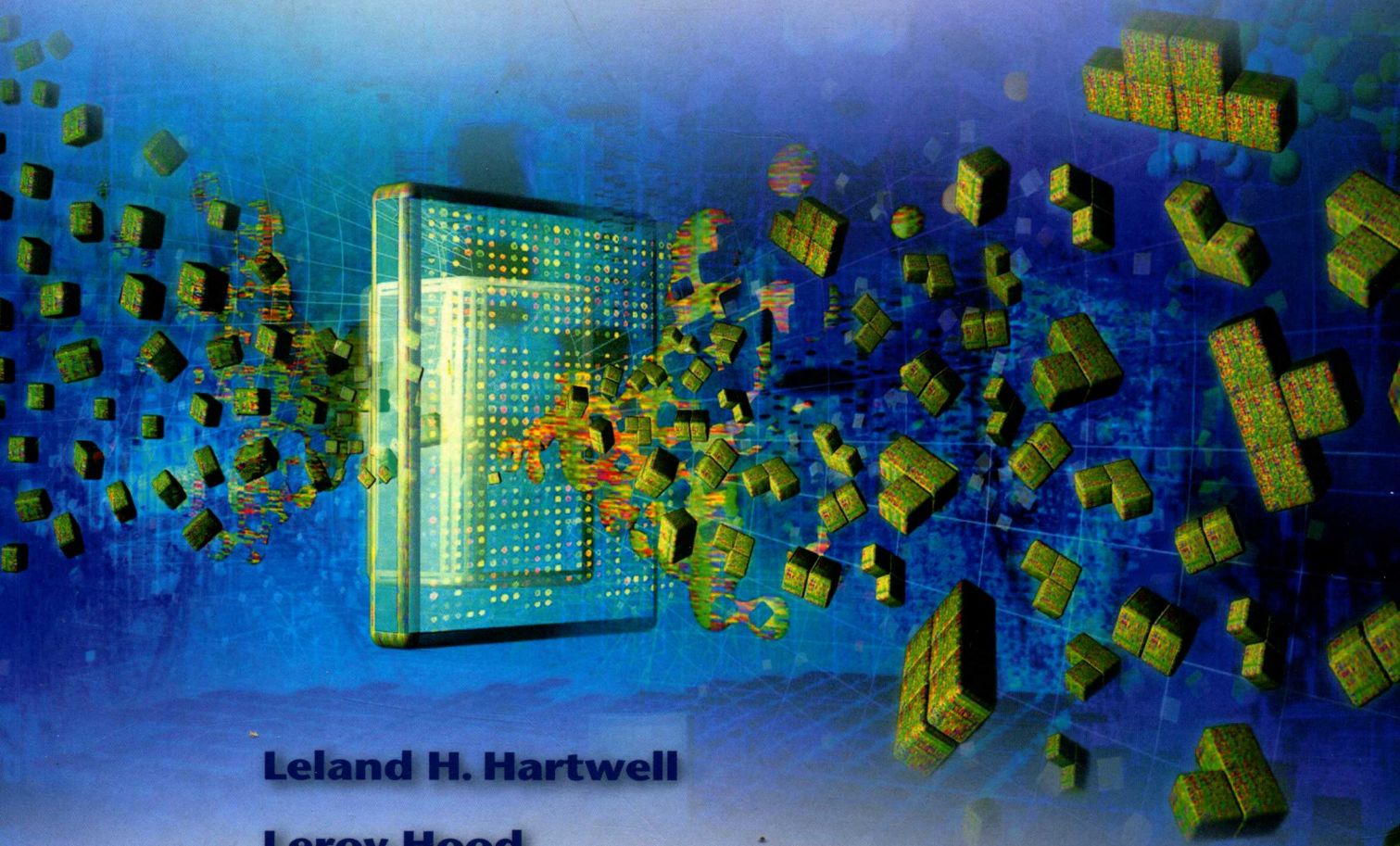
SECOND EDITION

Genetics

FROM GENES TO GENOMES



Leland H. Hartwell

Leroy Hood

Michael L. Goldberg

Ann E. Reynolds

Lee M. Silver

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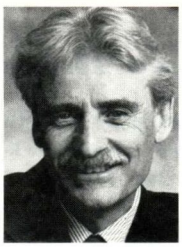
ABOUT THE AUTHORS



Dr. Leland Hartwell received his Ph.D from Massachusetts Institute of Technology. Dr. Hartwell held assistant and associate professorships at the University of California before joining the faculty of the University of Washington, where he continues as a full professor. In 1996, Dr. Hartwell joined the Fred Hutchinson Cancer Research Center as a full member and senior advisor for scientific affairs and was named president and director of the center in July 1997.

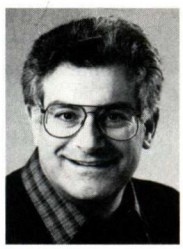
Combining mutants and time-lapse photomicroscopy, Dr. Hartwell identified 32 genes in yeast that regulate the cell cycle with specific defects in spindle pole body duplication and segregation, DNA replication, mitosis, cytokinesis, and budding. He discovered a control point in the cell cycle, Start, where yeast cells exit the cell cycle to mate, arrest after nutritional starvation, and integrate growth with division. He used genetics to define many of the steps in the signal transduction pathway that feed into Start, including the cell surface receptor for mating pheromone. The gene controlling Start, *CDC28,* was cloned in his lab and was the first CDK identified. He investigated the fidelity of chromosome transmission in the cell cycle, discovering that limitation or overexpression of many essential cell-cycle components lead to errors in chromosome transmission. Studies on how cells integrate the repair of DNA damage and cell division led to the discovery of cell-cycle checkpoints and the identification of six genes that control the DNA damage checkpoint.

Dr. Hartwell has received numerous awards and honors in the course of his career. Among them are the Brandeis University Rosenteil Award in 1993, the Sloan-Kettering Cancer Center Katherine Berkan Judd Award, and the Genetics Society of America Medal in 1994. In 1995 he was awarded the MGH Warren Triennial Prize and in 1996 the Columbia University Horwitz Award and the Passano Award. In 1998 Dr. Hartwell received the Albert Lasker Award for medical research. In 2001 he was awarded the Nobel Prize for Physiology or Medicine in recognition of his discovery of key regulators of the cell cycle.

Dr. Lee Hood received an M.D. from the Johns Hopkins Medical School and a Ph.D. in biochemistry from the California Institute of Technology. His research interests include immunology, development, and the development of biological instrumentation (for example, the protein sequenator and the automated fluorescent DNA sequencer). His research played a key role in unraveling the mysteries of antibody diversity.

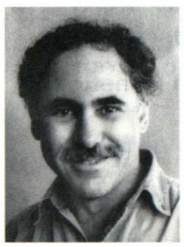
Dr. Hood has taught molecular evolution, immunology, molecular biology, and biochemistry. He was one of the advocates for the Human Genome Project and directed one of the federal genome centers that sequenced the human genome. Dr. Hood is currently the president and director (and cofounder) of the cross-disciplinary Institute for Systems Biology in Seattle, Washington.

Dr. Hood has received a variety of awards including the Albert Lasker Award for Medical Research (1987), Dickson Price Award (1987), Cefas Award for Biochemistry (1989), and Distinguished Service Award from the National Association of Teachers (1998). He is the 2002 recipient of the Kyoto Prize in Advanced Biotechnology. Dr. Hood received this award in recognition of his pioneering work in developing the protein and DNA synthesizers and sequencers that provide the technical foundation of modern biology. He is deeply involved in K–12 science education. His hobbies include running, mountain climbing, and reading.



Dr. Michael Goldberg is a professor at Cornell University, where he teaches introductory genetics. He was an undergraduate at Yale University and received his Ph.D. in biochemistry from Stanford University. Dr. Goldberg performed postdoctoral research at the Biozentrum of the University of Basel (Switzerland) and at Harvard University, and he received an NIH Fogarty Senior International Fellowship for study at Imperial College (England) and at the University of Rome (Italy). His current research uses the tools of *Drosophila* genetics to investigate the mechanisms that ensure proper chromosome segregation during mitosis and meiosis.

Dr. Ann Reynolds is an educator and author. She began teaching genetics and biology in 1990. An affiliate faculty member of the Genetics Department at the University of Washington, her research has included studies of gene regulation in *E. coli,* chromosome structure and DNA replication in yeast, and chloroplast gene expression in marine algae. She is a graduate of Mount Holyoke College and received her Ph.D. from Tufts University. Dr. Reynolds was a postdoctoral research fellow with the Harvard University Department of Molecular Biology. She was also an author and producer of the laserdisc and CD-ROM *Genetics: Fundamentals to Frontiers.*



Dr. Lee M. Silver received his Ph.D in biophysics from Harvard University. He was a research fellow in genetics at the Sloan-Kettering Institute for Cancer Research and a senior scientist at Cold Spring Harbor Laboratory before joining the faculty of Princeton University. Currently, Dr. Silver is a professor of molecular biology and public affairs at Princeton University, with appointments in Princeton's Department of Molecular Biology, the Woodrow Wilson School of Public and International Affairs, the Program in Science, Technology, and Environmental Policy, and the Office of Population Research. During his career in genetic research, Dr. Silver made intensive use of the mouse as a model organism for the study of mammalian reproduction, development, evolution, and behavior. His current research lies at the interface of biotechnology and society and focuses on the political, legal, religious, and ethical issues raised by advances in human genetics and stem cell research. These issues are discussed in Dr. Silver's book *Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family,* which has been published in 15 languages. Dr. Silver is also the author of *Mouse Genetics: Concepts and Applications.*

In 1993, Dr. Silver was elected a Fellow of the American Association for the Advancement of Science (AAAS). In 1995, he received a MERIT Award from the National Institutes of Health. Dr. Silver has been elected to the governing boards of the Genetics Society of America and the International Mammalian Genome Society. He was also a member of the New Jersey Bioethics Commission Task Force formed to recommend reproductive policy for the New Jersey state legislature.

Ruth C. Veres is a science writer and editor with 30 years of experience in textbook publishing. She received her B.A. from Swarthmore College, obtained M.A. degrees from Columbia University in New York and Tufts University, and taught writing and languages at the University of California at Berkeley.

In addition to developing and editing more than 30 texts in the fields of political science, economics, psychology, nutrition, chemistry, and biology, Veres has coauthored a book on the immune system and an introductory biology text. She is currently working on a book with Dr. Lee Hood that looks at biology as an information science.

Contributors

Genetics research tends to proceed down highly specialized paths. A number of experts in specific areas generously provided information in their areas of expertise. We thank them for their contributions to this edition of our text.

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A Note from the Authors

Completion of a rough draft of the human genome in February of 2001 changed the way we think about genetics and biology. The ability to sequence a genome quickly and efficiently has generated enormous amounts of genetic data and opened up avenues of inquiry that were previously closed to scientific investigation. The explosion of information and the potential for deciphering it with recently developed technologies and computational tools, in conjunction with hypothesis-driven experiments, make it possible to carry out large-scale molecular analyses of the complex systems that compose plants, animals, and fungi. Today's students are poised on the brink of an astonishing scientific frontier whose main features we hope to convey in this new edition of *Genetics: From Genes to Genomes.*

It was during the twentieth century that genetics emerged as a central discipline in biology. In 1900 Gregor Mendel's laws of heredity were rediscovered; in the 1950s, James Watson and Francis Crick revealed the structure of DNA, the molecule of heredity, as a double helix that encodes digital information; and in the 1990s, the Human Genome Project provided a nearly complete sequence of the human genome. For much of the century, the study of genetics focused on the identification of individual genes and their function. In the last decade of the century, however, another idea gained currency—the concept that no gene acts alone; instead it is through complex molecular interactions within and among vast networks of genes, proteins, and other molecules that organisms ultimately live and die. By the end of the twentieth century tools for analyzing genes, genomes, and their expression within these complex biological systems had progressed beyond the most optimistic expectations.

Our Focus—An Integrated Approach

Genetics: From Genes to Genomes reflects this new perspective. The book presents a new approach to an undergraduate course in genetics. It represents the way we, the authors, currently view the molecular basis of life. We integrate:

- **Formal genetics:** the rules by which genes are transmitted.
- **Molecular genetics:** the structure of DNA and how it directs the structure of proteins.
- **Genomics and information science:** the new technologies that allow a comprehensive analysis of the entire gene set and its expression in an organism.
- **Human genetics:** how genes contribute to health and disease.
- **The unity of life-forms:** the synthesis of information from many different organisms into coherent models that explain many biological systems.
- **Molecular evolution:** the molecular mechanisms by which biological systems and whole organisms have evolved and diverged.

The strength of this integrated approach is that students who complete the book will have a strong command of genetics as it is practiced today by academic and corporate researchers. These scientists are rapidly changing our understanding of living organisms, including ourselves; increasing our ability to prevent, treat, and diagnose disease and to engineer new life-forms for food and medical uses; and, ultimately, creating the ability to replace or correct detrimental genes.

The Genetic Way of Thinking

To encourage a genetic way of thinking, we begin the book with a presentation of Mendelian principles and the chromosomal basis of inheritance. From the outset, however, the integration of Mendelian genetics with fundamental molecular mechanisms is central to our approach. Chapter 1 presents the foundation of this integration. In Chapter 2, we tie Mendel's studies of pea-shape inheritance to the action of an enzyme that determines whether a pea is round or wrinkled. In the same chapter, we point to the relatedness of patterns of heredity in all organisms by using Mendelian principles to look at heredity in humans. Starting in Chapter 6, we focus on the physical characteristics of DNA, the implications and uses of mutations, and how the double helix structure of DNA encodes, copies, and transmits biological information. Beginning in Chapter 9 we look at modern genetic techniques, including such biotechnology tools as gene cloning, hybridization, PCR, and microarrays, exploring how researchers use them to reveal the modular construction and genetic relatedness of genomes. We then show how the complete genome sequences of humans and model organisms provide insights into the architecture and evolution of genomes; how modular genomic construction has contributed to the relatively rapid evolution of life and helped generate the enormous diversity of life-forms we see around us. References at the end of the book contain detailed discussions of model organisms, which clarify that their use in the study of human biology is possible only because of the genetic relatedness of all organisms. Throughout our book, we present the scientific reasoning of some of the ingenious researchers who have carried out genetic analysis, from Mendel, to Watson and Crick, to the collaborators on the Human Genome Project.

Student-Friendly Features

We have taken great pains to help the student make the leap to this deeper level of understanding. Numerous features of this book were developed with that goal in mind.

- ***One Voice*** The role of our science writer, Ruth Veres, is to create one voice for our author team. With 30 years experience in life science textbook publishing, Ms. Veres is uniquely suited to this task. By working closely with everyone on the team, she has created the friendly, engaging reading style that helps students master the concepts throughout this book. This team approach provides the student with the focus and continuity required to make the book successful in the classroom.
- ***Visualizing Genetics*** The highly specialized art program developed for this book integrates photos and line art in a manner that provides the most engaging visual presentation of genetics available. Our Feature Figure illustrations break down complex processes into step-by-step illustrations that lead to greater student understanding. All illustrations are rendered with a consistent color theme—for example, all presentations of phosphate groups are the same color, as are all presentations of mRNA.
- ***Problem Solving*** Developing strong problem-solving skills is vital for every genetics student. The authors have carefully created problem sets at the end of each chapter that allow students to improve upon their problem-solving ability.
  - **Social and Ethical Issues** questions require critical thinking analysis of the scientific issues that impact our society.
  - **Solved Problems** provide insight into the step-by-step process of problem solving.
  - **Review Problems** offer a variety of levels of questions that develop excellent problem-solving skills.
- ***Accessability*** Our intention is to bring cutting-edge content to the student level. A number of more complex illustrations have been revised and segmented to help the student follow the process. Legends have been streamlined to highlight only the most important ideas, and throughout the book, topics have been revised to focus on the most critical information.

New to the Second Edition

- **"Genetics: The Study of Biological Information:"** A completely new Chapter 1 presents the book's approach to the study of genetics and genomics. We describe the new tools and concepts (such as the use of DNA chips or microarrays) used to examine complex biological systems or develop individual health profiles. The chapter also raises several social concerns in the context of future challenges, for example, aging and the treatment of older people, and the use or abuse of genetic information.
- **Part III "Genomes"** (Chapters 9, 10, 11), focuses on the dramatic explosion of information that is the result of the completion of the Human Genome Project. It also presents the latest ways to carry out genomic research on a wide variety of organisms. These chapters are completely restructured and revised.

  "Deconstructing the Genome: DNA at High Resolution" (Chapter 9) covers the topics *fragmenting complex genomes for analysis, cloning fragments of DNA, PCR, DNA sequence analysis,* with a comprehensive example, and *understanding the genes for hemoglobin.*

  "Reconstructing the Genome Through Genetic and Molecular Analysis" (Chapter 10) covers the topics *analyses of genomes; high-density linkage maps; the integration of linkage, physical, and sequence maps; major insights from the human and model organism genome sequences; high-throughput genomic and proteomic platforms permit global analyses of gene products; systems biology;* and applications in *predictive/preventative medicine.*

  "The Direct Detection of Genotype Distinguishes Individual Genomes" (Chapter 11) includes topics such as *DNA variation, detecting DNA genotypes of different polymorphisms, positional cloning, genetic dissection of complex traits,* and *haplotype association studies for high-resolution mapping in humans.*
- **"Using Genetics to Study Development"—An entirely new chapter.** Chapter 19 covers the general principles of development with examples from the most commonly used model organisms, as well as humans. The chapter unfolds in an orderly, concept-based manner and again reflects how the information gained by the Human Genome Project has changed the way geneticists think.
- **Updates** throughout make this the most current and modern book available. Every chapter reflects the updated information generated by the breakthroughs of the past few years.
- **Expanded and refined problem sets.** The problem sets at the end of each chapter have been reviewed, revised, and expanded to provide an even stronger opportunity for students to develop their problem-solving skills.

A Word About the Portraits of Model Organisms

Five **Genetic Portraits** are included in the reference section at the back of the book, each one profiling a different model organism whose study has greatly contributed to genetic research. The

five selected were the ones chosen as the focus of the Human Genome Project. They are:

Saccharomyces cerevisiae: Genetic Portrait of Yeast
Arabidopsis thaliana: Genetic Portrait of a Model Plant
Caenorhabditis elegans: Genetic Portrait of a Simple Multicellular Animal
Drosophila melanogaster: Genetic Portrait of the Fruit Fly
Mus musculus: Genetic Portrait of the House Mouse

We anticipate that instructors will choose to cover one or two portrait references during the semester. Students may then use the specifics of the selected model organism to build an understanding of the principles and applications discussed in the book. The unique genetic manipulations and properties of each of the models make them important for addressing different biological questions using genetic analysis. In the portraits, we explain how biologists learned that the evolutionary relatedness of all organisms permits the extrapolation from a model to the analysis of other living forms. The portraits should thus help students understand how insights from one model organism can suggest general principles applicable to other organisms, including humans.

Media and Supplements

For the Instructor

- **Digital Content Manager CD-ROM.** Instructor resource CD-ROM containing easy-to-use JPEG files for all line art, tables, and most photos from the book; as well as animations, live art files, lecture outlines, and PowerPoint presentations for each chapter. See page xxvi for further details!
- **Instructor Testing and Resource CD-ROM.** 2000 questions available on a cross-platform CD-ROM, this test bank uses Brownstone Diploma testing software to quickly create customized exams. The user-friendly program allows instructors to search for questions by topic, format, or difficulty level; edit existing questions or add new ones; and scramble questions and answer keys for multiple versions of the same test.
- **Transparencies.** 150 four-color illustrations from the book will be available to adopters as well as 50 key illustrations with labels removed (for use in testing).

For the Student

- **Solutions Manual/Study Guide.** Extensively revised by Dr. Debra Nero of Cornell University, presents the solutions to the end-of-chapter problems and questions along with the step-by-step logic of each solution.
- ***Genetics: From Genes to Genomes* CD-ROM.** Developed with the content of this book, covers the most challenging concepts in the introductory genetics course. The CD presents animations of basic genetic processes and interactive exercises and simulations involving fundamental principles. Additional quizzing options allow students to self-test and identify those areas needing additional study. Glossary definitions can be reached via hot links. A correlation guide linking book topics to the related CD material is included on the CD.

Web-Based Material

Online Learning Center

The *Genetics: From Genes to Genomes* Online Learning Center (OLC) offers access to a wide array of premium content to fortify the learning and teaching experience. This web site may be reached at **www.mhhe.com/hartwell2** and provides additional materials for both students and instructors.

Student Center
The Student Center of the OLC features quizzes, study tools, web links library, and problem-solving exercises to help the student master genetics.

Instructor Center
Instructor's Manual and Integration Guide. Prepared by John Kemner of the University of Washington, this manual provides a guide to integrating all the available resources for *Genetics: From Genes to Genomes* into your course presentations.
PageOut. McGraw-Hill's exclusive tool for creating your own web site for your genetics course. It requires no knowledge of coding and is hosted by McGraw-Hill.
Course Management Systems. OLC content compatible with online course management systems like WebCT and Blackboard makes putting together your course web site easy. Contact your local McGraw-Hill sales representative for details.

Acknowledgments

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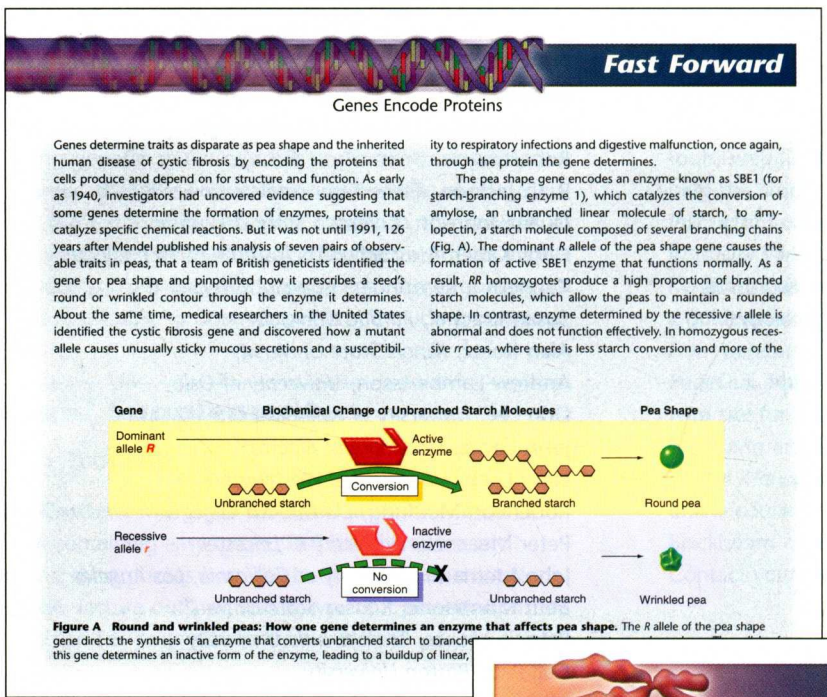
We would also like to thank the highly skilled publishing professionals who firmly guided the development of the second edition of *Genetics: From Genes to Genomes:* Jim Smith for his continuing support and understanding of the project; Jean Fornango for her almost daily communications, outstanding organizational skills, and spirited good humor; and Peggy Selle and her production team for their careful attention to details. We appreciate their input.

Integrating Genetic Concepts

Genetics: From Genes to Genomes **takes an integrated approach in its presentation of genetics, thereby giving students a strong command of genetics as it is practiced today by academic and corporate researchers. Principles are related throughout the text in examples, essays, case histories, and Connections sections to make sure students fully understand the relationships between topics.**



Fast Forward

Genes Encode Proteins

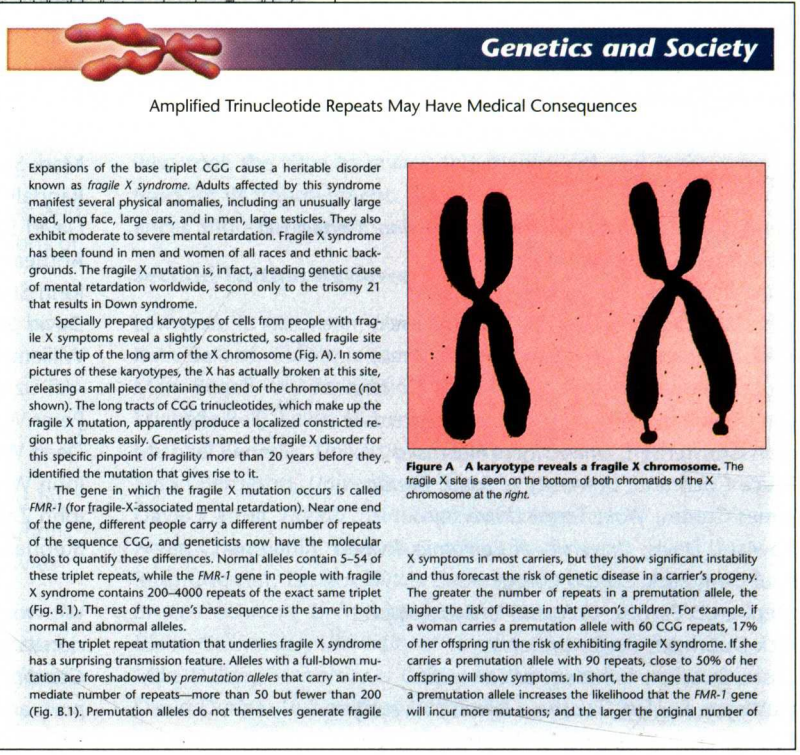
Genes determine traits as disparate as pea shape and the inherited human disease of cystic fibrosis by encoding the proteins that cells produce and depend on for structure and function. As early as 1940, investigators had uncovered evidence suggesting that some genes determine the formation of enzymes, proteins that catalyze specific chemical reactions. But it was not until 1991, 126 years after Mendel published his analysis of seven pairs of observable traits in peas, that a team of British geneticists identified the gene for pea shape and pinpointed how it prescribes a seed's round or wrinkled contour through the enzyme it determines. About the same time, medical researchers in the United States identified the cystic fibrosis gene and discovered how a mutant allele causes unusually sticky mucous secretions and a susceptibility to respiratory infections and digestive malfunction, once again, through the protein the gene determines.

The pea shape gene encodes an enzyme known as SBE1 (for starch-branching enzyme 1), which catalyzes the conversion of amylose, an unbranched linear molecule of starch, to amylopectin, a starch molecule composed of several branching chains (Fig. A). The dominant *R* allele of the pea shape gene causes the formation of active SBE1 enzyme that functions normally. As a result, *RR* homozygotes produce a high proportion of branched starch molecules, which allow the peas to maintain a rounded shape. In contrast, enzyme determined by the recessive *r* allele is abnormal and does not function effectively. In homozygous recessive *rr* peas, where there is less starch conversion and more of the

Figure A Round and wrinkled peas: How one gene determines an enzyme that affects pea shape. The *R* allele of the pea shape gene directs the synthesis of an enzyme that converts unbranched starch to branche… this gene determines an inactive form of the enzyme, leading to a buildup of linear,

Fast Forward Essays

This feature is one of the methods used to integrate the Mendelian principles presented early in the book with the molecular principles that will follow.



Genetics and Society

Amplified Trinucleotide Repeats May Have Medical Consequences

Expansions of the base triplet CGG cause a heritable disorder known as *fragile X syndrome*. Adults affected by this syndrome manifest several physical anomalies, including an unusually large head, long face, large ears, and in men, large testicles. They also exhibit moderate to severe mental retardation. Fragile X syndrome has been found in men and women of all races and ethnic backgrounds. The fragile X mutation is, in fact, a leading genetic cause of mental retardation worldwide, second only to the trisomy 21 that results in Down syndrome.

Specially prepared karyotypes of cells from people with fragile X symptoms reveal a slightly constricted, so-called fragile site near the tip of the long arm of the X chromosome (Fig. A). In some pictures of these karyotypes, the X has actually broken at this site, releasing a small piece containing the end of the chromosome (not shown). The long tracts of CGG trinucleotides, which make up the fragile X mutation, apparently produce a localized constricted region that breaks easily. Geneticists named the fragile X disorder for this specific pinpoint of fragility more than 20 years before they identified the mutation that gives rise to it.

The gene in which the fragile X mutation occurs is called *FMR-1* (for fragile-X-associated mental retardation). Near one end of the gene, different people carry a different number of repeats of the sequence CGG, and geneticists now have the molecular tools to quantify these differences. Normal alleles contain 5–54 of these triplet repeats, while the *FMR-1* gene in people with fragile X syndrome contains 200–4000 repeats of the exact same triplet (Fig. B.1). The rest of the gene's base sequence is the same in both normal and abnormal alleles.

The triplet repeat mutation that underlies fragile X syndrome has a surprising transmission feature. Alleles with a full-blown mutation are foreshadowed by *premutation alleles* that carry an intermediate number of repeats—more than 50 but fewer than 200 (Fig. B.1). Premutation alleles do not themselves generate fragile

Figure A A karyotype reveals a fragile X chromosome. The fragile X site is seen on the bottom of both chromatids of the X chromosome at the *right*.

X symptoms in most carriers, but they show significant instability and thus forecast the risk of genetic disease in a carrier's progeny. The greater the number of repeats in a premutation allele, the higher the risk of disease in that person's children. For example, if a woman carries a premutation allele with 60 CGG repeats, 17% of her offspring run the risk of exhibiting fragile X syndrome. If she carries a premutation allele with 90 repeats, close to 50% of her offspring will show symptoms. In short, the change that produces a premutation allele increases the likelihood that the *FMR-1* gene will incur more mutations; and the larger the original number of

Genetics and Society Essays

Dramatic essays explore the social and ethical issues created by the multiple applications of modern genetic research.

Comprehensive Examples

Comprehensive Examples are extensive case histories or research synopses that, through text and art, summarize the main points in the preceding section or chapter and show how they relate to each other.

How Gene Mutations Affect Light-Receiving Proteins and Vision: A Comprehensive Example

Researchers first described anomalies of color perception in humans close to 200 years ago. Since that time, they have discovered a large number of mutations that modify human vision. By examining the phenotype associated with each mutation and then looking directly at the DNA alterations inherited with the mutation, they have learned a great deal about the genes influencing human visual perception and the function of the proteins they encode.

Several attributes of human subjects facilitate the experi- of vision. First, people can recognize and de- in the way they see, from trivial differences in ed looks like, to not seeing any difference be- reen, to not seeing any color at all. Second, the d science of psychophysics provides sensitive, s for accurately defining and comparing pheno- nostic test, for example, is based on the fact that each color as a mixture of three different wave- —red, green, and blue—and ca blue light of different intensities fourth wavelength such as yell loes not combine to form the fo at way to the eye. A person wit ll select a well-defined propo atch a particular yellow, but a p en will permit any proportion o e same match. Finally, since inh n the visual system rarely affect fecundity or lo ern human societies, mutations generating m alleles that change visual perception remain over time.

Figure 7.30 How the world looks to a person with tritanopia. Compare with Fig. 4.22 on p. 103.

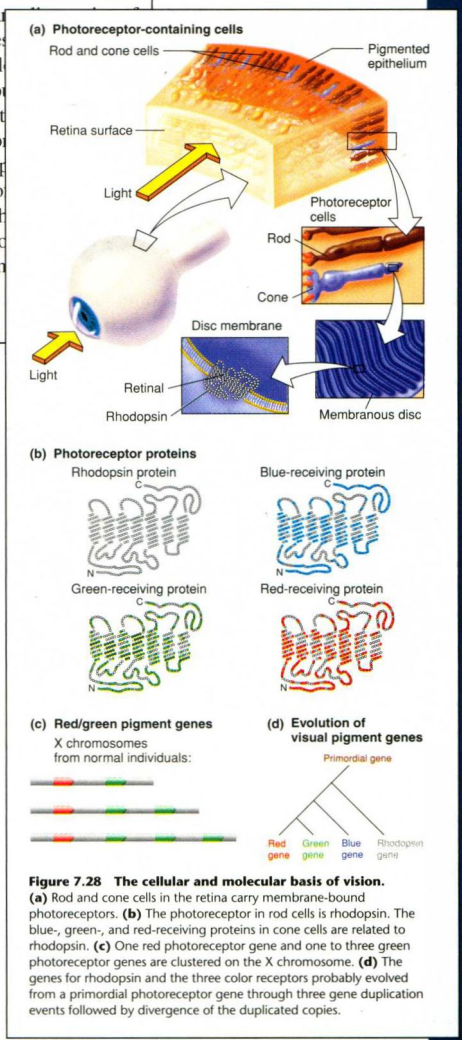


Figure 7.28 The cellular and molecular basis of vision. **(a)** Rod and cone cells in the retina carry membrane-bound photoreceptors. **(b)** The photoreceptor in rod cells is rhodopsin. The blue-, green-, and red-receiving proteins in cone cells are related to rhodopsin. **(c)** One red photoreceptor gene and one to three green photoreceptor genes are clustered on the X chromosome. **(d)** The genes for rhodopsin and the three color receptors probably evolved from a primordial photoreceptor gene through three gene duplication events followed by divergence of the duplicated copies.

Connections

Each chapter closes with a Connections section that serves as a bridge between the topics in the just-completed chapter and those in the upcoming chapter or chapters.

CONNECTIONS

The Watson-Crick model for the structure of DNA, the single most important biological discovery of the twentieth century, clarified how the genetic material fulfills its primary function of carrying information: Each long, linear or circular molecule carries one of a vast number of potential arrangements of the four nucleotide building blocks (A, T, G, and C). The model also suggested how base complementarity could provide a mechanism for both accurate replication and changes in sequence combinations that arise from recombination events.

Unlike its ability to carry information, DNA's capacities for replication and recombination are not solely properties of the DNA molecule itself. Rather they depend on the cell's complex enzymatic machinery. But even though they rely on the complicated orchestration of many different proteins acting on the DNA, replication and recombination both occur with extremely high fidelity—normally not a single base pair is gained or lost. Rarely, however, errors do occur, providing the genetic basis of evolution. While most errors are detrimental to the organism, a very small percentage produce dramatic changes in phenotype without killing the individual. For example, although most parts of the X and Y chromosomes are not similar enough to recombine, occasionally an "illegitimate" recombination does occur. Depending on the site of crossing-over, such illegitimate recombination may give rise to an XY individual who is female or an XX individual who is male (Fig. 6.23). The explanation is as follows. In the first six weeks of development, a human embryo has the potential to become either male or female, but in the critical seventh week, information from a small segment of DNA—the sex-determining region of the Y chromosome containing the *SRY* gene—determines the embryo's sex. An illegitimate recombination with an X chromosome containing *SRY* produces XX individuals that develop as males.

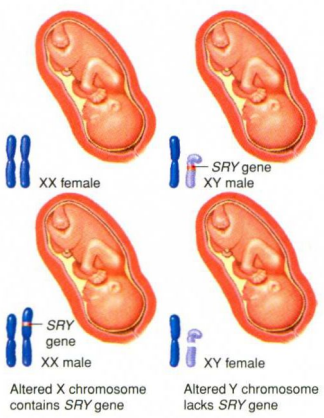


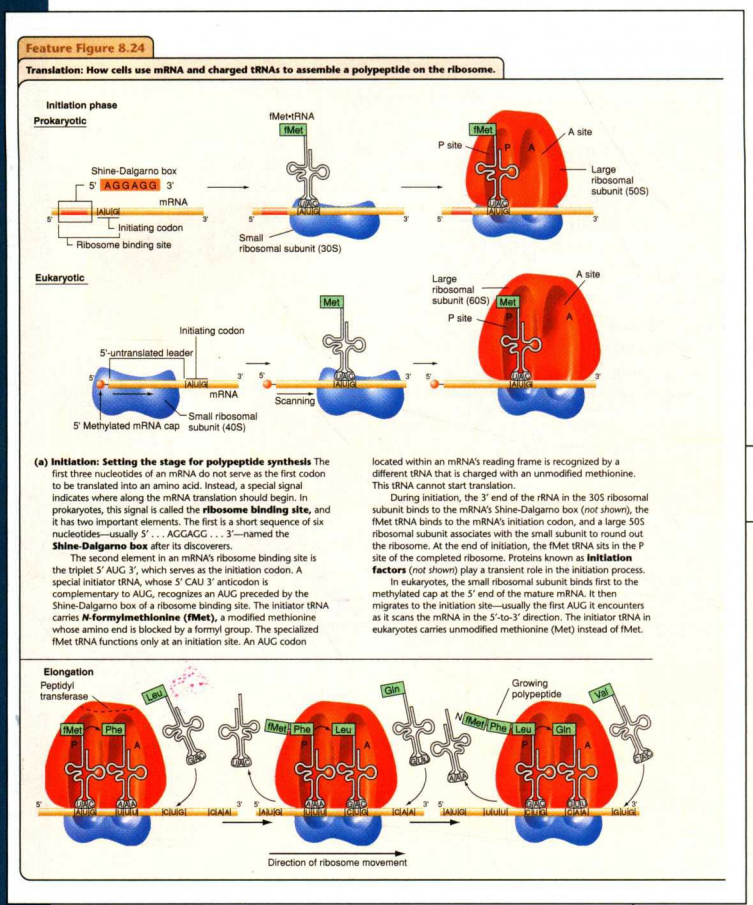
Figure 6.23 Illegitimate recombination may produce an XY female or an XX male. The *SRY* gene, normally located on the Y chromosome, dictates male development; in the absence of *SRY*, an embryo develops as a female. Rare, illegitimate recombination between the X and Y chromosome can create a Y chromosome without *SRY* and an X chromosome with *SRY*. Fertilization with gametes containing these unusual chromosomes will produce XY females or XX males.

Visualizing Genetics

Full-color illustrations and photographs bring the printed word to life. These visual reinforcements support and further clarify the topics discussed throughout the text.

Feature Figures

Special multipage spreads integrate line art, photos, and text to summarize in detail important genetic concepts.



Feature Figure 8.24

Translation: How cells use mRNA and charged tRNAs to assemble a polypeptide on the ribosome.

Initiation phase

Prokaryotic

fMet-tRNA

Shine-Dalgarno box

5′ AGGAGG 3′

mRNA

Initiating codon

Ribosome binding site

Small ribosomal subunit (30S)

P site

A site

Large ribosomal subunit (50S)

Eukaryotic

Initiating codon

5′-untranslated leader

mRNA

Scanning

5′ Methylated mRNA cap

Small ribosomal subunit (40S)

Large ribosomal subunit (60S)

(a) Initiation: Setting the stage for polypeptide synthesis The first three nucleotides of an mRNA do not serve as the first codon to be translated into an amino acid. Instead, a special signal indicates where along the mRNA translation should begin. In prokaryotes, this signal is called the **ribosome binding site,** and it has two important elements. The first is a short sequence of six nucleotides—usually 5′ . . . AGGAGG . . . 3′—named the **Shine-Dalgarno box** after its discoverers.

The second element in an mRNA's ribosome binding site is the triplet 5′ AUG 3′, which serves as the initiation codon. A special initiator tRNA, whose 5′ CAU 3′ anticodon is complementary to AUG, recognizes an AUG preceded by the Shine-Dalgarno box of a ribosome binding site. The initiator tRNA carries **N-formylmethionine (fMet),** a modified methionine whose amino end is blocked by a formyl group. The specialized fMet tRNA functions only at an initiation site. An AUG codon located within an mRNA's reading frame is recognized by a different tRNA that is charged with an unmodified methionine. This tRNA cannot start translation.

During initiation, the 3′ end of the rRNA in the 30S ribosomal subunit binds to the mRNA's Shine-Dalgarno box (*not shown*), the fMet tRNA binds to the mRNA's initiation codon, and a large 50S ribosomal subunit associates with the small subunit to round out the ribosome. At the end of initiation, the fMet tRNA sits in the P site of the completed ribosome. Proteins known as **initiation factors** (*not shown*) play a transient role in the initiation process.

In eukaryotes, the small ribosomal subunit binds first to the methylated cap at the 5′ end of the mature mRNA. It then migrates to the initiation site—usually the first AUG it encounters as it scans the mRNA in the 5′-to-3′ direction. The initiator tRNA in eukaryotes carries unmodified methionine (Met) instead of fMet.

Elongation

Peptidyl transferase

Growing polypeptide

Direction of ribosome movement

(b) Elongation: The addition of amino acids to a growing polypeptide With the mRNA bound to the complete two-subunit ribosome and with the initiating tRNA in the P site, the elongation of the polypeptide begins. A group of proteins known as **elongation factors** (*not shown*) usher the appropriate tRNA into the A site of the ribosome. The anticodon of this charged tRNA must recognize the next codon in the mRNA. The ribosome holds the initiating tRNA at its P site and the second tRNA at its A site so that peptidyl transferase can catalyze formation of a peptide bond between the amino acids carried by the two tRNAs. This bond-forming reaction connects the fMet at the P site to the amino acid carried by the tRNA at the A site; it also disconnects fMet from the initiating tRNA. As a result, the tRNA at the A site now carries two amino acids. The N terminus of this dipeptide is fMet; the C terminus is the second amino acid, whose carboxyl group remains covalently linked to its tRNA.

Once formation of the first peptide bond causes the initiating tRNA in the P site to release its amino acid, the ribosome moves, exposing the next mRNA codon. Like the first steps of elongation, the ribosome's movement requires the help of elongation factors and an input of energy. As the ribosome moves, the initiating tRNA in the P site, which no longer carries an amino acid, dissociates from the ribosome, and the other tRNA carrying the dipeptide shifts from the A site to the P site.

The empty A site now receives another tRNA, whose identity is determined by the next codon in the mRNA. Peptidyl transferase then catalyzes formation of a second peptide bond, generating a chain of three amino acids. This tripeptide is connected at its C terminus to the tRNA currently in the A site; the fMet at its N terminus hangs free. With each subsequent round of ribosome movement and peptide bond formation, the peptide chain grows one amino acid longer.

Because the elongation machinery adds amino acids to the C terminus of the lengthening polypeptide, polypeptide synthesis proceeds from the N terminus to the C terminus. As a result, fMet in prokaryotes (Met in eukaryotes), the first amino acid in the growing chain, will be the N-terminal amino acid of all finished polypeptides that do not undergo protein processing (see main text). Moreover, because the nucleotide triplets encoding amino acids progressively closer to a polypeptide's C terminus are found successively farther from the 5′ end of the mRNA, the ribosome must move along the mRNA in the 5′-to-3′ direction.

The movement of ribosomes along the mRNA has important implications. Once a ribosome has moved far enough away from the mRNA's ribosome binding site, that site becomes accessible to other ribosomes. In fact, several ribosomes can work on the same mRNA at one time. A complex of several ribosomes translating from the same mRNA is called a **polyribosome.** This complex allows the simultaneous synthesis of many copies of a polypeptide from a single mRNA.

Polyribosome

Ribosome

Growing polypeptide

RNA subunits released

mRNA

AUG

Stop

5′ – 3′ direction of ribosome movement

Released polypeptide

Termination

Polypeptide

Release factor

Termination codon

Polypeptide product

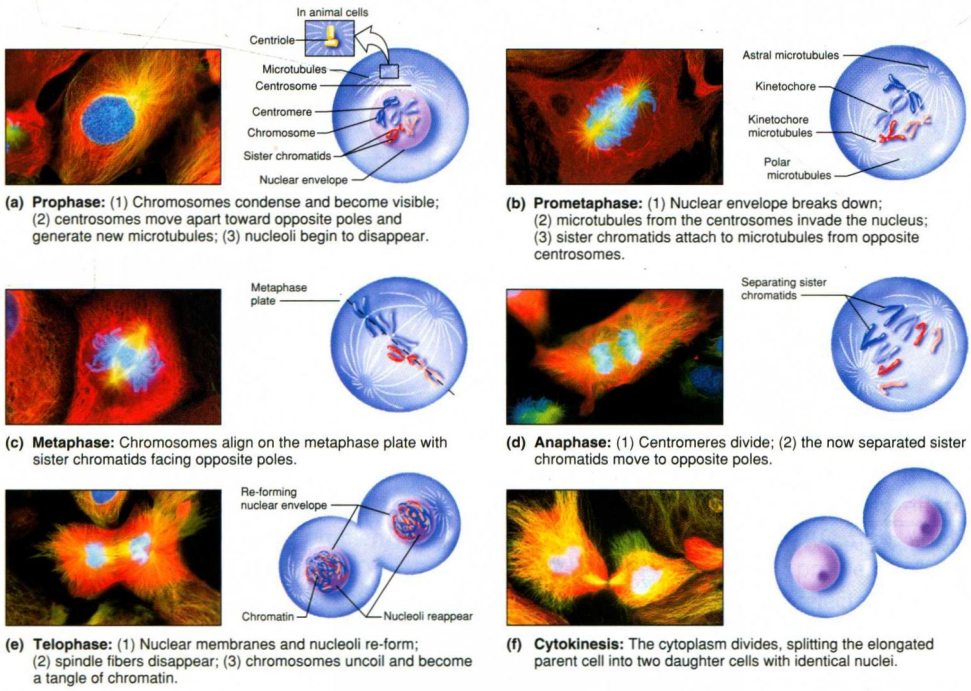
tRNA

Large subunit

Release factor

Small subunit

(c) Termination: The ribosome releases the completed polypeptide No normal tRNAs carry anticodons complementary to the three nonsense (stop) codons UAG, UAA, and UGA. Thus, when movement of the ribosome brings a nonsense codon into the ribosome's A site, no tRNAs can bind to that codon through complementary base pairing. Instead, proteins called **release factors** recognize the termination codons and bring polypeptide synthesis to a halt. During termination, three events must occur: the tRNA specifying the C-terminal amino acid releases the completed polypeptide, the same tRNA as well as the mRNA separate from the ribosome, and the ribosome dissociates into its large and small subunits.



(a) Prophase: (1) Chromosomes condense and become visible; (2) centrosomes move apart toward opposite poles and generate new microtubules; (3) nucleoli begin to disappear.

(b) Prometaphase: (1) Nuclear envelope breaks down; (2) microtubules from the centrosomes invade the nucleus; (3) sister chromatids attach to microtubules from opposite centrosomes.

(c) Metaphase: Chromosomes align on the metaphase plate with sister chromatids facing opposite poles.

(d) Anaphase: (1) Centromeres divide; (2) the now separated sister chromatids move to opposite poles.

(e) Telophase: (1) Nuclear membranes and nucleoli re-form; (2) spindle fibers disappear; (3) chromosomes uncoil and become a tangle of chromatin.

(f) Cytokinesis: The cytoplasm divides, splitting the elongated parent cell into two daughter cells with identical nuclei.

Figure 4.8 Mitosis maintains the chromosome number of the parent cell nucleus in the two daughter nuclei. In the photomicrographs of newt lung cells, chromosomes are stained *blue* and microtubules appear either *green* or *yellow*. The artist's sketches illustrate the stages of mitosis in the nematode *Ascaris*, where $2n = 4$.

Process Figures

Step-by-step descriptions allow the student to walk through a compact summary of important details.

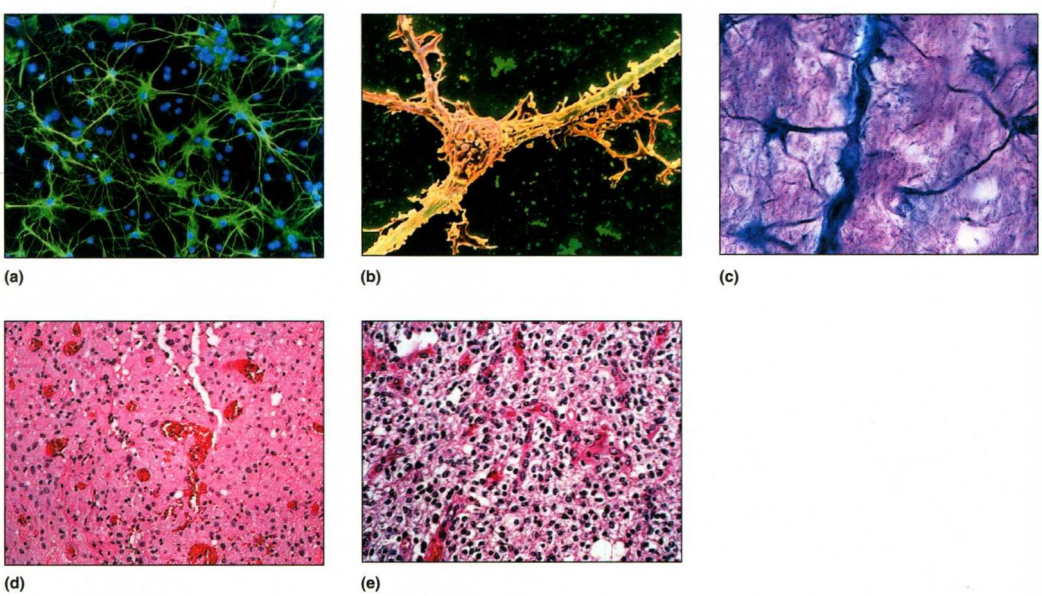


Figure 18.25 Mutations in three types of glial cells cause brain cancer. (a) Astrocyte brain cells from the cortex of a mammalian brain. **(b)** Oligodendrocyte cell (*orange structure in the middle*) attaching to an axon nerve cell at the start of myelination. **(c)** Ependymal cell. The astrocyte cells in (a) mutate to form astrocytomas (low-grade) shown in **(d).** The oligodendroglioma shown in **(e)** is the result of mutated oligodendrocyte cells (b). The tumors resulting from mutated ependymal cells are extremely rare and are not shown here.

Micrographs

Stunning micrographs bring the genetics world to life.

Visualizing Genetics

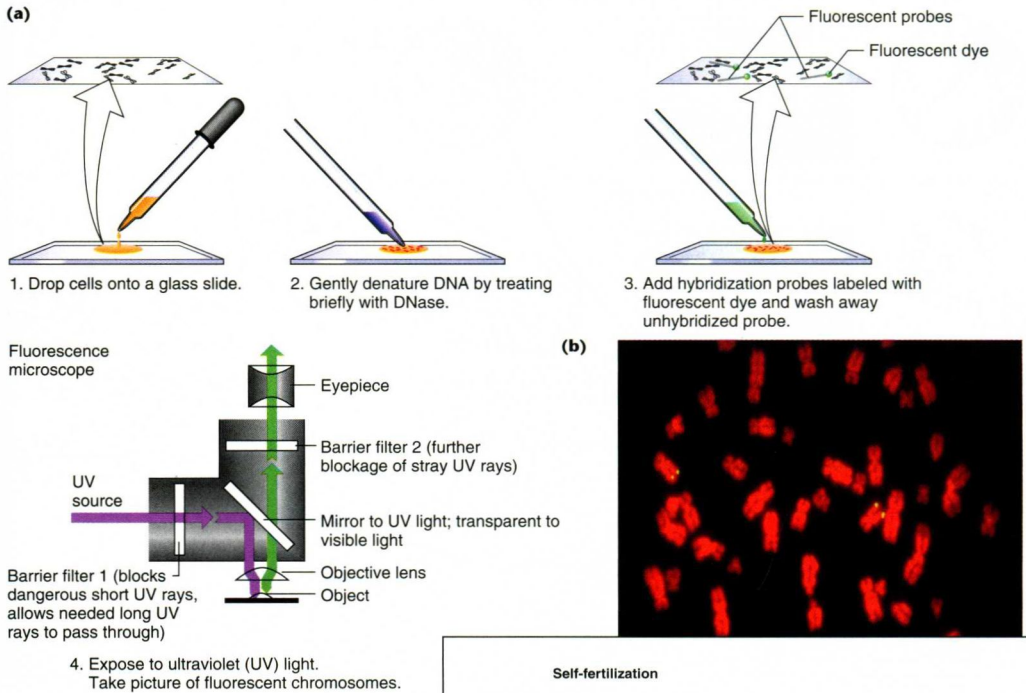


Figure 10.6 The FISH protocol. (a) The technique. (1) slide. The force of the droplet hitting the slide causes the cel and gently denature the DNA within them such that the ove up at numerous points. (3) Label a DNA probe with a fluore hybridization to occur, and wash away unhybridized probe. on the chromosomes. The UV light causes the bound probe through the eyepiece and photograph it. **(b)** A fluorescence shows the microtubular structure.

Experiment and Technique Figures

Illustrations of performed experiments and genetic analysis techniques highlight how scientific concepts and processes are developed.

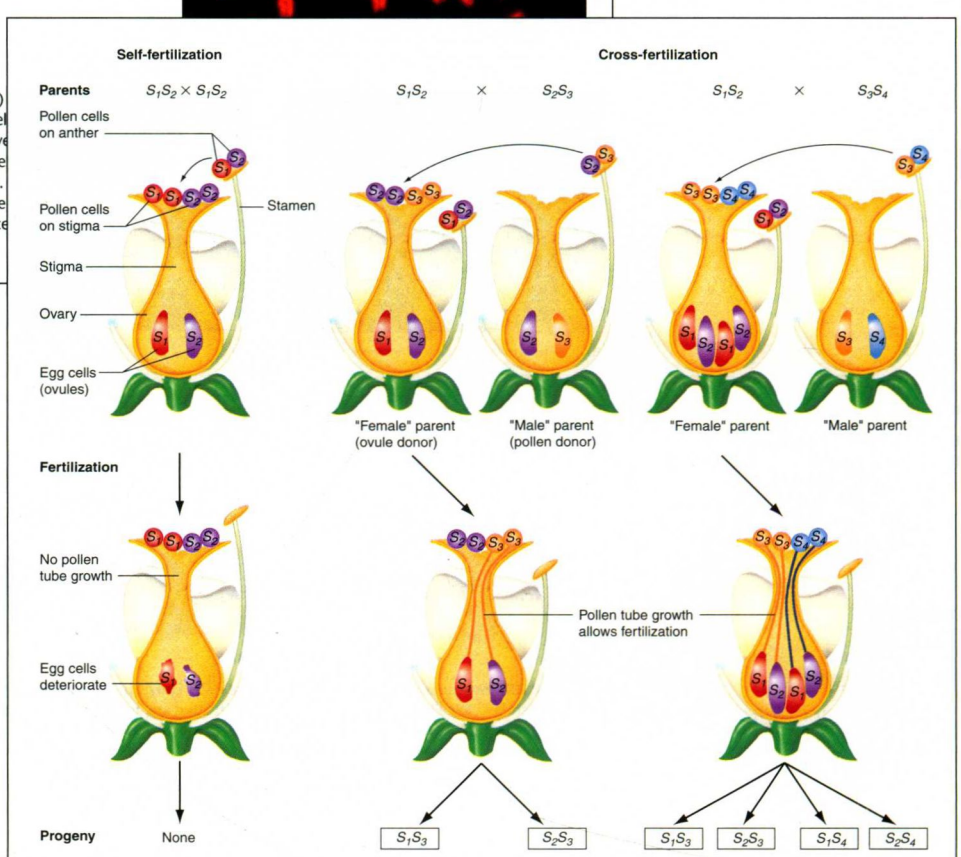


Figure 3.8 Plant incompatibility systems promote outbreeding and allele proliferation. A pollen grain carrying an allele of the self-incompatibility gene that is identical to either of the two alleles carried by a potential female parent is unable to grow a pollen tube; as a result, fertilization cannot take place. Because all the pollen grains produced by any one plant have one of the two alleles carried by the female reproductive parts of the same plant, self-fertilization is impossible.

Comparative Figures

Comparison illustrations lay out the basic differences of often confusing principles.

Solving Genetics Problems

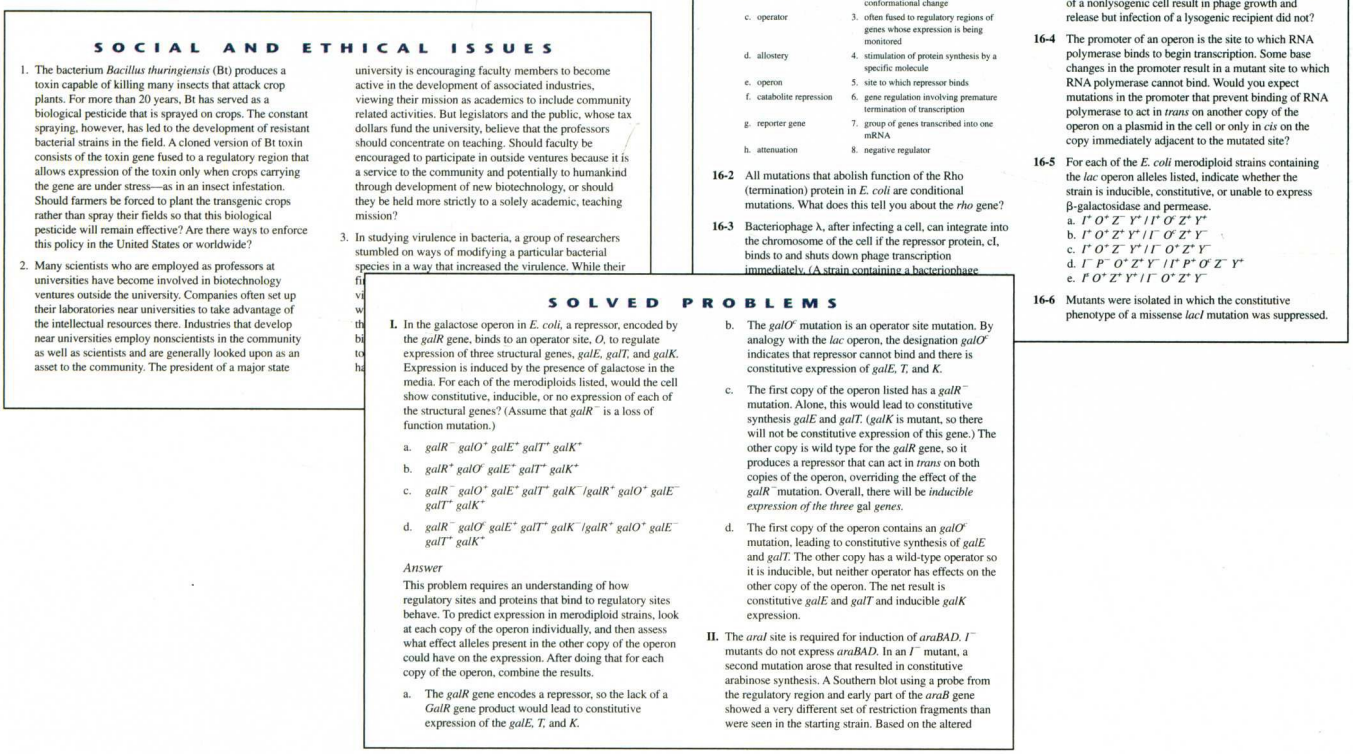
The best way for students to assess and increase their understanding of genetics is to practice through problems. Found at the end of each chapter, problem sets assist students in evaluating their grasp of key concepts and allows them to apply what they have learned to real-life issues.

Social and Ethical Issues

These challenging problems stir discussion and debate. The issues are presented within the context of real-life case studies and require the student to consider not only scientific issues but legal and ethical issues as well.

Review Problems

Revised and expanded, these problems offer a variety of levels of questions that develop strong problem-solving skills. The answers to selected problems can be found in an appendix in the back of the text.



SOCIAL AND ETHICAL ISSUES

1. The bacterium *Bacillus thuringiensis* (Bt) produces a toxin capable of killing many insects that attack crop plants. For more than 20 years, Bt has served as a biological pesticide that is sprayed on crops. The constant spraying, however, has led to the development of resistant bacterial strains in the field. A cloned version of Bt toxin consists of the toxin gene fused to a regulatory region that allows expression of the toxin only when crops carrying the gene are under stress—as in an insect infestation. Should farmers be forced to plant the transgenic crops rather than spray their fields so that this biological pesticide will remain effective? Are there ways to enforce this policy in the United States or worldwide?
2. Many scientists who are employed as professors at universities have become involved in biotechnology ventures outside the university. Companies often set up their laboratories near universities to take advantage of the intellectual resources there. Industries that develop near universities employ nonscientists in the community as well as scientists and are generally looked upon as an asset to the community. The president of a major state university is encouraging faculty members to become active in the development of associated industries, viewing their mission as academics to include community related activities. But legislators and the public, whose tax dollars fund the university, believe that the professors should concentrate on teaching. Should faculty be encouraged to participate in outside ventures because it is a service to the community and potentially to humankind through development of new biotechnology, or should they be held more strictly to a solely academic, teaching mission?
3. In studying virulence in bacteria, a group of researchers stumbled on ways of modifying a particular bacterial species in a way that increased the virulence. While their fi
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PROBLEMS

16-1 For each of the terms in the left column, choose the best matching phrase in the right column.

a. induction	1. glucose prevents expression of catabolic operons
b. repressor	2. protein undergoes a reversible conformational change
c. operator	3. often fused to regulatory regions of genes whose expression is being monitored
d. allostery	4. stimulation of protein synthesis by a specific molecule
e. operon	5. site to which repressor binds
f. catabolite repression	6. gene regulation involving premature termination of transcription
g. reporter gene	7. group of genes transcribed into one mRNA
h. attenuation	8. negative regulator

16-2 All mutations that abolish function of the Rho (termination) protein in *E. coli* are conditional mutations. What does this tell you about the *rho* gene?

16-3 Bacteriophage λ, after infecting a cell, can integrate into the chromosome of the cell if the repressor protein, cI, binds to and shuts down phage transcription immediately. (A strain containing a bacteriophage is a lysogen was crossed with a lysogenic F^- recipient cell and no phages were produced. However, when the Hfr lysogen donor strain transferred its DNA to a nonlysogenic F^- recipient cell, the recipient cell burst, releasing a new generation of phages. Why did infection of a nonlysogenic cell result in phage growth and release but infection of a lysogenic recipient did not?

16-4 The promoter of an operon is the site to which RNA polymerase binds to begin transcription. Some base changes in the promoter result in a mutant site to which RNA polymerase cannot bind. Would you expect mutations in the promoter that prevent binding of RNA polymerase to act in *trans* on another copy of the operon on a plasmid in the cell or only in *cis* on the copy immediately adjacent to the mutated site?

16-5 For each of the *E. coli* merodiploid strains containing the *lac* operon alleles listed, indicate whether the strain is inducible, constitutive, or unable to express β-galactosidase and permease.

a. $I^+ O^+ Z^- Y^+ / I^+ O^c Z^+ Y^+$
b. $I^+ O^+ Z^+ Y^+ / I^- O^c Z^+ Y^-$
c. $I^+ O^+ Z^- Y^+ / I^- O^+ Z^+ Y^-$
d. $I^- P^- O^+ Z^+ Y^- / I^+ P^+ O^c Z^- Y^+$
e. $I^s O^+ Z^+ Y^+ / I^- O^+ Z^+ Y^-$

16-6 Mutants were isolated in which the constitutive phenotype of a missense *lacI* mutation was suppressed.

SOLVED PROBLEMS

I. In the galactose operon in *E. coli*, a repressor, encoded by the *galR* gene, binds to an operator site, *O*, to regulate expression of three structural genes, *galE, galT,* and *galK*. Expression is induced by the presence of galactose in the media. For each of the merodiploids listed, would the cell show constitutive, inducible, or no expression of each of the structural genes? (Assume that $galR^-$ is a loss of function mutation.)

a. $galR^- galO^+ galE^+ galT^+ galK^+$

b. $galR^+ galO^c galE^+ galT^+ galK^+$

c. $galR^- galO^+ galE^+ galT^+ galK^- / galR^+ galO^+ galE^- galT^+ galK^+$

d. $galR^- galO^c galE^+ galT^+ galK^- / galR^+ galO^+ galE^- galT^+ galK^+$

Answer

This problem requires an understanding of how regulatory sites and proteins that bind to regulatory sites behave. To predict expression in merodiploid strains, look at each copy of the operon individually, and then assess what effect alleles present in the other copy of the operon could have on the expression. After doing that for each copy of the operon, combine the results.

a. The *galR* gene encodes a repressor, so the lack of a *GalR* gene product would lead to constitutive expression of the *galE, T,* and *K*.

b. The $galO^c$ mutation is an operator site mutation. By analogy with the *lac* operon, the designation $galO^c$ indicates that repressor cannot bind and there is constitutive expression of *galE, T,* and *K*.

c. The first copy of the operon listed has a $galR^-$ mutation. Alone, this would lead to constitutive synthesis *galE* and *galT*. (*galK* is mutant, so there will not be constitutive expression of this gene.) The other copy is wild type for the *galR* gene, so it produces a repressor that can act in *trans* on both copies of the operon, overriding the effect of the $galR^-$ mutation. Overall, there will be *inducible expression of the three* gal *genes*.

d. The first copy of the operon contains an $galO^c$ mutation, leading to constitutive synthesis of *galE* and *galT*. The other copy has a wild-type operator so it is inducible, but neither operator has effects on the other copy of the operon. The net result is constitutive *galE* and *galT* and inducible *galK* expression.

II. The *araI* site is required for induction of *araBAD*. I^- mutants do not express *araBAD*. In an I^- mutant, a second mutation arose that resulted in constitutive arabinose synthesis. A Southern blot using a probe from the regulatory region and early part of the *araB* gene showed a very different set of restriction fragments than were seen in the starting strain. Based on the altered

Solved Problems

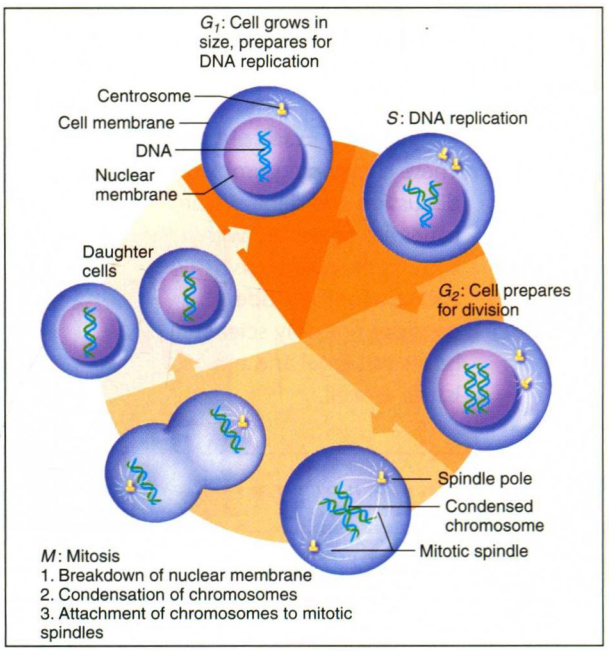
Solved problems offer step-by-step guidance needed to understand the problem-solving process.

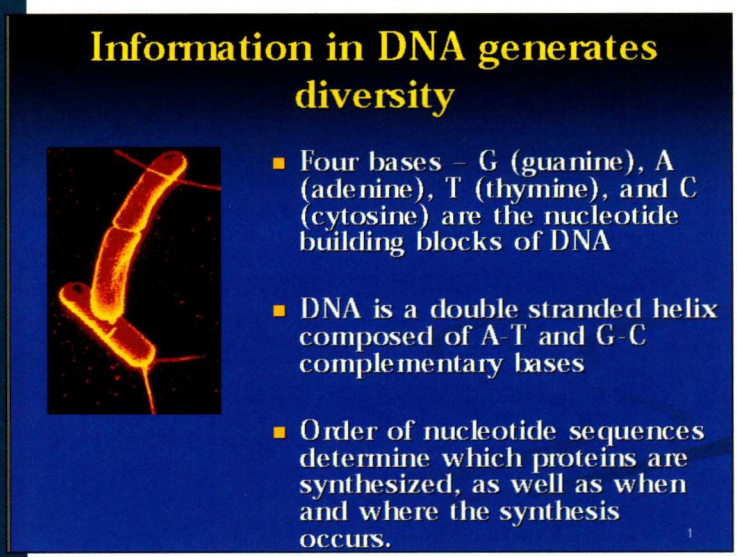
A Powerful Lecture Resource

This multimedia collection of visual resources allows instructors to utilize artwork from the text in multiple formats to create customized classroom presentations, visually-based tests and quizzes, dynamic course website content, or attractive printed support materials. The digital assets on this cross-platform CD-ROM are grouped within the following easy-to-use folders.

Art and Photo Library

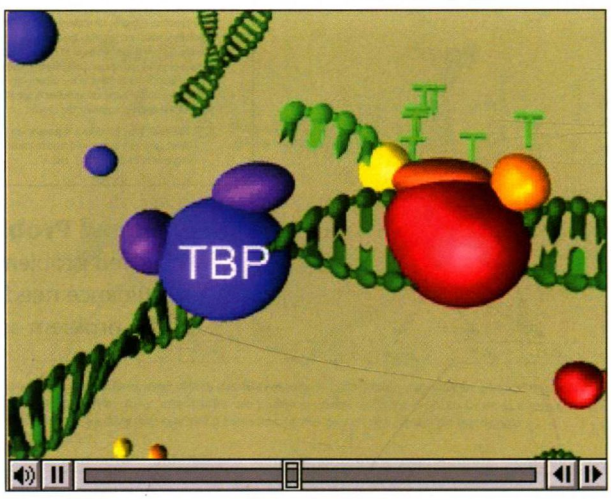
Full-color digital files of all the tables and illustrations and many of the photos in *Genetics: From Genes to Genomes* can be readily incorporated into lecture presentations, exams, or custom-made classroom materials.





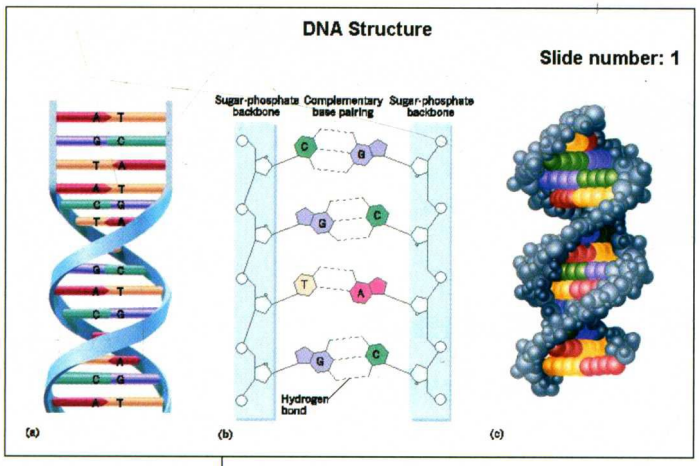
PowerPoint Lecture Outlines

Ready-made presentations that combine art and lecture notes cover each of the 21 chapters of the text. These lectures can be used as they are or can be tailored to reflect your preferred lecture topics and sequences.



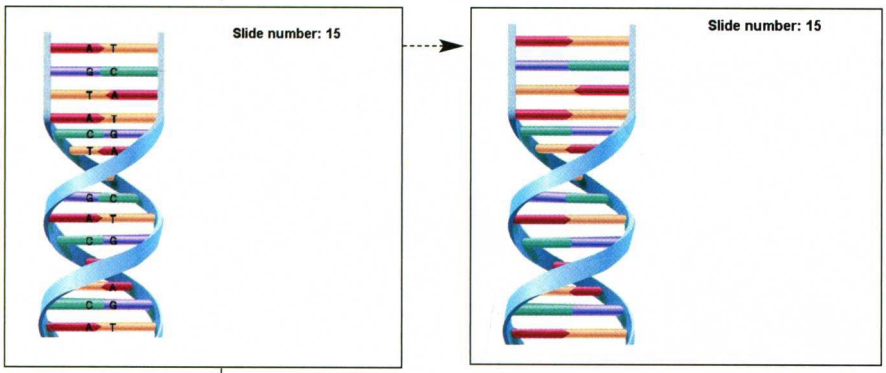
Animations

Instructive, full-color animations are available to harness the visual impact of processes in motion. Import these animations into classroom presentations or online course materials.

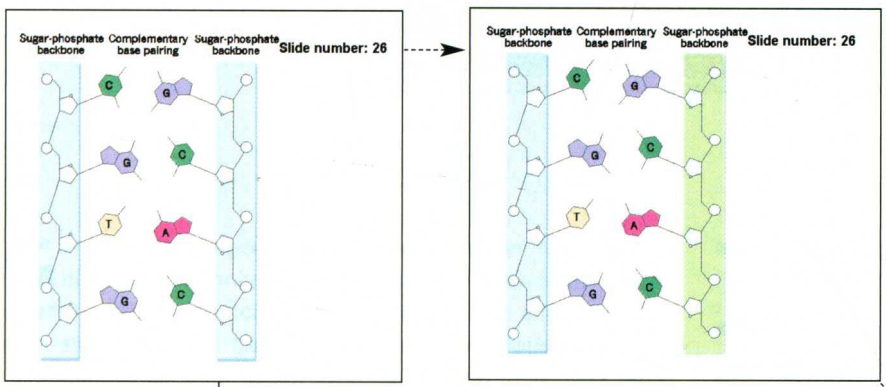


Active Art

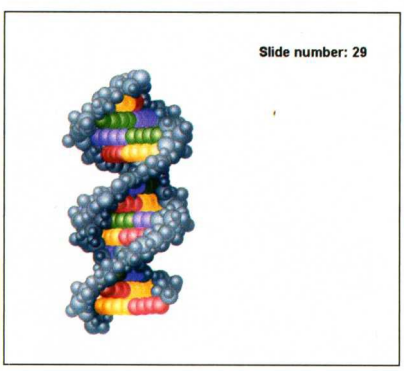
Active Art allows you to customize key figures from the text to complement your lecture! Figures have been broken into smaller digestable parts so each piece can be used in whatever order or format chosen. Using Microsoft PowerPoint's ungroupable art feature, instructors can also move, resize, or change the color of any or all objects in a piece of art.



Remove Labels Labels and leader lines can be easily repositioned, edited, or removed. Your customized images can then be used for course assignments or additional quizzing for your students.



Change Colors Colors can be removed and/or changed from any Active Art slide or object. Black and white images can be created for use in lecture supplements or exams.



Resize Objects The entire image or parts of the image can be made larger or smaller depending on what you choose to emphasize.