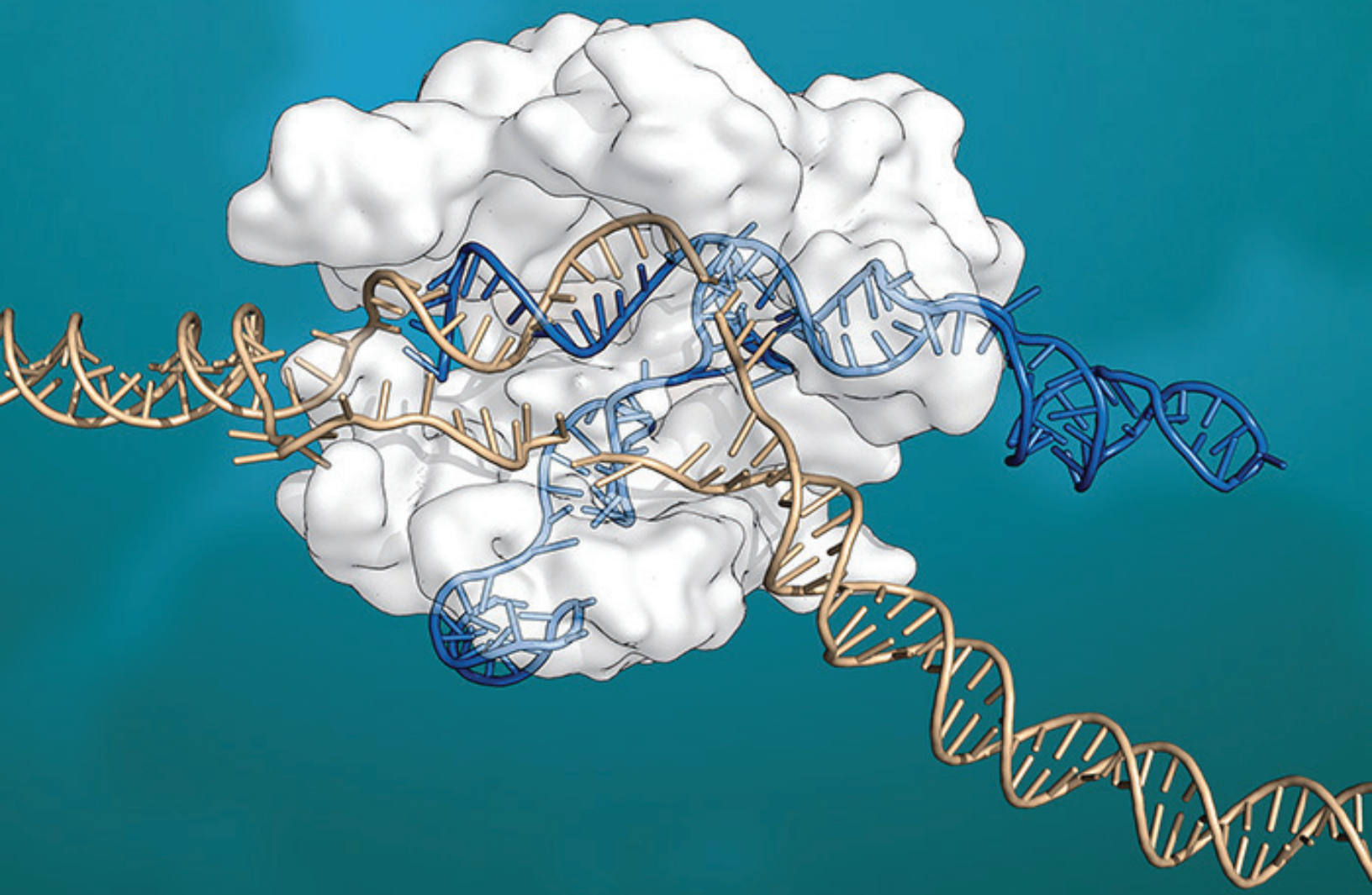
CONCEPTS OF GENETICS

TWELFTH EDITION



Klug | Cummings | Spencer
Palladino | Killian

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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

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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

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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.

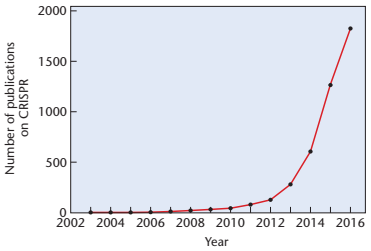

FIGURE ST 1.1 The number of publications returned in a search for "CRISPR" in PubMed by year.

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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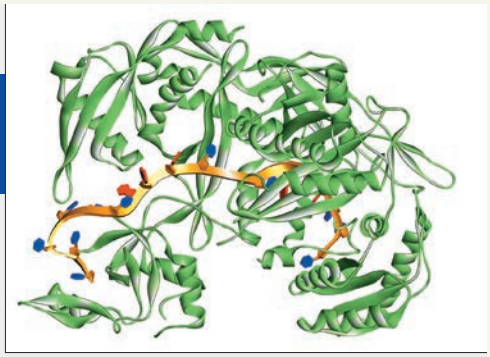

Posttranscriptional Regulation in Eukaryotes

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

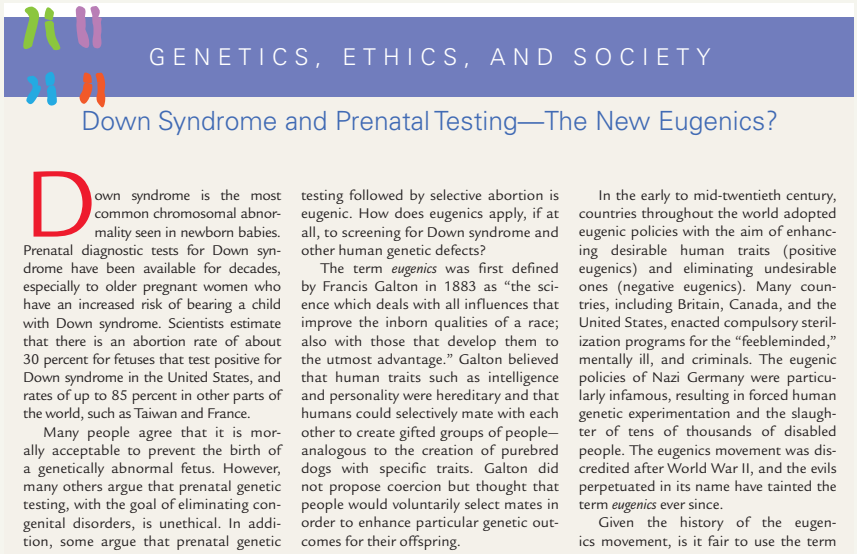
In toadflax, the shape of individual flowers changes from bilateral symmetry (photo on the left) to radial symmetry (photo on the right) in a naturally occurring, heritable gene silencing epimutation associated with the methylation of a single gene. There is no alteration of the DNA sequence at this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

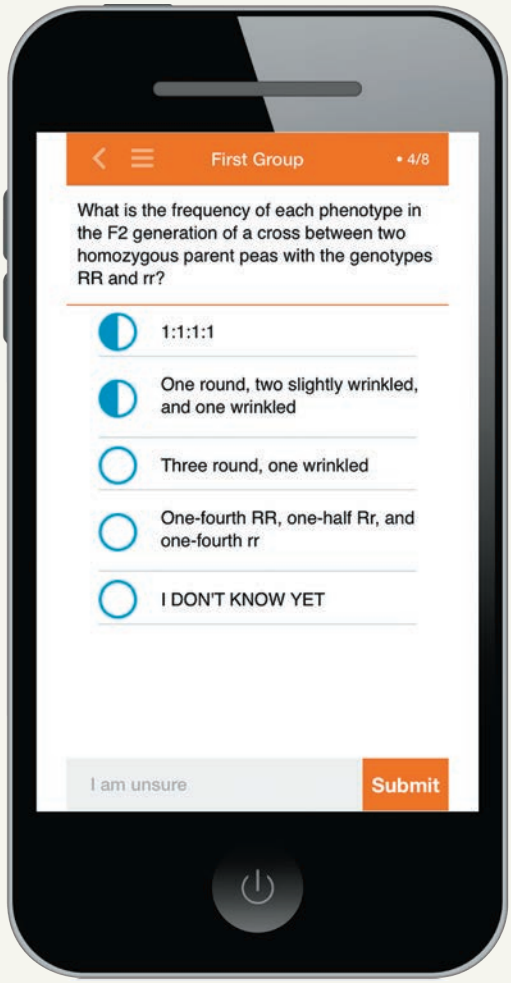
Controlling the overgrowth of invasive aquatic vegetation is a significant problem in the waterways of most U.S. states. Originally, herbicides and dredging were used for control, but in 1963, diploid Asian carp were introduced in Alabama and Arkansas. Unfortunately, through escapes and illegal introductions, 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

Mastering™ Genetics helps students master key genetics concepts while reinforcing problem-solving skills with hints and feedback specific to their misconceptions. Mastering Genetics includes content and tools for before, during, and after class. Learn more at www.pearson.com/mastering/genetics



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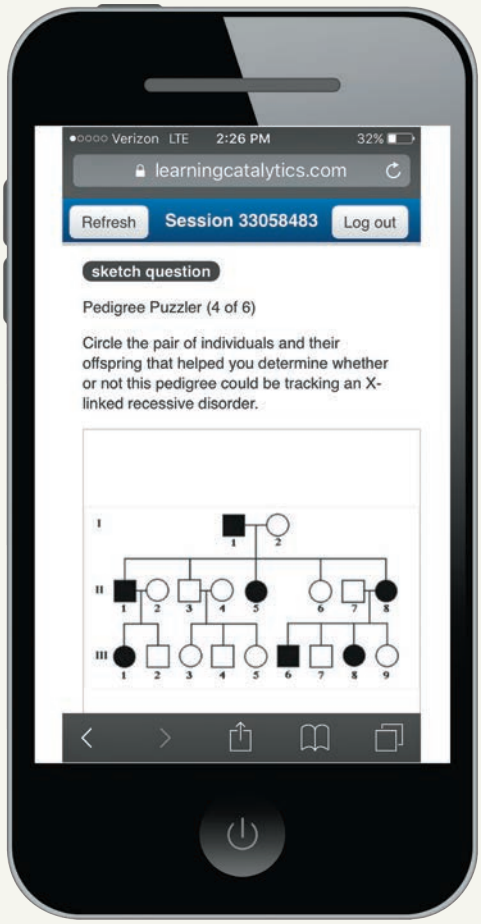

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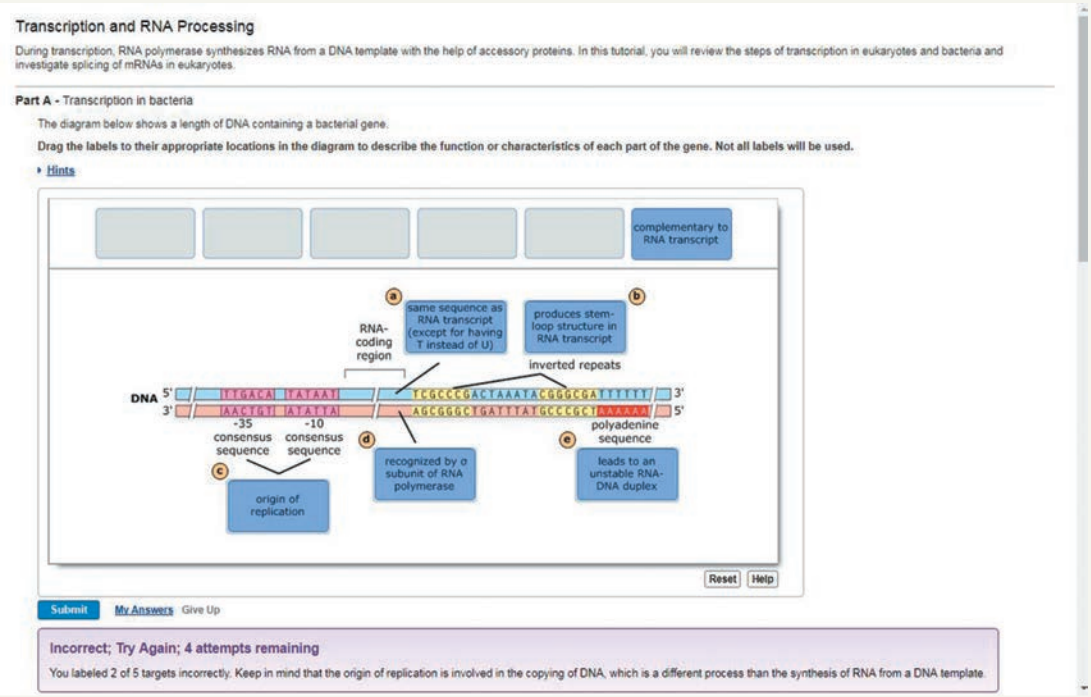

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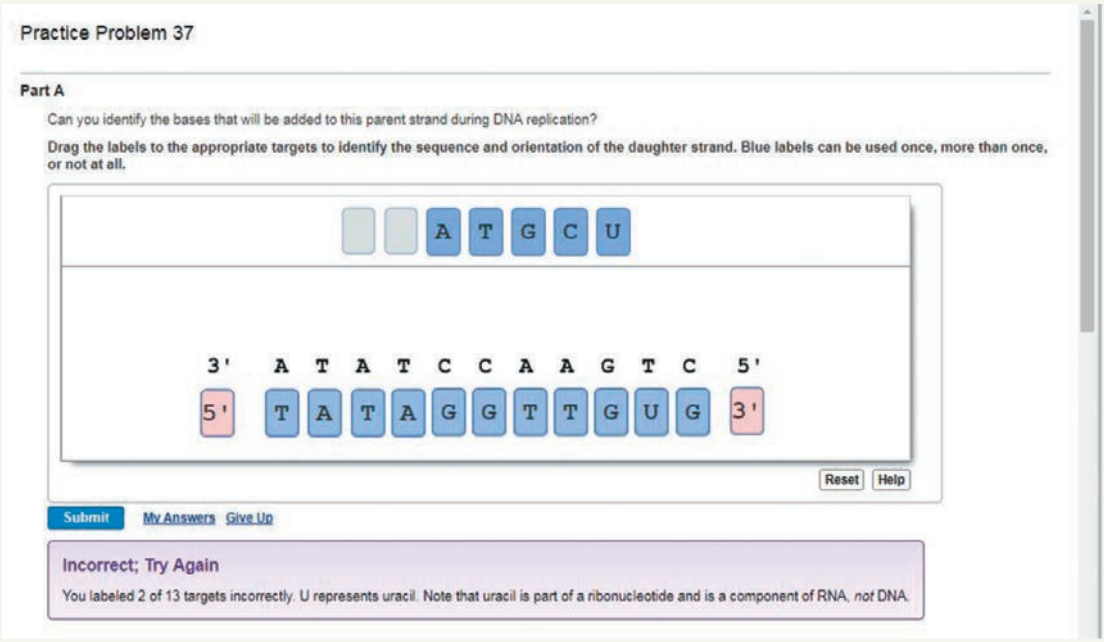

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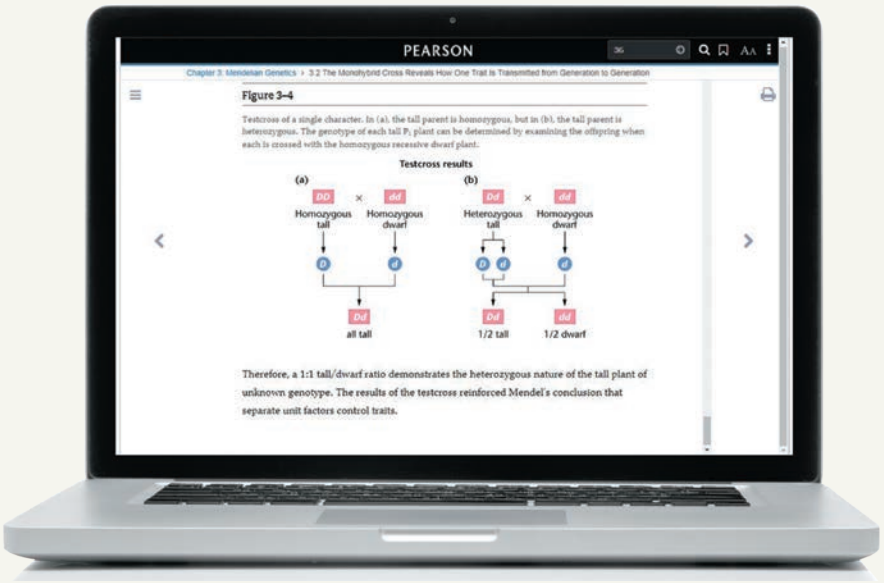

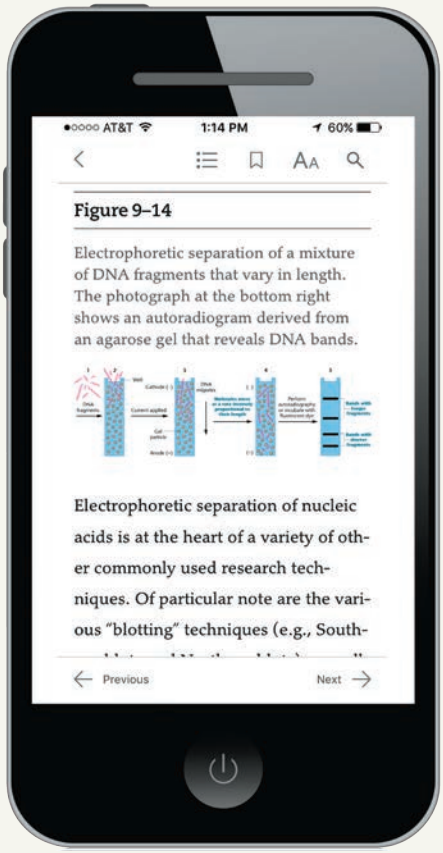

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