammals.

1600–1850: The Dawn of Modern Biology

Between about 300 B.C. and 1600 A.D., there were few significant new ideas about genetics. However, between 1600 and 1850, major strides provided insight into the biological basis of life. In the 1600s, William Harvey studied reproduction and development and proposed the theory of **epigenesis**, which states that an organism develops from the fertilized egg by a succession of developmental events that eventually transform the egg into an adult. The theory of epigenesis directly conflicted with the theory of **preformation**, which stated that the fertilized egg contains a complete miniature adult, called a **homunculus** (Figure 1.1). Around 1830, Matthias Schleiden and Theodor Schwann proposed the **cell theory**, stating that all organisms are composed of basic structural units called cells, which are derived from preexisting cells. The idea of **spontaneous generation**, the creation of living organisms from nonliving components, was disproved by Louis Pasteur later in the century, and living organisms were then considered to be derived from preexisting organisms and to consist of cells.

In the mid-1800s the revolutionary work of Charles Darwin and Gregor Mendel set the stage for the rapid development of genetics in the twentieth and twenty-first centuries.

Charles Darwin and Evolution

With this background, we turn to a brief discussion of the work of Charles Darwin, who published *The Origin of Species*, in 1859, describing his ideas about evolution.

FIGURE 1.1 Depiction of the *homunculus*, a sperm containing a miniature adult, perfect in proportion and fully formed.

Darwin's geological, geographical, and biological observations convinced him that existing species arose by descent with modification from ancestral species. Greatly influenced by his voyage on the HMS *Beagle* (1831–1836), Darwin's thinking led him to formulate the theory of **natural selection**, which presented an explanation of the mechanism of evolutionary change. Formulated and proposed independently by Alfred Russel Wallace, natural selection is based on the observation that populations tend to contain more offspring than the environment can support, leading to a struggle for survival among individuals. Those individuals with heritable traits that allow them to adapt to their environment are better able to survive and reproduce than those with less adaptive traits. Over a long period of time, advantageous variations, even very slight ones, will accumulate. If a population carrying these inherited variations becomes reproductively isolated, a new species may result.

Darwin, however, lacked an understanding of the genetic basis of variation and inheritance, a gap that left his theory open to reasonable criticism well into the twentieth century. Shortly after Darwin published his book, Gregor Johann Mendel published a paper in 1866 showing how traits were passed from generation to generation in pea plants and offering a general model of how traits are inherited. His research was little known until it was partially duplicated and brought to light by Carl Correns, Hugo de Vries, and Erich Tschermak around 1900.

By the early part of the twentieth century, it became clear that heredity and development were dependent on genetic information residing in genes contained in chromosomes, which were then contributed to each individual by gametes—the so-called *chromosomal theory of inheritance*. The gap in Darwin's theory was closed, and Mendel's research has continued to serve as the foundation of genetics.

1.2 Genetics Progressed from Mendel to DNA in Less Than a Century

Because genetic processes are fundamental to life itself, the science of genetics unifies biology and serves as its core. The starting point for this branch of science was a monastery garden in central Europe in the late 1850s.

Mendel's Work on Transmission of Traits

Gregor Mendel, an Augustinian monk, conducted a decade-long series of experiments using pea plants. He applied quantitative data analysis to his results and showed that traits are passed from parents to offspring in predictable ways.

He further concluded that each trait in the plant is controlled by a pair of factors (which we now call genes) and that during gamete formation (the formation of egg cells and sperm), members of a gene pair separate from each other. His work was published in 1866 but was largely unknown until it was cited in papers published by others around 1900. Once confirmed, Mendel's findings became recognized as explaining the transmission of traits in pea plants and all other higher organisms. His work forms the foundation for **genetics**, which is defined as the branch of biology concerned with the study of heredity and variation. Mendelian genetics will be discussed later in the text (see Chapters 3 and 4).

The Chromosome Theory of Inheritance: Uniting Mendel and Meiosis

Mendel did his experiments before the structure and role of chromosomes were known. About 20 years after his work was published, advances in microscopy allowed researchers to identify chromosomes (**Figure 1.2**) and establish that, in most eukaryotes, members of each species have a characteristic number of chromosomes called the **diploid number (2*n*)** in most of their cells. For example, humans have a diploid number of 46 (**Figure 1.3**). Chromosomes in diploid cells exist in pairs, called **homologous chromosomes**.

Researchers in the last decades of the nineteenth century also described chromosome behavior during two forms of cell division, **mitosis** and **meiosis**. In mitosis (**Figure 1.4**), chromosomes are copied and distributed so that each daughter cell receives a diploid set of chromosomes identical to those in the parental cell. Meiosis is associated with gamete formation. Cells produced by meiosis receive only one chromosome from each chromosome pair, and the resulting number of chromosomes is called the **haploid number (*n*)**. This reduction in chromosome number is essential if the offspring arising from the fusion of egg and sperm are to maintain the constant number of chromosomes characteristic of their parents and other members of their species.

Early in the twentieth century, Walter Sutton and Theodor Boveri independently noted that the behavior

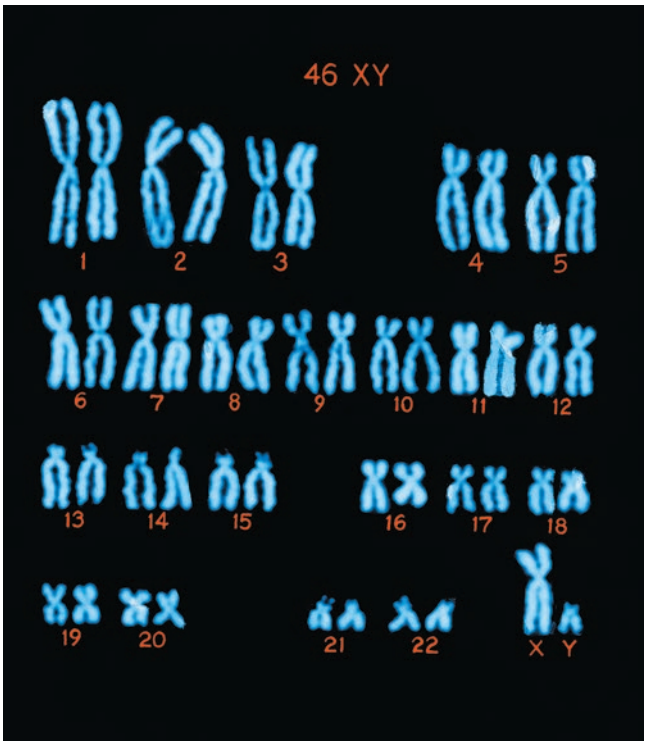

FIGURE 1.3 A colorized image of the human male chromosome set. Arranged in this way, the set is called a karyotype.

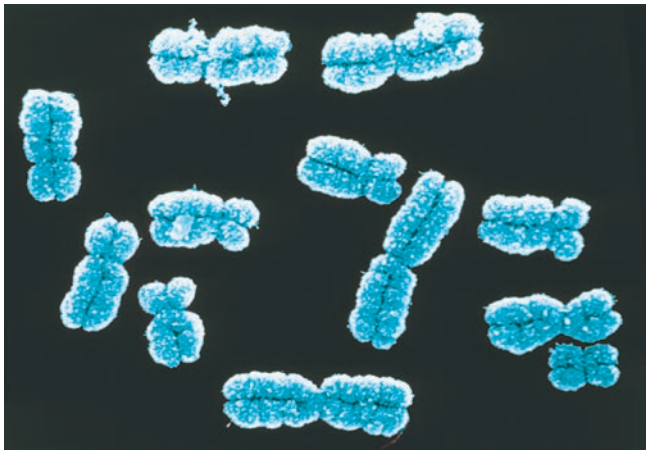

FIGURE 1.2 A colorized image of human chromosomes that have duplicated in preparation for cell division, as visualized using a scanning electron microscope.

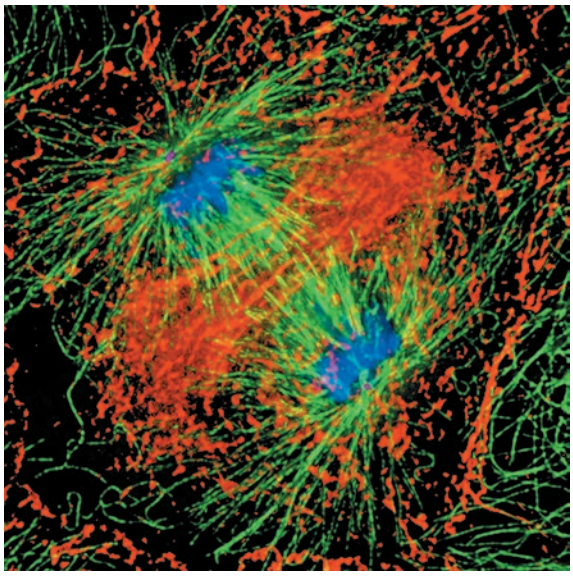

FIGURE 1.4 A late stage in mitosis after the chromosomes (stained blue) have separated.

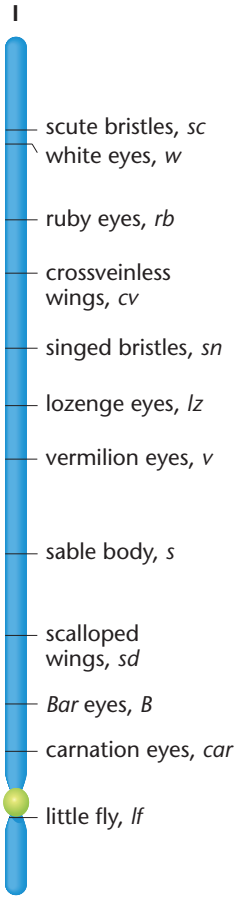

FIGURE 1.5 A drawing of chromosome I (the X chromosome, one of the sex-determining chromosomes) of *D. melanogaster*, showing the location of several genes. Chromosomes can contain hundreds of genes.

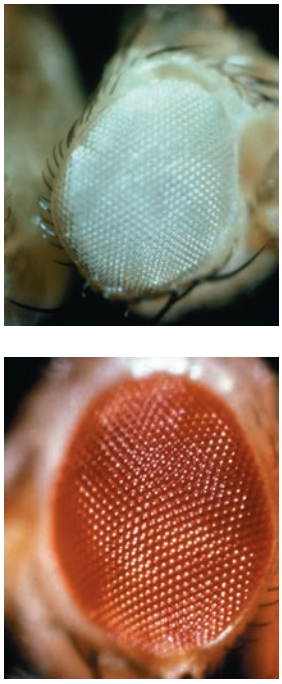

FIGURE 1.6 The white-eyed mutation in *D. melanogaster* (top) and the normal red eye color (bottom).

of chromosomes during meiosis is identical to the behavior of genes during gamete formation described by Mendel. For example, genes and chromosomes exist in pairs, and members of a gene pair and members of a chromosome pair separate from each other during gamete formation. Based on these and other parallels, Sutton and Boveri each proposed that genes are carried on chromosomes (**Figure 1.5**). They independently formulated the **chromosome theory of inheritance**, which states that inherited traits are controlled by genes residing on chromosomes faithfully transmitted through gametes, maintaining genetic continuity from generation to generation.

Genetic Variation

About the same time that the chromosome theory of inheritance was proposed, scientists began studying the inheritance of traits in the fruit fly, *Drosophila melanogaster*. Early in this work, a white-eyed fly (**Figure 1.6**) was discovered among normal (wild-type) red-eyed flies. This variation was produced by a **mutation** in one of the genes controlling eye color. Mutations are defined as any heritable change in the DNA sequence and are the source of all genetic variation.

The white-eye variant discovered in *Drosophila* is an **allele** of a gene controlling eye color. Alleles are defined as alternative forms of a gene. Different alleles may produce differences in the observable features, or **phenotype**, of an organism. The set of alleles for a given trait carried by an organism is called the **genotype**. Using mutant genes as markers, geneticists can map the location of genes on chromosomes (Figure 1.5).

The Search for the Chemical Nature of Genes: DNA or Protein?

Work on white-eyed *Drosophila* showed that the mutant trait could be traced to a single chromosome, confirming the idea that genes are carried on chromosomes. Once this relationship was established, investigators turned their attention to identifying which chemical component of chromosomes carries genetic information. By the 1920s, scientists knew that proteins and DNA were the major chemical components of chromosomes. There are a large number of different proteins, and because of their universal distribution in the nucleus and cytoplasm, many researchers thought proteins were the carriers of genetic information.

In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty, researchers at the Rockefeller Institute in New York, published experiments showing that DNA was the carrier

of genetic information in bacteria. This evidence, though clear-cut, failed to convince many influential scientists. Additional evidence for the role of DNA as a carrier of genetic information came from Hershey and Chase who worked with viruses. This evidence that DNA carries genetic information, along with other research over the next few years, provided solid proof that DNA, not protein, is the genetic material, setting the stage for work to establish the structure of DNA.

1.3 Discovery of the Double Helix Launched the Era of Molecular Genetics

Once it was accepted that DNA carries genetic information, efforts were focused on deciphering the structure of the DNA molecule and the mechanism by which information stored in it produces a phenotype.

The Structure of DNA and RNA

One of the great discoveries of the twentieth century was made in 1953 by James Watson and Francis Crick, who described the structure of DNA. DNA is a long, ladder-like macromolecule that twists to form a double helix (**Figure 1.7**). Each linear strand of the helix is made up of subunits called **nucleotides**. In DNA, there are four different nucleotides, each of which contains a nitrogenous base, abbreviated A (adenine), G (guanine), T (thymine), or C (cytosine). These four bases, in various sequence combinations, ultimately encode genetic information. The two strands of DNA are exact complements of one another, so that the rungs of the ladder in the double helix always consist of A=T and G=C base pairs. Along with Maurice Wilkins, Watson and Crick were awarded a Nobel Prize in 1962 for their work on the structure of DNA. We will discuss the structure of DNA later in the text (see Chapter 9).

Another nucleic acid, RNA, is chemically similar to DNA but contains a different sugar (ribose rather than deoxyribose) in its nucleotides and contains the nitrogenous base uracil in place of thymine. RNA, however, is generally a single-stranded molecule.

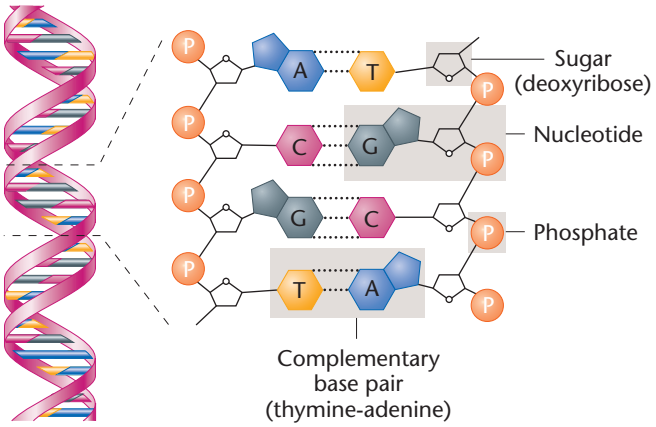

FIGURE 1.7 Summary of the structure of DNA, illustrating the arrangement of the double helix (on the left) and the chemical components making up each strand (on the right). The dotted lines on the right represent weak chemical bonds, called hydrogen bonds, which hold together the two strands of the DNA helix.

Gene Expression: From DNA to Phenotype

The genetic information encoded in the order of nucleotides in DNA is expressed in a series of steps that results in the formation of a functional gene product. In the majority of cases, this product is a protein. In eukaryotic cells, the process leading to protein production begins in the nucleus with **transcription**, in which the nucleotide sequence in one strand of DNA is used to construct a complementary RNA sequence (top part of **Figure 1.8**). Once an RNA molecule is produced, it moves to the cytoplasm, where the RNA—called **messenger RNA**, or **mRNA** for short—binds to a **ribosome**. The synthesis of proteins under the direction of mRNA is called **translation** (center part of Figure 1.8). The information encoded in mRNA (called the **genetic code**) consists of a linear series of nucleotide triplets. Each triplet, called a **codon**, is complementary to the information stored

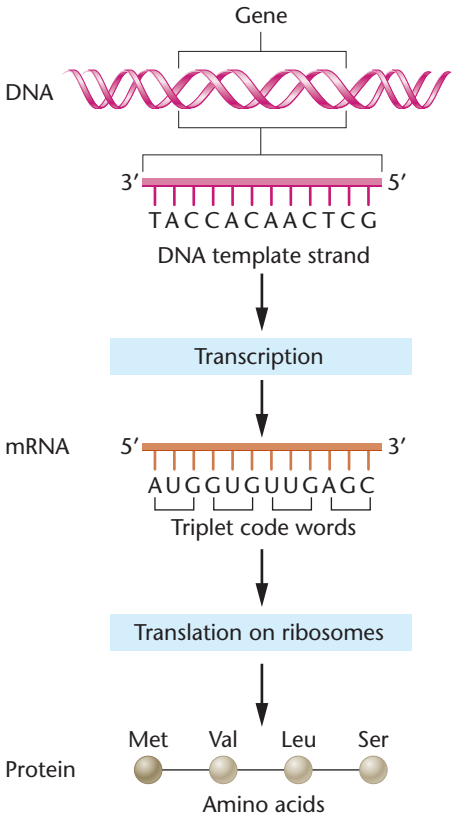

FIGURE 1.8 Gene expression consists of transcription of DNA into mRNA (top) and the translation (center) of mRNA (with the help of a ribosome) into a protein (bottom).

in DNA and specifies the insertion of a specific amino acid into a protein. Proteins (lower part of Figure 1.8) are polymers made up of amino acid monomers. There are 20 different amino acids commonly found in proteins.

Protein assembly is accomplished with the aid of adapter molecules called **transfer RNA (tRNA)**. Within the ribosome, tRNAs recognize the information encoded in the mRNA codons and carry the proper amino acids for construction of the protein during translation.

We now know that gene expression can be more complex than outlined here. Some of these complexities will be discussed later in the text (see Chapters 14 and 19).

Proteins and Biological Function

In most cases, proteins are the end products of gene expression. The diversity of proteins and the biological functions they perform—the diversity of life itself—arises from the fact that proteins are made from combinations of 20 different amino acids. Consider that a protein chain containing 100 amino acids can have at each position any one of 20 amino acids; the number of possible different 100-amino-acid proteins, each with a unique sequence, is therefore equal to

$$20^{100}$$

Obviously, proteins are molecules with the potential for enormous structural diversity and serve as the mainstay of biological systems.

Enzymes form the largest category of proteins. These molecules serve as biological catalysts, lowering the energy of activation in reactions and allowing cellular metabolism to proceed at body temperature.

Proteins other than enzymes are critical components of cells and organisms. These include hemoglobin, the oxygen-binding molecule in red blood cells; insulin, a pancreatic hormone; collagen, a connective tissue molecule; and actin and myosin, the contractile muscle proteins. A protein's shape and chemical behavior are determined by its linear sequence of amino acids, which in turn is dictated by the stored information in the DNA of a gene that is transferred to RNA, which then directs the protein's synthesis.

Linking Genotype to Phenotype: Sickle-Cell Anemia

Once a protein is made, its biochemical or structural properties play a role in producing a phenotype. When mutation alters a gene, it may modify or even eliminate the encoded protein's usual function and cause an altered phenotype. To trace this chain of events, we will examine sickle-cell anemia, a human genetic disorder.

Sickle-cell anemia is caused by a mutant form of hemoglobin, the protein that transports oxygen from the lungs to cells in the body. Hemoglobin is a composite molecule made up of two different proteins, α-globin and β-globin, each encoded by a different gene. In sickle-cell anemia,

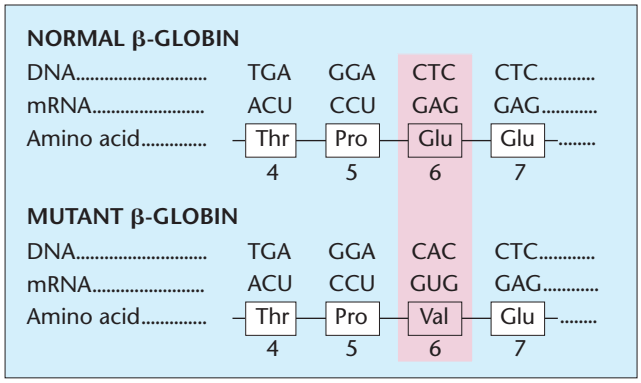

FIGURE 1.9 A single-nucleotide change in the DNA encoding β-globin (CTC → CAC) leads to an altered mRNA codon (GAG → GUG) and the insertion of a different amino acid (Glu → Val), producing the altered version of the β-globin protein that is responsible for sickle-cell anemia.

a mutation in the gene encoding β-globin causes an amino acid substitution in 1 of the 146 amino acids in the protein. **Figure 1.9** shows the DNA sequence, the corresponding mRNA codons, and the amino acids occupying positions 4–7 for the normal and mutant forms of β-globin. Notice that the mutation in sickle-cell anemia consists of a change in one DNA nucleotide, which leads to a change in codon 6 in mRNA from GAG to GUG, which in turn changes amino acid number 6 in β-globin from glutamic acid to valine. The other 145 amino acids in the protein are not changed by this mutation.

Individuals with two mutant copies of the β-globin gene have sickle-cell anemia. Their mutant β-globin proteins cause hemoglobin molecules in red blood cells to polymerize when the blood's oxygen concentration is low, forming long chains of hemoglobin that distort the shape of red blood cells (**Figure 1.10**). The deformed cells are fragile and break

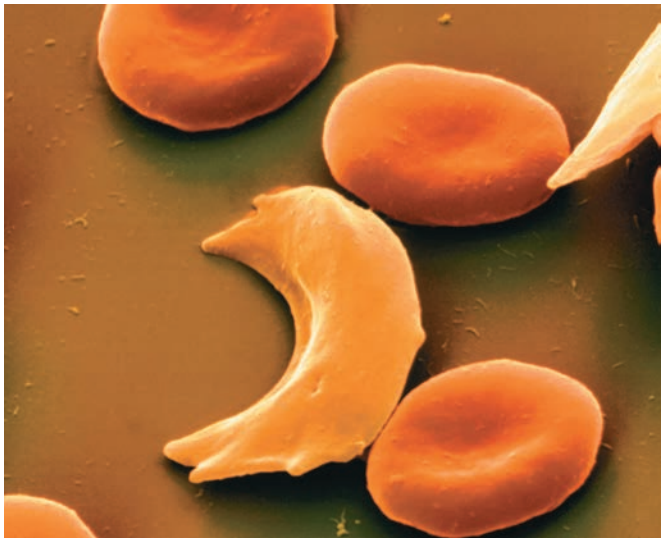

FIGURE 1.10 Normal red blood cells (round) and sickled red blood cells. The sickled cells block capillaries and small blood vessels.

easily, reducing the number of red blood cells in circulation (anemia is an insufficiency of red blood cells). Sickle-shaped blood cells block blood flow in capillaries and small blood vessels, causing severe pain and damage to the heart, brain, muscles, and kidneys. All the symptoms of this disorder are caused by a change in a single nucleotide in a gene that changes one amino acid out of 146 in the β-globin molecule, demonstrating the close relationship between genotype and phenotype.

1.4 Development of Recombinant DNA Technology Began the Era of DNA Cloning

The era of recombinant DNA began in the early 1970s, when researchers discovered that **restriction enzymes**, used by bacteria to cut and inactivate the DNA of invading viruses, could be used to cut any organism's DNA at specific nucleotide sequences, producing a reproducible set of fragments.

Soon after, researchers discovered ways to insert the DNA fragments produced by the action of restriction enzymes into carrier DNA molecules called **vectors** to form recombinant DNA molecules. When transferred into bacterial cells, thousands of copies, or **clones**, of the combined vector and DNA fragments are produced during bacterial reproduction. Large amounts of cloned DNA fragments can be isolated from these bacterial host cells. These DNA fragments can be used to isolate genes, to study their organization and expression, and to study their nucleotide sequence and evolution.

Collections of clones that represent an organism's **genome**, defined as the complete haploid DNA content of a specific organism, are called genomic libraries. Genomic libraries are now available for hundreds of species.

Recombinant DNA technology has not only accelerated the pace of research but also given rise to the biotechnology industry, which has grown to become a major contributor to the U.S. economy.

1.5 The Impact of Biotechnology Is Continually Expanding

The use of recombinant DNA technology and other molecular techniques to make products is called **biotechnology**. In the United States, biotechnology has quietly revolutionized many aspects of everyday life; products made by biotechnology are now found in the supermarket, in health care, in agriculture, and in the court system. A later chapter (see Chapter 22) contains a detailed discussion of biotechnology, but for now, let's look at some everyday examples of biotechnology's impact.

Plants, Animals, and the Food Supply

The use of recombinant DNA technology to genetically modify crop plants has revolutionized agriculture. Genes for traits including resistance to herbicides, insects, and genes for nutritional enhancement have been introduced into crop plants. The transfer of heritable traits across species using recombinant DNA technology creates **transgenic** organisms. Herbicide-resistant corn and soybeans were first planted in the mid-1990s, and transgenic strains now represent about 88 percent of the U.S. corn crop and 93 percent of the U.S. soybean crop. It is estimated that more than 70 percent of the processed food in the United States contains ingredients from transgenic crops.

We will discuss the most recent findings involving genetically modified organisms later in the text. (Special Topics Chapter 4—Genetically Modified Foods).

New methods of cloning livestock such as sheep and cattle have also changed the way we use these animals. In 1996, Dolly the sheep (**Figure 1.11**) was cloned by nuclear transfer, a method in which the nucleus of an adult cell is transferred into an egg that has had its nucleus removed. This method makes it possible to produce dozens or hundreds of genetically identical offspring with desirable traits and has many applications in agriculture, sports, and medicine.

Biotechnology has also changed the way human proteins for medical use are produced. Through use of gene transfer, transgenic animals now synthesize these therapeutic

FIGURE 1.11 Dolly, a Finn Dorset sheep cloned from the genetic material of an adult mammary cell, shown next to her first-born lamb, Bonnie.

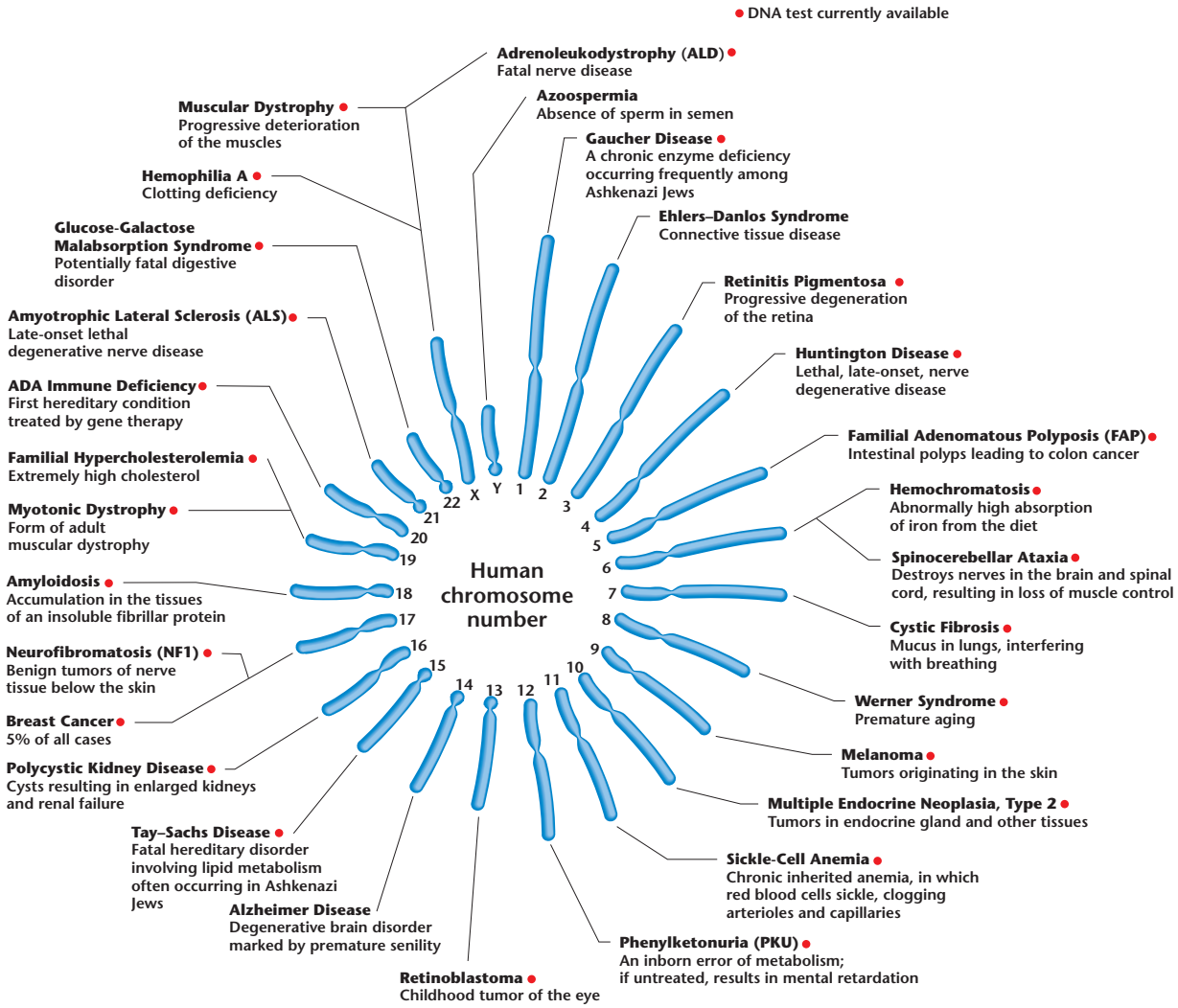

FIGURE 1.12 The human chromosome set, showing the location of some genes whose mutant forms cause hereditary diseases. Conditions that can be diagnosed using genetic testing are indicated by a red dot.

proteins. In 2009, an anticlotting protein derived from the milk of transgenic goats was approved by the U.S. Food and Drug Administration for use in the United States. Other human proteins from transgenic animals are now being used in clinical trials to treat several diseases. The biotechnology revolution will continue to expand as new methods are developed to make an increasing array of products.

Biotechnology in Genetics and Medicine

More than 10 million children or adults in the United States suffer from some form of genetic disorder, and every childbearing couple faces an approximately 3 percent risk of having a child with a genetic anomaly. The molecular basis for hundreds of genetic disorders is now known, and many of these genes have been mapped, isolated, and cloned (**Figure 1.12**). Biotechnology-derived genetic testing is now available to perform prenatal diagnosis of heritable disorders and to test parents for their status as "carriers" of more than 100 inherited disorders. Newer methods now under development offer the possibility of scanning an entire genome to establish an individual's risk of developing a genetic disorder or having an affected child. The use of genetic testing and related technologies raises ethical concerns that have yet to be resolved.

1.6 Genomics, Proteomics, and Bioinformatics Are New and Expanding Fields

The use of recombinant DNA technology to create genomic libraries prompted scientists to consider sequencing all the clones in a library to derive the nucleotide sequence of an organism's genome. This sequence information would be used to identify each gene in the genome and establish its function.