

C **G**ENETICS

From Genes to Genomes

LELAND H. HARTWELL

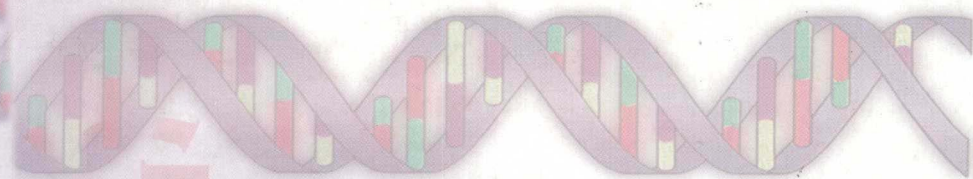
LEROY HOOD

MICHAEL L. GOLDBERG

ANN E. REYNOLDS

LEE M. SILVER

RUTH C. VERES



GENETICS

From Genes to Genomes

LELAND HARTWELL

Fred Hutchinson Cancer Research Center

LEROY HOOD

University of Washington

MICHAEL L. GOLDBERG

Cornell University

ANN E. REYNOLDS

University of Washington

LEE M. SILVER

Princeton University

RUTH C. VERES



Boston Burr Ridge, IL Dubuque, IA Madison, WI New York San Francisco St. Louis
Bangkok Bogotá Caracas Lisbon London Madrid
Mexico City Milan New Delhi Seoul Singapore Sydney Taipei Toronto

McGraw-Hill Higher Education 

A Division of The McGraw-Hill Companies

GENETICS: FROM GENES TO GENOMES

Copyright © 2000 by The McGraw-Hill Companies, Inc. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

4 5 6 7 8 9 0 VNH/VNH 9 0 9 8 7 6 5 4 3 2

ISBN 0-07-540923-2

Vice president and editorial director: *Kevin T. Kane*
Publisher: *James M. Smith*
Developmental editor: *Jean Sims Fornango*
Marketing manager: *Martin J. Lange*
Project manager: *Cathy Ford Smith*
Production supervisor: *Enboge Chong*
Design manager: *Stuart D. Paterson*
Senior photo research coordinator: *Carrie K. Burger*
Supplement coordinator: *Brenda A. Ennen*
Compositor: *Carlisle Communications, Ltd.*
Typeface: *10/12 Times Roman*
Printer: *Von Hoffmann Press, Inc.*

Cover/interior design: *Chris Reese*
Photo research: *Jill Birschbach/Feldman & Associates, Inc.*

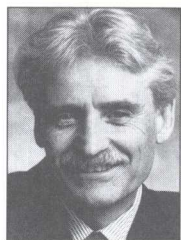
The credits section for this book begins on page C-1 and is considered an extension of the copyright page.

Library of Congress Cataloging-in-Publication Data

Genetics : from genes to genomes / Leland Hartwell . . . [et. al.].—
1st ed.
p. cm.
Includes index.
ISBN 0-07-540923-2
1. Genetics. I. Hartwell, Leland.
QH430.G458 2000
576.5—dc21

99-15119
CIP

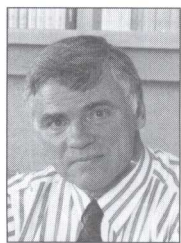
ABOUT THE AUTHORS



Dr. Leland Hartwell received his Ph.D. from the 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.

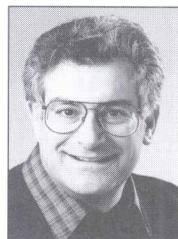
Combining mutants and time-lapse photomicroscopy, Dr. Hartwell identified 32 genes in yeast that regulate the cell cycle with specific defects in spindle pole body duplication and segregation, DNA replication, mitosis, cytokinesis, and budding. He discovered a control point in the cell cycle, Start, 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 over-expression 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 he received the Brandeis University Rosenteil Award in 1993 and the Sloan-Kettering Cancer Center Katherine Berkan Judd Award as well as the Genetics Society of America Medal in 1994. In 1995 he was awarded the MGH Warren Triennial Prize, and in 1996 he was awarded the Columbia University Horwitz Award and the Passano Award. Dr. Hartwell received the Albert Lasker Award for medical research in 1998.



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 (e.g., 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 is currently the chairman (and founder) of

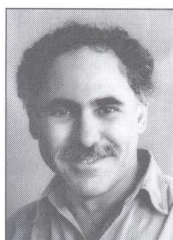
the cross-disciplinary Department of Molecular Biotechnology at the University of Washington. Dr. Hood has received a variety of awards including the Albert Lasker Award for Medical Research and the Dickson Prize in 1987, the Cefas Award for Biochemistry in 1989, and the Distinguished Service Award from the National Association of Teachers in 1998. He is deeply involved in K-12 science education. His hobbies include running, mountain climbing, and reading.



Dr. Michael L. 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 in Switzerland and at Harvard University. He received an NIH Fogarty Senior International Fellowship for study at Imperial College in England and at the University of Rome, Italy. His current research utilizes the tools of *Drosophila* genetics to investigate the mechanisms that ensure proper chromosome segregation during mitosis and meiosis.



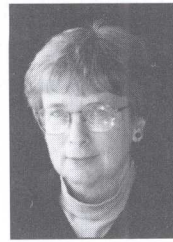
Dr. Ann Reynolds is an educator and author who has been teaching genetics and biology since 1990. An affiliate faculty member of the Genetics Department at the University of Washington, her research has included studies of gene regulation in *E. coli*, chromosome structure and DNA replication in yeast, 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. Dr. Reynolds was also an author and producer of the laser disc and CD ROM *Genetics: Fundamentals to Frontiers*.



Dr. Lee M. Silver is a professor at Princeton University in the Departments of Molecular Biology, Ecology, and Evolutionary Biology and in the Program in Neuroscience. Dr. Silver graduated from the University of Pennsylvania with B.A. and M.S. degrees in physics and from Harvard University with a Ph.D. in biophysics. He was a research fellow at the Sloan-Kettering Institute for Cancer Research and a senior scientist at Cold Spring Harbor Laboratory before coming to Princeton. He is the author of

Remaking Eden: Cloning and Beyond in a Brave New World. He is also coeditor in chief of *Mammalian Genome*, the official journal of the International Mammalian Genome Society. In 1993 Dr. Silver was elected a fellow of the American Association for the Advancement of Science (AAAS).

Dr. Silver's own research has made intensive use of the mouse as a model organism to study the genetics of reproduction, development, and evolution. His current research focuses on the genetic components of behavior. At Princeton, he has taught courses in genetics, mammalian genetics, biotechnology and society, and developmental biology in the Department of Molecular Biology and human genetics, reproduction, and public policy in Princeton's Woodrow Wilson School of Public and International Affairs.



Ruth C. Veres is a science writer and editor with 25 years of experience in textbook publishing. She obtained her B.A. from Swarthmore College and M.A. degrees from Columbia University in New York and Tufts University. In addition to developing and editing more than 30 texts in the fields of political science, economics, psychology, nutrition, chemistry, and biology, she has coauthored a book on the immune system and an introductory biology text. She has also taught writing and languages at the University of California at Berkeley. She lives in San Francisco with her husband.

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 text.

Eric E. Alani, *Cornell University*
 Charles F. Aquadro, *Cornell University*
 Anthony B. Bleecker, *University of Wisconsin*
 Deborah Brosnan, *University of Oregon*
 Ronald A. Butow, *University of Texas, Southwestern Medical Center, Dallas*
 Rita A. Calvo, *Cornell University*
 Michael Culbertson, *University of Wisconsin*
 Ian Duncan, *Washington University, St. Louis*
 Sarah Elgin, *Washington University, St. Louis*
 Thomas D. Fox, *Cornell University*
 Leonard P. Guarente, *Massachusetts Institute of Technology*
 Kenneth J. Kemphues, *Cornell University*
 Joel G. Kingsolver, *University of Washington*

John T. Lis, *Cornell University*
 Ross J. MacIntyre, *Cornell University*
 Patrick H. Masson, *University of Wisconsin*
 Jeffery B. Mitton, *University of Colorado*
 Martha A. Mutschler, *Cornell University*
 June B. Nasrallah, *Cornell University*
 Debra Nero, *Cornell University*
 Richard D. Palmiter, *University of Washington*
 Philip S. Perlman, *University of Texas, Southwestern Medical Center, Dallas*
 Fabio Piano, *Cornell University*
 Harry T. Stinson, Jr., *Cornell University*
 William T. Sullivan, *University of California, Santa Cruz*
 Volker M. Vogt, *Cornell University*
 Douglas Wallace, *Emory University*
 Jonathan Widom, *Northwestern University*
 Mariana F. Wolfner, *Cornell University*
 William B. Wood, *University of Colorado*
 Andrew Wright, *Tufts University*
 Stanley A. Zahler, *Cornell University*

The twentieth century witnessed the emergence of genetics as a central discipline in biology. In 1900 Gregor Mendel's laws of heredity were rediscovered; in the 1950s, James Watson and Francis Crick found that DNA, the molecule of heredity, is a double helix; and in the 1990s, the Human Genome Project progressed beyond expectations. 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 and proteins that organisms ultimately live and die.

Genetics: From Genes to Genomes reflects this new perspective. This book represents 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 enable gene isolation and a comprehensive analysis of the entire gene set in an organism; human genetics—how genes control health and disease; the unity of life forms—synthesis of information from many different organisms into one coherent whole; and molecular evolution—how species have evolved and diverged. The strength of this integrated approach is that students who have completed the text will have a strong command of genetics as it is practiced today by university and corporate researchers who 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.

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. The Prologue presents the foundation of this integration. In Chapter 1, 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 5, we focus on the physical dimensions of DNA; the implications and uses of mutations; and how the double helix of DNA encodes, copies, and transmits biological information. Beginning in Chapter 8 we also look at modern genetic techniques, including such biotechnology tools as gene cloning, hybridization, and PCR, exploring how researchers have used them to reveal the modular construction and genetic relatedness of genomes. We

then show how the modular construction of genomes has contributed to the relatively rapid evolution of life and helped generate the enormous diversity of life forms we see around us. A detailed discussion of model organisms clarifies that their use in the study of human biology is possible only because of the genetic relatedness of all organisms. Throughout our text, 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.

ORGANIZATION

The Prologue outlines the central themes of *Genetics: From Genes to Genomes*. We hope students will read this section carefully because it establishes the foundation for our integrated presentation of Mendelian and molecular genetics.

Part I (Chapters 1, 2, 3, and 4) on the *Basic Principles: How Traits Are Transmitted* presents a thorough discussion of Mendelian genetics; the chromosome theory of inheritance; and linkage, recombination, and mapping.

Part II (Chapters 5, 6, and 7) covers *What Genes Are and What They Do*, including the structure and function of DNA, the role of mutation in defining genes, and the details of gene expression.

Part III (Chapters 8, 9, and 10) describes the *Use of Genetic Engineering to Unravel the Information in Genomes* and includes topics on mapping and analysis of genomes, detection of genotype, and the use of cloning, PCR, and hybridization in genetic analysis.

Part IV (Chapters 11, 12, 13, and 14) on *How Genes Travel* presents the molecular mechanisms underlying the chromosomal transmission of genetic information in eukaryotes and prokaryotes.

Part V (Chapters 15, 16, and 17) on *How Genes Are Regulated* discusses prokaryotic and eukaryotic gene regulation as well as the regulation of the cell cycle.

Part VI (Chapters 18–22) presents *Gene Regulation and Development: Portraits of Model Eukaryotic Organisms*. This **Genetic Portraits** unit contains five chapters, each one profiling a different model organism whose study has greatly contributed to genetic research. Included are

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

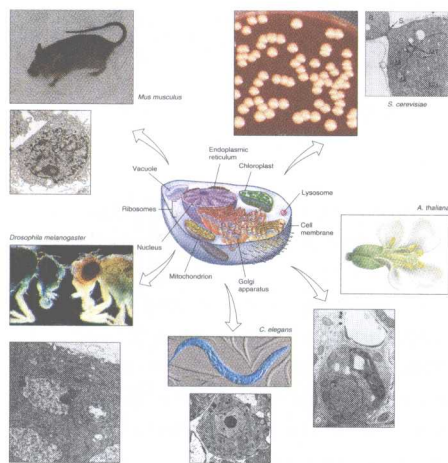


Figure 1.4 Eukaryotic cells have many features in common. The similarity of cellular structure in our five model organisms is visible in the micrographs accompanying the photos of each of the entire organisms above. As discussed in Chapter 11, each cell contains a variety of complex, membranous organelles in the cytoplasmic matrix and have the majority of their genetic material contained within membrane-enclosed nuclei. Review chapter 14 for the details of gene regulation in eukaryotes. Each model had characteristic variations, but the basic cellular plan is the same.

We anticipate that instructors will choose to cover one or two portrait chapters 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 text. The unique genetic manipulations and properties of each model 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 enables 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.

Part VII (Chapters 23 and 24) on **How Genes Change** explains the evolution of genes and genomes in populations and at the molecular level.

The **Epilogue** discusses **Human Genetics and the Future of Biology**. The focus of this closing essay is on the changing role of genetics research as a way to decipher biological networks and systems. Biology is now a science based on three levels of molecular information: information encoded in DNA, and information in proteins, and information encompassed in interactions among cells and tissues. The potential impact on the field of preventive medicine intensifies the need to confront many social and ethical issues.

CHAPTER FEATURES

Introduction Each chapter begins with an engaging story related to the key ideas and principles of the chapter. This opening story is followed by a description of one or more overarching themes that unify the discussion, and then, in turn, by an advance organizer—a short, bulleted list of the chapter's topics in the order in which they appear in the text. The intent of the introduction is to create a narrative and conceptual framework that will help students organize and remember the vast amount of vocabulary and experimental data they encounter.

Feature Figures These special two-page spreads integrate line art and text to summarize important genetic processes in detail. For example, in Chapter 5 on *DNA: How the Molecule of Heredity Carries, Replicates, and Recombines Information*, the Feature Figure details a “Model of Recombination at the Molecular Level,” walking students through the basic steps of the process. In Chapter 17,

Cell-Cycle Regulation and the Genetics of Cancer, the Feature Figure details “Phenotypic Changes That Distinguish Tumor Cells from Normal Cells” outlines changes that produce uncontrolled cell growth, genomic and karyotypic instability, a potential for cellular immortality, and disruptions of local tissues that enable a tumor to invade distant tissues.

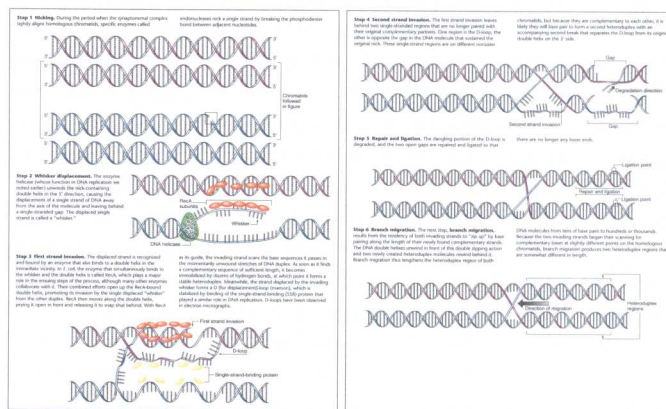


Figure 1.21 A model of recombination at the molecular level.

Comprehensive Examples These sections of the text are extensive case histories or research synopses that summarize the main points in the preceding section or chapter and show how they relate to each other. Very often these developed examples expand on the chapter's introductory story. In Chapter 6, *Anatomy and Function of a Gene: Dissection through Mutation*, for example, the opening story locates the rhodopsin gene on human chromosome 3 and explains that different mutations in the gene lead to night blindness or total blindness. The Comprehensive Example at the end of the chapter describes in detail “How Gene Mutations Affect Light-Receiving Proteins and Vision,” covering such topics as the cellular and molecular basis of vision; the evolution of the rhodopsin gene family; and many of the mutations, amino-acid substitutions, and unequal crossing over events that affect both black and white and color vision.

Fast Forward Essays

This feature prefigures detailed discussions of concepts and principles in later chapters, serving as a tool to integrate Mendelian and molecular genetics. Chapter 1, *Mendel's Breakthrough: Patterns, Particles, and Principles of Heredity*, contains two Fast Forward essays, one on the fact that “Genes Encode Proteins,” the other on techniques for “The Direct Analysis of Human Genotype.” These essays help students understand that Mendel's laws

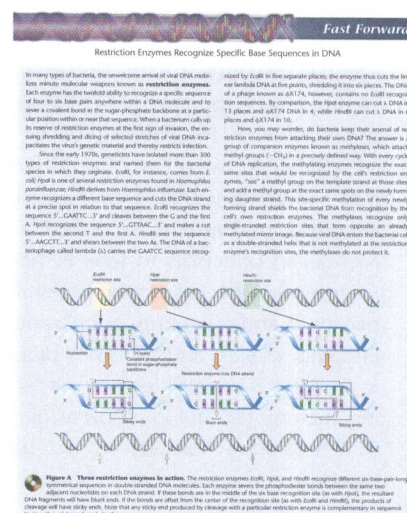


Figure 3 Three restriction enzymes in action. The restriction enzymes EcoRI, SmaI, and NotI recognize different base-pair sequences in double-stranded DNA molecules. Each enzyme cuts the phosphodiester bond between the sugar and adjacent nucleotides on each DNA strand. If these bonds are in the middle of the base-pair sequence (as with SmaI), the resulting DNA fragments will have blunt ends. If the bonds are offset from the center of the recognition site (as with EcoRI and NotI), the products of cleavage will have sticky ends. Note that any sticky end produced by cleavage with a particular restriction enzyme is complementary in sequence to any other sticky end made by the same enzyme.

have a molecular basis. In Chapter 5, *DNA: How the Molecule of Heredity Carries, Replicates, and Recombines Information*, where we present in detail the structure of the DNA molecule, the Fast Forward essay explains how “Restriction Enzymes Recognize Specific Base Sequences in DNA.” This simple introduction of restriction enzymes foreshadows a discussion in Chapter 8, *DNA at High Resolution: The Use of DNA Cloning, PCR, and Hybridization as Tools of Genetic Analysis*, about the use of restriction enzymes in DNA cloning. It thus relates the basic concept of DNA structure to the tools of biotechnology that depend on a knowledge of that structure.

Genetics and Society Essays These essays explore the social and ethical issues created by the multiple applications of modern genetic research. They cover a wide variety of topics from the right to privacy to the question of who has the right to make reproductive decisions. In Chapter 9, the Genetics and Society essay asks “Does DNA Fingerprinting Serve the Interests of Justice?” In Chapter 10, the essay examines “The Patentability of DNA.” In Chapter 13, it looks at “How Bacteria Can Cause Disease,” presenting the mechanisms of bacterial pathogenesis step by step and describing the defense mechanisms that fight infection.

Genetics and Society

How Bacteria Cause Disease

Bacteria that cause disease in other organisms are known as pathogens. Their ability to infect hosts is their virulence. Most pathogens cause relatively mild symptoms; virulent pathogens, however, cause severe disease. They damage the host's cells, destroy the host's tissues, and damage the host's organs. A pathogen must avoid the varied defenses of a host organism, multiply inside the host, and be transmitted to other hosts. How do bacterial pathogens accomplish all this in humans?

The Steps of Bacterial Pathogenesis

Every one of the human skin is a protective barrier that excludes most bacteria, but there are several ways to breach its defenses. Some species of bacteria gain entry to the body via wounds that damage the skin. *Clostridium botulinum*, the agent of botulism, is one such species. Other bacteria gain entry through openings established by insect bites. *Yersinia pestis*, the agent of bubonic plague, for example, is transmitted from rodents to humans via fleas and their bites. A third means of access to the human host is transmission to mucous membranes. *Mycobacterium tuberculosis*, the agent of tuberculosis, infects the respiratory tract via aerosols produced by sneezing or coughing. *N. gonorrhoeae*, the agent of gonorrhea, infects the urogenital tract via sexual transmission. Finally, the agent of cholera, *Vibrio cholerae*, infects the digestive tract via ingestion.

Once inside the host, some bacteria adhere to the surface of eukaryotic cells. In the region of entry, attachment depends on interactions between proteins on the bacterial cell surface—similar to the cell that help initiate coagulation—and specific receptors, usually composed of carbohydrates, on the surface of the host's eukaryotic cells (Fig. 4). Adherence is the first step in pathogenesis. One illustration of this fact is the observation that the few pathogenic strains of *E. coli* that are able to synthesize attachment proteins, while the large majority of nontoxicogenic *E. coli* strains make no attachment proteins and are unable to attach to cells of the intestinal mucosa, after adherence, pathogenic bacteria begin to replicate.

Some bacteria penetrate to deeper layers of host cells. *Helicobacter pylori*, the bacteria associated with many cases of ulcers, burrows through the layer of mucus protecting the stomach and adheres to cells on the surface of the stomach wall. After penetrating the mucus with mucous binding, it produces enzymes, an enzyme that generates ammonia, which in turn, neutralizes the stomach acid in the area. Other penetrating bacteria form a path into tissues within the body by secreting enzymes such as collagenase, which break down the molecules that help hold tissues together. These penetrating bacteria then adhere to cells and begin to replicate.

Some bacteria invade host cells. Multiplication inside these cells leads to cell lysis (Fig. 6). *Staphylococcus aureus*, the agent of bacterial dysentery, invades the epithelial cells of the intestines; *Legionella pneumophila* (the agent of Legionnaire's disease) and *M. tuberculosis* are able to invade and multiply within host cells.

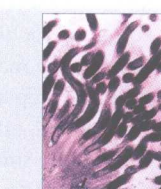


Figure 4 Bacteria can adhere to the surface of eukaryotic cells. Shown here are *Staphylococcus aureus* cells attached to liver cells.

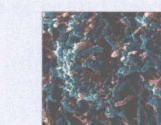


Figure 6 Some bacteria, such as *Mycobacterium tuberculosis* (green cells), can invade and multiply within host cells.

Legionella pneumophila (the agent of Legionnaire's disease) and *M. tuberculosis* are able to invade and multiply within host cells.

Bacterial replication can damage the host in several ways. First, the presence of a large number of bacteria at one site can block the normal flow of materials. In the respiratory system, for example, a

CONNECTIONS

The detrimental consequences of most changes in chromosome organization and number cause considerable distress in humans (Table 12.2). Approximately 4 of every 1,000 live births has an abnormal phenotype associated with altered chromosome organization or number. Most of these abnormalities result from errors occurring during the chromosome or meiosis 21. By comparison, about 10 people per 1,000 live births are born with Down syndrome, a single gene mutation.

The incidence of chromosomal abnormalities among humans would be much larger were it not for the fact that many fetuses with abnormal karyotypes abort spontaneously early in pregnancy. Fully 15% to 20% of recognized pregnancies end with detectable spontaneous abortions, and half of the spontaneously aborted fetuses show chromosomal abnormalities, particularly trisomy, sex chromosome monosomy, and triploidy. These figures probably underestimate the rate of spontaneous abortions caused by chromosomal variations, since fetuses carrying abnormalities for larger chromosomes, such as monosomy 2 or trisomy 4, may abort so early that the pregnancy goes unrecognized.

But despite all the negative effects of chromosomal rearrangements and changes in chromosome number, a few departures from diploidy survive to become instruments of evolution by natural selection.

As we see in the next chapter, chromosomal rearrangements occur in bacteria as well as in eukaryotic organisms. Interestingly, in bacteria, transposable elements catalyze many of the changes in chromosomal organization, and the resulting flight of genes between different DNA molecules in the same cell catalyzes the transfer of genetic information from one bacterial cell to another.

TABLE 12.2 Data on Human Health Problems Resulting from Changes in Chromosome Organization and Number—Amplified Abnormalities in the Human Population

Chromosomes	Syndrome	Frequency at Birth
Autosomes		
Tsaiou 21	Down	1/700
Tsaiou 13	Phenylketonuria	1/5,000
Tsaiou 18	Edwards	1/3,000
Sex chromosomes, females		
XO, monosomy	Turner	1/5,000
XXX, trisomy		
XXXX, tetrasomy		1/700
XXXXX, pentasomy		
Sex chromosomes, males		
XYY, trisomy	Normal	1/10,000
XXYY, tetrasomy		
XXXY, pentasomy	Klinefelter	1/500
XXXXY, hexasomy		

Note: 4 of 10 of all babies born have a detectable chromosomal abnormality that produces a detectable phenotype.

ESSENTIAL CONCEPTS

- The Hardy-Weinberg law uses the binomial equation of $p^2 + 2pq + q^2 = 1$ to correlate allele, genotype, and phenotype frequencies in a very large ideal population. In this ideal population, individuals mate at random, no new mutations appear, no individuals enter or leave, and there are no genotype-dependent differences in fitness. In the binomial equation, p represents the frequency of one allele and q represents the frequency of the other, and p^2 , $2pq$, and q^2 represent the frequencies of the two homozygous and one heterozygous genotypes.
- A population satisfying the Hardy-Weinberg assumptions is said to be in Hardy-Weinberg equilibrium. In such a population, allele frequencies remain constant from one generation to the next, and the genotype frequencies of p^2 , $2pq$, and q^2 appear in one generation, after which they are maintained.
- Evolution consists of changes in allele frequency over time. Selection acting on genotype-dependent differences in fitness can drive evolution. Selection does not entirely eliminate deleterious recessive alleles from a population. One reason for this is heterozygote advantage.
- The existence of an evolutionary equilibrium is another reason deleterious recessive alleles persist in populations. The evolutionary equilibrium is a balance between the evolutionary pressure to remove a deleterious allele and selection against that allele. For most of a disease, deleterious selection against the disease allele, while genetic drift has an unpredictable effect on the evolutionary equilibrium.
- For quantitative traits, the environmental variance is a measure of the influence of environment on phenotype.

variation. Similarly, genetic variance measures the contribution of genes to phenotypic variation. Total phenotypic variance is the sum of genetic variance and environmental variance. With traits for which the number and identity of contributing genes remain unknown and there is no way to obtain genetic clones, it is possible to correlate phenotypic variation with the genetic relatedness of individuals—that is, the average fraction of common alleles at all gene loci that the individuals share because they inherited them from a common ancestor—to measure the heritability of a trait.

To ascertain the heritability of a human trait, population geneticists often turn to studies of twins. The most useful approach is to compare the phenotypic differences between pairs of monozygotic and dizygotic twins. Environmental changes can always influence heritability.

9. Variations in polygenic traits arise at a rapid rate through selection because changes at many loci contribute to changes in phenotype. Nevertheless, it is possible that many polygenic traits are determined by genes, rather than thousands, of loci.

tions section is followed by an **Essential Concepts** section that helps students focus on the most critical information—the chapter's “take-home” messages. The end-of-chapter exercises include solved problems, **Social and Ethical Issues** discussion questions, and a diverse set of problems and questions for the student to solve.

Outstanding Art Work The quality of the art is critical to the success of this text, and you will find that the photos, electron micrographs, and line art have been carefully selected and rendered to give students the best presentation possible. Color consistency has been used in rendering the line art to aid student comprehension. The following key is a guide to the use of color in our illustrations.

"old" DNA		protein 1	
"new" DNA		protein 2	
"new new" DNA		protein 3	
mRNA (messenger)		phosphate group	
tRNA (transfer)		ribosomes	
rRNA (ribosomal)		membrane	
mRNA (mitochondrial)		nucleus	
sugar (for ribose)		chromatin	
		mitochondria	

REFERENCE SECTION

In the back of the text, we provide a **Genetic Nomenclature Appendix**. Since the study of genetics is a relatively new science, a completely consistent nomenclature, similar to those found in more established sciences, does not exist. Instead, the details of gene notation differ from model organism to model organism. To assist students in understanding the use of gene symbols throughout the book, and particularly in the section on model organisms, this concise appendix details the minor differences in notation by organism.

Mastering the vocabulary of genetics is critical to understanding the science. To aid in that mastery, we provide a detailed **Glossary**.

The **Answer Appendix** contains answers to selected end-of-chapter problems. Students can build their problem-solving skills by working through the solved problems within each chapter and then, for the unsolved problems, checking the solutions they arrive at on their own against the answers in the Answer Appendix.

ACKNOWLEDGMENTS

The creation of a project of this scope is never solely the work of the authors. We are grateful to our colleagues around the world who took the time to review this manuscript and make suggestions for its improvement. Their willingness to share their experiences and expertise was a tremendous help to us.

Ken Belanger, *University of North Carolina, Chapel Hill*
 John Belote, *Syracuse University*
 Anna Berkovitz, *Purdue University*
 John Botsford, *New Mexico State University*
 Michael Breindl, *San Diego State University*
 Bruce Chase, *University of Nebraska, Omaha*
 Lee Chatfield, *University of Central Lancashire*
 Alan Christensen, *University of Nebraska*
 Bruce Cochrane, *University of South Florida*
 James Curran, *Wake Forest University*
 Rowland Davis, *University of California, Irvine*
 Paul Demchick, *Barton College*
 Stephen D'Surney, *University of Mississippi*
 Rick Duhrkopf, *Baylor University*
 Susan Dutcher, *University of Colorado*
 DuWayne Englert, *Southern Illinois University*
 Bentley Fane, *University of Arkansas*
 Victoria Finnerty, *Emory University*
 David Foltz, *Louisiana State University*
 David Futch, *San Diego State University*
 Ann Gerber, *University of North Dakota*
 Richard Gethmann, *University of Maryland, Baltimore County*
 Mike Goldman, *San Francisco State University*
 Elliott Goldstein, *Arizona State University*
 Nels Granholm, *South Dakota State University*
 Charles Green, *Rowan College of New Jersey*
 Poonam Gulati, *University of Houston*
 Stephen Hedman, *University of Minnesota*
 Ralph Hillman, *Temple University*
 Christine Holler-Dinsmore, *Fort Peck Community College*
 Martin Hollingsworth, *Tallahassee Community College*
 Nancy Hollingsworth, *State University of New York, Stony Brook*
 Andrew Hoyt, *Johns Hopkins University*
 Lynne Hunter, *University of Pittsburgh*
 Robert Ivarie, *University of Georgia*
 R. C. Jackson, *Texas Technological University*
 Duane Johnson, *Colorado State University*
 Chris Kaiser, *Massachusetts Institute of Technology*
 Kenneth J. Kemphues, *Cornell University*
 Susan Kracher, *Purdue University*
 Alan Koetz, *Illinois State University*
 Andrew Lambertsson, *University of Oslo*
 Don Lee, *University of Nebraska*
 John Locke, *University of Alberta*
 Larry Loeb, *University of Washington*
 Robertson McClung, *Dartmouth College*
 Peter Meacock, *University of Leicester*
 John Merriam, *University of California, Los Angeles*
 Beth Montelone, *Kansas State University*
 Patricia Moore, *Pennsylvania State University*
 Gail Patt, *Boston University*
 Michael Perlin, *University of Louisville*
 Richard Richardson, *University of Texas, Austin*
 Mary Rykowski, *University of Arizona*
 Mark Sanders, *University of California, Davis*
 Randall Scholl, *Ohio State University*

David Sheppard, *University of Delaware*
 Anthea Stavroulakis, *Kingsborough Community College*
 John Sternick, *Mansfield University*
 David Sullivan, *Syracuse University*
 William Thwaites, *San Diego State University*
 Akif Uzman, *University of Houston*
 Peter Webster, *University of Massachusetts*
 Dean Whited, *North Dakota State University*
 John Williamson, *Davidson College*
 John Zamora, *Middle Tennessee State University*
 Stephan Zweifel, *Carleton College*

Over the years a number of highly skilled publishing professionals helped us develop this book. We'd like to express our appreciation to Eirik Borge for his vision in launching the project, Laurel Smith for her refined and intelligent approach to art development, Marjorie Anderson for her editorial acumen, Kathi Prancan for her able and enthusiastic management (and dining-out extravaganzas), Kathy Naylor for her unusual combination of skills in art and text development; Jean Fornango for her top-notch, no-nonsense organizational skills in readying the manuscript for production; Richard Morel for his insightful preparation of the art manuscript; Ron Worthington for his scientific understanding and firm backing in a time of transition; and Jim Smith for his strong support throughout the final years of development and production. All have made a significant contribution to the final shape of this project.

SUPPLEMENTS

For the Student

- The **Solutions Manual/ Study Guide** was written by text author Ann Reynolds, of the University of Washington. The solutions to the end-of-chapter problems and questions will aid the students in developing their problem-solving skills by providing the step-by-step logic of each solution.
- **Genetics: From Genes to Genomes CD ROM**, developed with the content of the text, covers the most challenging concepts in the introductory genetics course. The CD attempts to make concepts more understandable by using animations of basic genetic processes and interactive exercises and simulations involving fundamental principles. Icons in the text indicate that there are related topics on the CD. A correlation guide linking text topics marked by icons to the related CD material is included in the *Instructor's Manual*, on our web site, and on the CD ROM itself. Additional quizzing options allow students to self-test and identify those areas needing additional study. Glossary definitions can be reached via hot links. The CD also has links that connect to the book's own web site.

For the Instructor

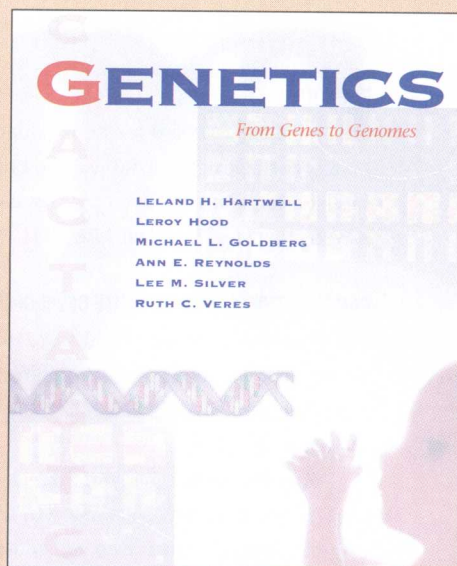
- The **Instructor's Manual/ Test Bank** contains the CD ROM correlation guide, a list of transparencies, plus a test

bank containing approximately 2000 questions. The test bank is also available in computerized form compatible with either Windows or Macintosh machines.

- **Transparencies:** One hundred and fifty four-color illustrations from the text will be available to adopters.
- **Visual Resource Library:** A CD ROM product containing 200 key illustrations will be available in four-color digital files. The presentation software enables you to create custom slide shows and multimedia presentations. Images

can also be exported for use in word-processing programs. Additional features enable the images to be sorted by name, type, locations, and user-defined keywords. Multiple images can be viewed at one time by using the Small Gallery View function. Jpeg files for all remaining line art is included, plus lecture outlines.

- **Web Site:** This text-specific web site can be reached at the URL **www.mhhe.com/hartwell** and provides additional materials for both students and instructors.



**MCGRAW-HILL IS PROUD TO OFFER AN EXCITING
NEW SUITE OF MULTIMEDIA PRODUCTS AND
SERVICES CALLED **COURSE SOLUTIONS**.**

Designed specifically to help you with your individual course needs, **Course Solutions** will assist you in integrating your syllabus with our premier titles and state-of-the-art new media tools that support them.

AT THE HEART OF COURSE SOLUTIONS YOU'LL FIND:

- Fully integrated multimedia
- A full-scale Online Learning Center
- A Course Integration Guide

AS WELL AS THESE UNPARALLELED SERVICES:

- McGraw-Hill Learning Architecture
- McGraw-Hill Course Consultant Service
- Visual Resource Library (VRL) Image Licensing
- McGraw-Hill Student Tutorial Service
- McGraw-Hill Instructor Syllabus Service
- PageOut Lite
- PageOut: The Course Web Site Development Center
- Other Delivery Options

COURSE SOLUTIONS truly has the solutions to your every teaching need. Read on to learn how we can specifically help you with your classroom challenges.

SPECIAL ATTENTION

to your specific needs.

These “perks” are all part of the extra service delivered through McGraw-Hill’s **Course Solutions**:

MCGRAW-HILL LEARNING ARCHITECTURE

Each McGraw-Hill *Online Learning Center* is ready to be ported into our *McGraw-Hill Learning Architecture*—a full course management software system for Local Area Networks and Distance Learning Classes. Developed in conjunction with Top Class software, *McGraw-Hill Learning Architecture* is a powerful course management system available upon special request.

MCGRAW-HILL COURSE CONSULTANT SERVICE

In addition to the *Course Integration Guide*, instructors using **Course Solutions** textbooks can access a special curriculum-based *Course Consultant Service* via a web-based threaded discussion list within each *Online Learning Center*. A **McGraw-Hill Course Solutions Consultant** will personally help you—as a text adopter—integrate this text and media into your course to fit your specific needs. This content-based service is offered in addition to our usual software support services.

VISUAL RESOURCE LIBRARY (VRL) IMAGE LICENSING

Most of our **Course Solutions** titles are accompanied by a *Visual Resource Library (VRL) CD-ROM*, which features text figures in electronic format. Previously, use of these images was restricted to in-class presentation only. Now, McGraw-Hill will license adopters the right to use appropriate VRL image files—**FREE OF CHARGE**—for placement on their local Web site! Some restrictions apply. Consult your McGraw-Hill sales representative for more details.

MCGRAW-HILL INSTRUCTOR SYLLABUS SERVICE

For new adopters of **Course Solutions** textbooks, McGraw-Hill will help correlate all text, supplement, and appropriate materials and services to your course syllabus. Simply call your McGraw-Hill sales representative for assistance.

PAGEOUT LITE

Free to **Course Solutions** textbook adopters, *PageOut Lite* is perfect for instructors who want to create their own Web site. In just a few minutes, even novices can turn their syllabus into a Web site using *PageOut Lite*.

PAGEOUT: THE COURSE WEB SITE DEVELOPMENT CENTER

For those that want the benefits of *PageOut Lite*’s no-hassle approach to site development, but with even more features, we offer *PageOut: The Course Web Site Development Center*.

PageOut shares many of *PageOut Lite*’s features, but also enables you to create links that will take your students to your original material, other Web site addresses, and to *McGraw-Hill Online Learning Center* content. This means you can assign *Online Learning Center* content within your syllabus-based Web site. *PageOut*’s gradebook function will tell you when each student has taken a quiz or worked through an exercise, automatically recording their scores for you. *PageOut* also features a discussion board list where you and your students can exchange questions and post announcements, as well as an area for students to build personal Web pages.

OTHER DELIVERY OPTIONS

Online Learning Centers are also compatible with a number of full-service online course delivery systems or outside educational service providers. For a current list of compatible delivery systems, contact your McGraw-Hill sales representative.

And for your students...

MCGRAW-HILL STUDENT TUTORIAL SERVICE

Within each *Online Learning Center* resides a **FREE Student Tutorial Service**. This web-based “homework hotline”—available via a threaded discussion list—features guaranteed, 24-hour response time on weekdays.

www.mhhe.com/hartwell

BRIEF CONTENTS

ABOUT THE AUTHORS VI

PREFACE XIX

PROLOGUE 1

PART I

BASIC PRINCIPLES: HOW TRAITS ARE TRANSMITTED 8

CHAPTER 1

MENDEL'S BREAKTHROUGH: PATTERNS, PARTICLES, AND PRINCIPLES OF HEREDITY 10

CHAPTER 2

EXTENSIONS TO MENDEL: COMPLEXITIES IN RELATING GENOTYPE TO PHENOTYPE 38

CHAPTER 3

THE CHROMOSOME THEORY OF INHERITANCE 70

CHAPTER 4

LINKAGE, RECOMBINATION, AND THE MAPPING OF GENES ON CHROMOSOMES 105

PART II

WHAT GENES ARE AND WHAT THEY DO 142

CHAPTER 5

DNA: HOW THE MOLECULE OF HEREDITY CARRIES, REPLICATES, AND RECOMBINES 144

CHAPTER 6

ANATOMY AND FUNCTION OF A GENE: DISSECTION THROUGH MUTATION 179

CHAPTER 7

GENE EXPRESSION: THE FLOW OF GENETIC INFORMATION FROM DNA VIA RNA TO PROTEIN 222

PART III

USING GENETIC ENGINEERING TO UNRAVEL THE INFORMATION IN GENOMES 260

CHAPTER 8

DNA AT HIGH RESOLUTION: USE OF DNA CLONING, PCR, AND HYBRIDIZATION AS THE TOOLS OF GENETIC ANALYSIS 262

CHAPTER 9

THE DIRECT DETECTION OF GENOTYPE 308

CHAPTER 10

THE MAPPING AND ANALYSIS OF GENOMES 341

PART IV

HOW GENES TRAVEL 388

CHAPTER 11

THE EUKARYOTIC CHROMOSOME: AN ORGANELLE FOR PACKAGING AND MANAGING DNA 390

CHAPTER 12

CHROMOSOMAL REARRANGEMENTS AND CHANGES IN CHROMOSOME NUMBER RESHAPE EUKARYOTIC GENOMES 419

CHAPTER 13

THE PROKARYOTIC CHROMOSOME: GENETIC ANALYSIS IN BACTERIA 461

CHAPTER 14

THE CHROMOSOMES OF ORGANELLES OUTSIDE THE NUCLEUS EXHIBIT NON-MENDELIAN PATTERNS OF INHERITANCE 501

CONTENTS

ABOUT THE AUTHOR VI

PREFACE XIX

PROLOGUE 1

GENETICS: THE STUDY OF BIOLOGICAL INFORMATION 1

BIOLOGICAL INFORMATION IS ENCODED IN DNA MOLECULES 2

BIOLOGICAL FUNCTION EMERGES FROM PROTEIN MOLECULES 2

ALL LIVING THINGS ARE CLOSELY RELATED 3

THE MODULAR CONSTRUCTION OF GENOMES HAS ALLOWED THE RELATIVELY RAPID EVOLUTION OF COMPLEXITY 4

GENETIC TECHNIQUES PERMIT THE DISSECTION OF COMPLEXITY 6

OUR FOCUS IS ON HUMAN GENETICS 6

PART I

BASIC PRINCIPLES: HOW TRAITS ARE TRANSMITTED 8

CHAPTER 1

MENDEL'S BREAKTHROUGH: PATTERNS, PARTICLES, AND PRINCIPLES OF HEREDITY 10

BACKGROUND: THE HISTORICAL PUZZLE OF INHERITANCE 12

Artificial Selection Was the First Applied Genetic Practice 12

The Puzzle of Passing on Desirable Traits 12

A New Experimental Approach 14

GENETIC ANALYSIS ACCORDING TO MENDEL 16

Monohybrid Crosses Reveal Units of Inheritance and the Law of Segregation 16

Mendel's Results Reflect Basic Rules of Probability 18

Fast Forward 20

Genes Encode Proteins 20

Dihybrid Crosses Reveal the Law of Independent Assortment 21

Why Mendel's Work Was Unappreciated Before 1900 24

MENDELIAN INHERITANCE IN HUMANS:
A COMPREHENSIVE EXAMPLE 25

A Vertical Pattern of Inheritance Indicates a Rare Dominant Trait 26

A Horizontal Pattern of Inheritance Indicates a Rare Recessive Trait 27

Fast Forward 28

The Direct Analysis of Human Genotype 28

Genetics and Society 30

Developing Guidelines for Genetic Screening 30

CHAPTER 2

EXTENSIONS TO MENDEL: COMPLEXITIES IN RELATING GENOTYPE TO PHENOTYPE 38

EXTENSION TO MENDEL FOR SINGLE-GENE INHERITANCE 39

Dominance Is Not Always Complete 39

A Gene May Have More Than Two Alleles 42

One Gene May Contribute to Several Visible Characteristics 44

A Comprehensive Example: Sickle-Cell Syndrome Illustrates Many Extensions to Mendel's Analysis of Single-Gene Inheritance 47

EXTENSIONS TO MENDEL FOR MULTIFACTORIAL INHERITANCE 49

Two Genes Can Interact to Determine One Trait 49

Breeding Studies Help Decide How a Trait Is Inherited 55

The Same Genotype Does Not Always Produce the Same Phenotype 57

Genetics and Society 59

Disease Prevention versus the Right to Privacy 59

Even Continuous Variation Can Be Explained by Extensions to Mendelian Analysis 60

The Mouse's Coat and Tail: A Comprehensive Example of Multiple Alleles and Multifactorial Traits 62

CHAPTER 3

THE CHROMOSOME THEORY OF INHERITANCE 70

CHROMOSOMES CONTAIN THE GENETIC MATERIAL 71

Evidence That Genes Reside in the Nucleus 72

Evidence That Genes Reside in the Chromosomes 72

MITOSIS ENSURES THAT EVERY CELL IN AN ORGANISM CARRIES THE SAME CHROMOSOMES 76

During Interphase, Cells Grow and Replicate Their Chromosomes 76

During Mitosis (M Phase), Sister Chromatids Separate and Are Apportioned to Different Daughter Nuclei 77

Regulatory Checkpoints Ensure Correct Chromosome Separation During Mitosis 79

Fast Forward 80

How Gene Mutations Cause Errors in Mitosis 80

MEIOSIS PRODUCES HAPLOID GERM CELLS, OR GAMETES 82*Meiosis Consists of One Round of Chromosome Replication but Two Rounds of Nuclear Division 82**During Meiosis I, Homologous Chromosomes Pair, Exchange Parts, and Then Segregate from Each Other 83**During Meiosis II, Sister Chromatids Separate to Produce Haploid Gametes 87**A Summary of the Significant Events of Meiosis 87**Meiosis Contributes to Genetic Diversity 87**Meiosis and Mitosis: A Comparison 88***GAMETOGENESIS REQUIRES BOTH MITOTIC AND MEIOTIC DIVISIONS 90***Egg Formation in Humans: Asymmetrical Meiotic Divisions Produce One Large Ovum 90**Spermatogenesis in Humans: Symmetrical Meiotic Divisions Produce Four Sperm 91***VALIDATION OF THE CHROMOSOME THEORY 91***The Chromosome Theory Correlates Mendel's Laws with Chromosome Behavior during Meiosis 91**Specific Traits Are Transmitted with Specific Chromosomes 93**The Chromosome Theory Integrates Many Aspects of Gene Behavior 98***CHAPTER 4****LINKAGE, RECOMBINATION, AND THE MAPPING OF GENES ON CHROMOSOMES 105****GENE LINKAGE AND RECOMBINATION 106***Some Genes on the Same Chromosome Assort Together More Often than Not 106**Recombination Results When Crossing Over During Meiosis Separates Linked Genes 112***Genetics and Society 114***Mitotic Recombination and Cancer Formation 114**Linkage and Recombination: A Summary 118***MAPPING: LOCATING GENES ALONG A CHROMOSOME 118***Two-Point Crosses: Comparisons Help Establish Relative Gene Positions 119**Three-Point Crosses: A Faster, More Accurate Way to Map Genes 119**How Close Is the Correlation Between a Genetic Map and Physical Reality? 123***Fast Forward 124***Gene Mapping Leads to a Possible Cure for Cystic Fibrosis 124**Multiple Factor Crosses Help Establish Linkage Groups by Inference 124**Tetrad Analysis in Fungi: A Powerful Tool for Mapping and for Understanding the Mechanisms of Recombination 125***PART II****WHAT GENES ARE AND WHAT THEY DO 142****CHAPTER 5****DNA: HOW THE MOLECULE OF HEREDITY CARRIES, REPLICATES, AND RECOMBINES INFORMATION 144****EXPERIMENTS DESIGNATE DNA AS THE GENETIC MATERIAL 145***Chemical Characterization Localizes DNA in the Chromosomes 145**Bacterial Transformation Implicates DNA as the Substance of Genes 146**Convincing Evidence That Genes Are DNA: The Molecule Carries the Information Required for the Replication of Bacterial Viruses 149***THE WATSON-CRICK MODEL: DNA IS A DOUBLE HELIX 150***Nucleotides Are the Basic Building Blocks of DNA 150**The Double Helix Contains Two Antiparallel Chains That Associate by Complementary Base Pairing 152**The Double Helix May Assume Alternative Forms 153**DNA Structure Is the Foundation of Genetic Function 153***DNA STORES INFORMATION IN THE SEQUENCE OF ITS BASES 156***Much of DNA's Sequence-Specific Information Is Accessible Only When the Double Helix Is Unwound 156**Some Genetic Information Is Accessible Even in Intact, Double-Stranded DNA Molecules 156**A Few Viruses Use RNA as the Repository of Genetic Information 157***DNA REPLICATION: COPYING GENETIC INFORMATION FOR TRANSMISSION TO THE NEXT GENERATION 157***Complementary Base Pairing Produces Semiconservative Replication: An Overview 157**The Molecular Mechanism of Replication: Doubling the Double Helix 160**The Mechanics of DNA Replication at the Chromosomal Level 161**Cells Must Ensure the Accuracy of Their Genetic Information—Before, During, and After Replication 161***RECOMBINATION RESHUFFLES THE INFORMATION CONTENT OF DNA 164***During Recombination, DNA Molecules Break and Rejoin 165***Fast Forward 166***Restriction Enzymes Recognize Specific Base Sequences in DNA 166**A Molecular Model of Crossing Over 169*

CHAPTER 6

ANATOMY AND FUNCTION OF A GENE: DISSECTION THROUGH MUTATION 179

MUTATIONS: PRIMARY TOOLS OF GENETIC ANALYSIS 180

Mutations Are Heritable Changes in Base Sequences That Modify the Information Content of DNA 180

Spontaneous Mutations Affecting Genes Occur at a Very Low Rate 181

Mutations Arise from Many Kinds of Random Events 182

Genetics and Society 188

A New Class of Human Mutation: Amplified Repeats with Medical Consequences 188

Impact: Mutations Have Consequences for the Evolution of Species and the Survival of Organisms 190

WHAT MUTATIONS TELL US ABOUT GENE STRUCTURE 191

Complementation Testing Reveals Whether Two Mutations Are in the Same or Different Genes 191

A Gene Is a Linear Sequence of Nucleotide Pairs That Can Mutate Independently and Recombine with Each Other 194

A Gene Is a Discrete Linear Set of Nucleotides 197

WHAT MUTATIONS TELL US ABOUT GENE FUNCTION 201

The One Gene, One Enzyme Hypothesis: A Gene Contains the Information for Producing a Specific Enzyme 201

Genes Direct the Synthesis of Proteins by Specifying the Identity and Order of Amino Acids in a Polypeptide Chain 203

HOW GENOTYPE CORRELATES WITH PHENOTYPE 207

Fast Forward 208

Using Mutagenesis to Look at Biological Processes 208

Dominance Relations Between Alleles Depend on the Relation Between Protein Function and Phenotype 208

HOW GENE MUTATIONS AFFECT LIGHT-RECEIVING PROTEINS AND VISION: A COMPREHENSIVE EXAMPLE 212

The Cellular and Molecular Basis of Vision 212

How Mutations in the Rhodopsin Family Influence the Way We See 213

CHAPTER 7

GENE EXPRESSION: THE FLOW OF GENETIC INFORMATION FROM DNA VIA RNA TO PROTEIN 222

THE GENETIC CODE: HOW PRECISE GROUPINGS OF THE 4 NUCLEOTIDES SPECIFY 20 AMINO ACIDS 224

In the Genetic Code, A Triplet Codon Represents Each Amino Acid 224

Mapping Studies Confirmed That a Gene's Nucleotide Sequence Is Colinear with a Polypeptide's Amino-Acid Sequence 225

Genetic Analysis Revealed That Nonoverlapping Codons Are Set in a Reading Frame 225

Cracking the Code: Biochemical Manipulations Revealed Which Codons Represent Which Amino Acids 228

The Genetic Code: A Summary 230

Using Genetics to Verify the Code 231

The Genetic Code Is Almost, But Not Quite, Universal 232

TRANSCRIPTION: RNA POLYMERASE SYNTHESIZES A SINGLE-STRANDED RNA COPY OF A GENE 232

Details of the Process 232

In Eukaryotes, RNA Processing after Transcription Produces a Mature Messenger RNA 232

TRANSLATION: BASE-PAIRING BETWEEN MRNA AND TRNAs DIRECTS ASSEMBLY OF A POLYPEPTIDE ON THE RIBOSOME 240

Transfer RNAs 240

Genetics and Society 242

HIV and Reverse Transcription: An Unusual DNA Polymerase Helps Give the AIDS Virus an Evolutionary Edge 242

Ribosomes Are the Sites of Polypeptide Synthesis 244

The Mechanism of Translation 244

Processing after Translation Can Change a Polypeptide's Structure 245

COMPREHENSIVE EXAMPLE: A COMPUTERIZED ANALYSIS OF GENE EXPRESSION IN *C. ELEGANS* 248

HOW MUTATIONS AFFECT GENE EXPRESSION 249

Mutations in a Gene's Coding Sequence Can Alter the Gene Product 249

Mutations in a Gene Outside the Coding Sequence Can Also Alter Gene Expression 249

Mutations in Genes Encoding the Molecules That Implement Expression May Affect Transcription, mRNA Splicing, or Translation 250

PART III

USING GENETIC ENGINEERING TO UNRAVEL THE INFORMATION IN GENOMES 260

CHAPTER 8

DNA AT HIGH RESOLUTION: USE OF DNA CLONING, PCR, AND HYBRIDIZATION AS THE TOOLS OF GENETIC ANALYSIS 262

CUTTING THE DNA: RESTRICTION ENZYMES SERVE AS MOLECULAR SCISSORS 264

Restriction Enzymes Fragment the Genome at Specific Sites 264

Different Restriction Enzymes Produce Fragments of Different Lengths 264

Genetics and Society 266

Serendipity in Science: The Discovery of Restriction Enzymes 266

Different Restriction Enzymes Produce Different Numbers of Fragments from the Same Genome 266

PURIFICATION AND AMPLIFICATION OF FRAGMENTS FOR STORAGE AND ANALYSIS 268

Cloning Step 1: Ligation of Fragments to Cloning Vectors Creates Recombinant DNA Molecules 268

Cloning Step 2: Host Cells Take Up Vector-Insert Recombinants and Amplify Them When They Copy Their Own Chromosomes 269

Cloned DNA Is Purified by Various Means That Separate Recombinant Plasmid from Host DNA, Then Insert from Vector 272

Libraries Are Collections of Cloned Fragments 273

IDENTIFYING AND ISOLATING CLONES OF INTEREST 277

Screening with DNA Probes: Hybridization to Complementary Sequences Picks Out Fragments of Interest 277

Screening through Expression: Genes Cloned in Specialized Vectors Produce Proteins That Light Up with Specific Labeled Antibodies 279

CHARACTERIZING CLONED FRAGMENTS BY THEIR SIZE, POSITION, AND SEQUENCE 280

Gel Electrophoresis Distinguishes DNA Fragments According to Size 280

Restriction Maps Provide a Rough Roadmap of a Clone 284

Hybridization Can Also Serve as a Tool of Characterization 284

Sequencing Provides the Highest Resolution of a Cloned DNA Fragment: A Complete Description of Its Nucleotide Sequence 285

Computer Analysis of DNA Sequences Can Identify Significant Genetic Motifs as well as Resemblances to Previously Determined Sequences 287

The Polymerase Chain Reaction Can Amplify Small DNA Fragments of Partially Known Sequence for Further Analysis 287

UNDERSTANDING THE GENES FOR HEMOGLOBIN: A COMPREHENSIVE EXAMPLE 293

The Genes Encoding Hemoglobin Occur in Two Clusters on Two Separate Chromosomes 293

A Variety of Mutations Accounts for the Diverse Symptoms of Globin-Related Diseases 294

The α - and β -Globin Loci House Multiple Genes that Evolved from One Ancestral Gene 296

CHAPTER 9

THE DIRECT DETECTION OF GENOTYPE 308

DNA VARIATIONS PROVIDE THE BASIS FOR THE DIRECT DETECTION OF GENOTYPE 311

Individual Members of the Same Species Show Enormous Sequence Variation in their Genomes 311

Genetics and Society 312

Social and Ethical Issues Surrounding Preimplantation Embryo Diagnosis 312

For the Purposes of Genotype Detection, Geneticists Categorize DNA Polymorphisms in Five Different Classes 312

PROTOCOLS OF DETECTION: IDENTIFYING SPECIFIC VARIANTS WITHIN INDIVIDUAL GENOMES 316

A Variety of Protocols Detect Single-Base Changes 316

For Microsatellites: PCR-Based Protocols Detect Polymorphisms 322

For Minisatellites, Because of Their Size, Detection of Polymorphisms Depends on Southern Blotting and Hybridization Probes 323

Deletions, Duplications, and Other Insertions: Protocols Detect Disruptions of Wild-Type Sequences 323

Complex Haplotypes: For Efficient Detection, Sequencing Is the Technique of Choice 324

Karyotype Analysis Detects Gross Chromosomal Rearrangements 324

On the Horizon: The Simultaneous Analysis of Hundreds of Thousands of Alleles by DNA Arrays on Microchips 324

TWO APPLICATIONS OF GENOTYPE DETECTION: DISEASE DIAGNOSIS AND DNA FINGERPRINTING 326

Disease Diagnosis: Discovering Whether an Individual Carries One, Two, or No Copies of a Particular Allele 326

DNA Fingerprinting: Comparing Genotypic Patterns for Many Loci to Distinguish and Determine the Relationship of Different Individuals 330

Genetics and Society 332

Does DNA Fingerprinting Serve the Interests of Justice? 332

CHAPTER 10

THE MAPPING AND ANALYSIS OF GENOMES 341

LARGE-SCALE MAPS SERVE AS GUIDES TO WHOLE GENOMES 344

High-Density Linkage Maps: Computerized Analyses of Transmission Data Position Unlimited Numbers of Markers in Relation to Each Other 344

Long-Range Physical Maps: Karyotypes and Genomic Libraries Provide the Basis for Positioning Markers on Chromosomes 345

Long-Range Sequence Maps: Molecular Protocols Make It Possible to Obtain a Readout of Every Nucleotide in a Chromosome 350

How the Different Kinds of Maps Relate to Each Other 351

POSITIONAL CLONING: USING LARGE-SCALE MAPS TO MOVE FROM PHENOTYPE TO A CLONE OF THE RESPONSIBLE GENE 351

Correlating Phenotypic Transmission with One Area of the Genome (a) 351

Genetics and Society 358

Using Human Pedigrees and LOD Scores to Calculate the Probability That Two Loci Are Linked 358

Identifying Candidate Genes (b) 360

Finding the One Gene among All the Candidates That Is Responsible for the Phenotype (c) 363

Summary: Positional Cloning of the Cystic Fibrosis Gene Leads to a Potential Disease Therapy 365

USING SEQUENCE MAPS AS A STARTING POINT FOR MOVING FROM THE CLONE OF A GENE TO ITS FUNCTION 365

A Gene's Sequence Can Provide Insight into the Structure and Function of the Polypeptide It Encodes 367