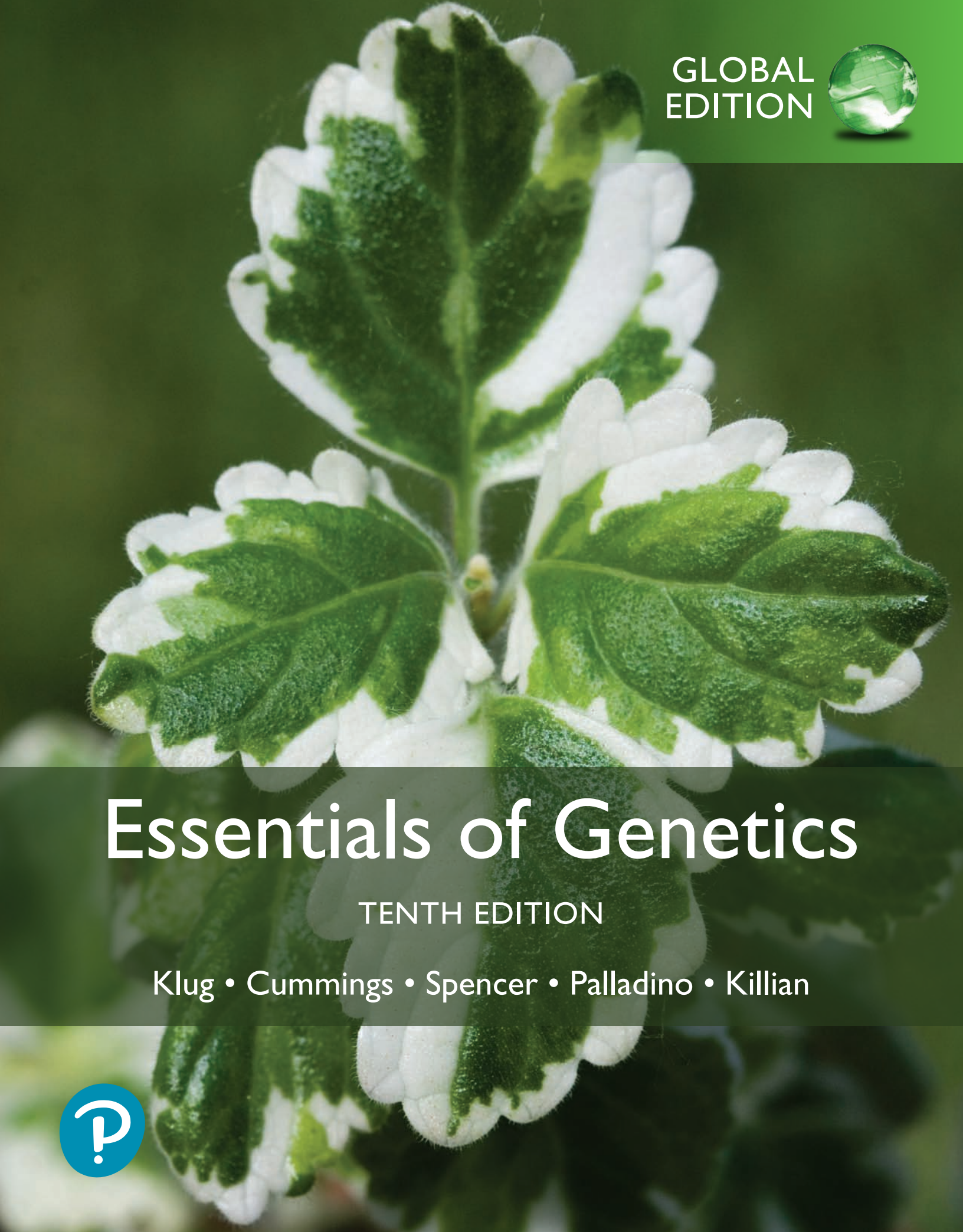
GLOBAL
EDITION
Essentials of Genetics
TENTH EDITION
Klug • Cummings • Spencer • Palladino • Killian

EVOLVING CONCEPT OF THE GENE

The Evolving Concept of the Gene is a unique feature, integrated into key chapters, which highlights how scientists' understanding of the gene has changed over time. By underscoring how the conceptualization of the gene has evolved, our goal is to help students appreciate the process of discovery that has led to an ever more sophisticated understanding of hereditary information.

CHAPTER 3 pg. 66 Based on the pioneering work of Gregor Mendel, the gene was viewed as a heritable unit factor that determines the expression of an observable trait, or phenotype. ■

CHAPTER 4 pg. 82 Based on the work of many geneticists following the rediscovery of Mendel's work in the very early part of the twentieth century, the chromosome theory of inheritance was put forward, which hypothesized that chromosomes are the carriers of genes and that meiosis is the physical basis of Mendel's postulates. In the ensuing 40 years, the concept of a gene evolved to reflect the idea that this hereditary unit can exist in multiple forms, or alleles, each of which can have an impact on the phenotype in different ways, leading to incomplete dominance, codominance, and even lethality. It became clear that the process of mutation was the source of new alleles. ■

CHAPTER 7 pg. 160 Based on the gene-mapping studies in *Drosophila* and many other organisms from the 1920s through the mid-1950s, geneticists regarded genes as hereditary units organized in a specific sequence along chromosomes, between which recombination could occur. Genes were thus viewed as indivisible "beads on a string." ■

CHAPTER 9 pg. 199 Based on the model of DNA put forward by Watson and Crick in 1953, the gene was viewed for the first time in molecular terms as a sequence of nucleotides in a DNA helix that encodes genetic information. ■

CHAPTER 12 pg. 260 The elucidation of the genetic code in the 1960s supported the concept that the gene is composed of a linear series of triplet nucleotides encoding the amino acid sequence of a protein. While this is indeed the case in bacteria and viruses, in 1977, it became apparent that in eukaryotes, the gene is divided into coding sequences, called exons, which are interrupted by noncoding sequences, called introns (intervening sequences), which must be spliced out during production of the mature mRNA. ■

CHAPTER 13 pg. 278 In the 1940s, a time when the molecular nature of the gene had yet to be defined, groundbreaking work of Beadle and Tatum provided the first experimental evidence concerning the product of genes, their "one-gene:one-enzyme" hypothesis. This idea received further support and was later modified to indicate that one gene specifies one polypeptide chain. ■

CHAPTER 15 pg. 319 The groundbreaking work of Jacob, Monod, and Lwoff in the early 1960s, which established the operon model for the regulation of gene expression in bacteria, expanded the concept of the gene to include noncoding regulatory sequences that are present upstream (5′) from the coding region. In bacterial operons, the transcription of several contiguous structural genes whose products are involved in the same biochemical pathway is regulated in a coordinated fashion. ■

CHAPTER 18 pg. 383 Based on the work of the ENCODE project, we now know that DNA sequences that have previously been thought of as "junk DNA," because they do not encode proteins, are nonetheless often transcribed into what we call noncoding RNA (ncRNA). Since the function of some of these RNAs is now being determined, we must consider whether the concept of the gene should be expanded to include DNA sequences that encode ncRNAs. At this writing, there is no consensus, but it is important for you to be aware of these current findings as you develop your final interpretation of a gene. ■

ESSENTIALS *of* GENETICS

Tenth Edition
Global Edition

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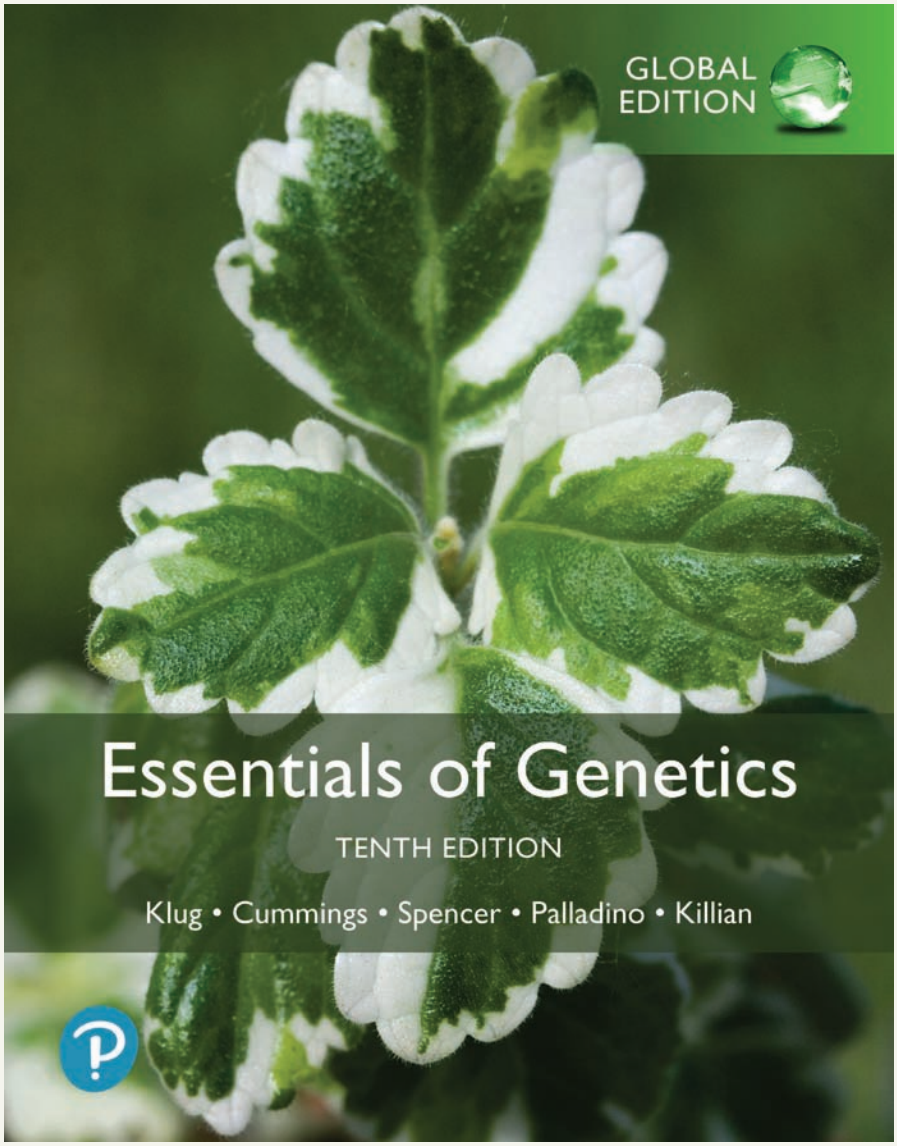
Focus on essential genetic topics and explore the latest breakthroughs

Known for its focus on conceptual understanding, problem solving, and practical applications, the bestselling *Essentials of Genetics* strengthens problem-solving skills and explores the essential genetics topics that today's students need to understand. The 10th Edition has been extensively updated to provide comprehensive coverage of important, emerging topics such as CRISPR-Cas, epigenetics, and genetic testing and Mastering Genetics includes new tutorials on these topics, which prepare students for class and support the learning of key concepts.



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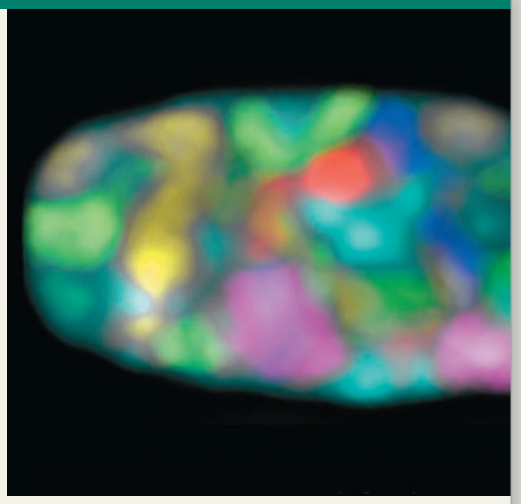
16

Regulation of Gene Expression in Eukaryotes



Chromosome territories in a human fibroblast cell nucleus. Each chromosome is stained with a different-colored probe.

CHAPTER CONCEPTS

- While transcription and translation are tightly coupled in bacteria, in eukaryotes, these processes are spatially and temporally separated, and thus independently regulated.
- Chromatin remodeling, as well as modifications to DNA and histones, play important roles in regulating gene expression in eukaryotes.
- Eukaryotic transcription initiation requires the assembly of transcription regulatory proteins on DNA sites known as promoters, enhancers, and silencers.
- Following transcription, there are several mechanisms that regulate gene expression, referred to as posttranscriptional regulation.
- Alternative splicing allows for a single gene to encode different protein isoforms with different functions.
- RNA-binding proteins regulate mRNA stability, degradation, localization, and translation.
- Noncoding RNAs may regulate gene

Virtually all cells in a multicellular eukaryotic organism contain a complete genome; however, such organisms often possess different cell types with diverse morphologies and functions. This simple observation highlights the importance of the regulation of gene expression in eukaryotes. For example, skin cells and muscle cells differ in appearance and function because they express different genes. Skin cells express keratins, fibrous structural proteins that bestow the skin with protective properties. Muscle cells express high levels of myosin II, a protein that mediates muscle contraction. Skin cells do not express myosin II, and muscle cells do not express keratins.

In addition to gene expression that is cell-type specific, some genes are only expressed under certain conditions or at certain times. For example, when oxygen levels in the blood are low, such as at high altitude or after rigorous exercise, expression of the hormone erythropoietin is upregulated, which leads to an increase in red blood cell production and thus oxygen-carrying capacity.

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NEW! Regulation of gene expression has been expanded and is now divided into coverage of bacteria in Chapter 15 and coverage of eukaryotes in Chapter 16.

Coverage of CRISPR-Cas is expanded and integrated in multiple chapters – Chapters 1, 15, 17, and Special Topics Chapters ST3 and ST6.

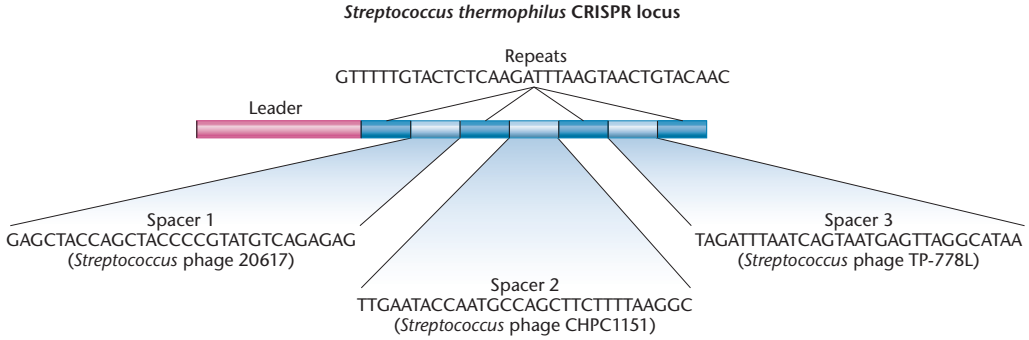

FIGURE 15.13 A CRISPR locus from the bacterium *Streptococcus thermophilus* (LMG18311). Spacer sequences are derived from portions of bacteriophage genomes and are flanked on either side by a repeat sequence. Only 3 of 33 total spacers in this CRISPR locus are shown.

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with current high interest topics

SPECIAL TOPICS IN MODERN GENETICS 2

Genetic Testing

SPECIAL TOPIC X

Earlier in the text (see Chapters 17 and 18), we reviewed essential concepts of recombinant DNA technology and genomic analysis. Because of the Human Genome Project and related advances in genomics, researchers have been making rapid progress in identifying genes involved in both single-gene diseases and complex genetic traits. As a result, **genetic testing**—the ability to analyze DNA, and increasingly RNA, for the purposes of identifying specific genes or sequences associated with different genetic conditions—has advanced very rapidly.

Genetic testing, including genomic analysis by DNA sequencing, is transforming medical diagnostics. Technologies for genetic testing have had major impacts on the diagnosis of disease and are revolutionizing medical treatments based on the development of specific and effective pharmaceuticals. In this Special Topics chapter we provide an overview of applications that are effective for the genetic testing of children and adults and examine historical and modern methods. We consider the impact of different genetic technologies on the diagnosis of human diseases and dystrophy. Other tests have been developed for disorders that may involve multiple genes such as certain types of cancers.

Gene tests are used for prenatal, childhood, and adult prognosis and diagnosis of genetic diseases; to identify carriers; and to identify genetic diseases in embryos created by *in vitro* fertilization, among other applications. For genetic testing of adults, DNA from white blood cells is commonly used. Alternatively, many genetic tests can be carried out on cheek cells, collected by swabbing the inside of the mouth, or on hair cells. Some genetic testing can be carried out on gametes.

"Genetic testing, including genomic analysis by DNA sequencing, is transforming medical diagnostics. Technologies for genetic testing have had major

What does it mean when a genetic test is performed for *prognostic* purposes, and how does this differ from a *diagnostic* test? A prognostic test predicts a person's likelihood of developing a particular genetic disorder. A diagnostic test for a genetic condition

NEW! Special Topics chapter on Genetic Testing guides students through the many contexts in which genetic testing is becoming prominent and explores many questions and ethical concerns related to its use.

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SPECIAL TOPICS IN MODERN GENETICS 4

Advances in Neurogenetics: The Study of Huntington Disease

SPECIAL TOPIC 4

As the result of groundbreaking advances in molecular genetics and genomics made since the 1970s, new fields in genetics and related disciplines have emerged. One new field is **neurogenetics**—the study of the genetic basis of normal and abnormal functioning of the nervous system, with emphasis on brain functions. Research in this field includes the genes associated with neurodegenerative disorders, with the ultimate goal of developing effective therapies to combat these devastating conditions. Of the many such diseases, including Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis (ALS), **Huntington disease (HD)** stands out as a model for the genetic investigation of neurodegenerative disorders. Not only is it monogenic and 100 percent penetrant, but nearly all analytical approaches in molecular genetics have been successfully applied to the study of HD, validating its significance as a model for these diseases.

HD is an autosomal dominant disorder characterized by adult onset of defined and progressive behavioral changes, including uncontrolled movements (chorea), cognitive decline, and psychiatric disturbances, with death occurring within 10 to 15 years after symptoms appear. HD was one of the first examples of complete dominance in human inheritance, with no differences in phenotypes between homozygotes and heterozygotes. In the vast majority of cases, symptoms do not develop until about age 45. Overall, HD currently affects about 25,000 to 30,000 people in North America.

The disease is named after George Huntington, a nineteenth-century physician. He was not the first to describe the disorder, know about the molecular and cellular mechanisms associated with the disorder, particularly those discovered during the study of transgenic model systems. Finally, we will consider how this information is being used to develop a range of therapies.

"Driving with my father through a wooded road leading from Easthampton to Amagansett, we suddenly came upon two women, mother and daughter, both bowing, twisting, grimacing. I stared in wonderment, almost in fear. What could it mean?"

ST 4.1 The Search for the Huntington Gene

Mapping the gene for Huntington disease was one of the first attempts to employ a method from a landmark 1980 paper by Botstein, White, and Davis in which the authors proposed that DNA sequence variations in humans could be detected as differences in the length of DNA fragments produced by cutting DNA with restriction enzymes. These differences, known as restriction fragment length polymorphisms (RFLPs), could be visualized using Southern blots (see Chapter 18 for a discussion of RFLPs, and Chapter 17 for a discussion of Southern blots). The authors estimated that a collection of about 150 RFLPs distributed across the genome could be used with pedigrees to detect linkage anywhere in the genome between an RFLP marker and a disease gene of interest. In practical terms, this meant that it would be possible to map a disease gene with no information about the gene, its gene product, or its function—an approach referred to as reverse genetics.

NEW! Special Topics chapter on Advances in Neurogenetics: The Study of Huntington Disease, explores how genetic analysis has informed scientists about the disease's causes, symptoms, and future treatment. All Special Topics chapters include a series of questions that help students review key ideas or facilitate personal contemplations and group discussions, and are assignable in Mastering Genetics.

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Explore the latest ethical considerations

GENETICS, ETHICS, AND SOCIETY

Down Syndrome and Prenatal Testing—The New Eugenics?

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

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

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

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

Given the history of the eugenics movement, is it fair to use the term *eugenics* when we speak about genetic testing for Down syndrome and other genetic disorders? Some people argue that it is not eugenic to select for healthy children because there is no coercion, the state is not involved, and the goal is the elimination of suffering. Others point out that such voluntary actions still constitute eugenics, since they involve a form of bioengineering for "better" human beings.

Now that we are entering an era of unprecedented knowledge about our genomes and our predisposition to genetic disorders, we must make decisions about whether our attempts to control or improve human genomes are ethical and what limits we should place on these efforts. The story of the eugenics movement provides us with a powerful cautionary tale about the potential misuses of genetic information.

Your Turn

Take time, individually or in groups, to consider the following questions. Investigate the references and links to help you discuss some of the ethical issues surrounding genetic testing and eugenics.

1. Do you think that modern prenatal and preimplantation genetic testing followed by selective abortion is eugenic? Why or why not?

For background on these questions, see McCabe, L., and McCabe, E. (2011). Down syndrome: Coercion and eugenics. *Genet. Med.* 13:708–710. *Another useful discussion can be found in* Wilkinson, S., (2015). Prenatal screening, reproductive choice, and public health. *Bioethics* 29:26–35.

2. If genetic technologies were more advanced than today, and you could choose the traits of your children, would you take advantage of that option? Which traits would you choose—height, weight, intellectual abilities, athleticism, artistic talents? If so, would this be eugenic? Would it be ethical?

To read about similar questions answered by groups of Swiss law and medical students, read Elger, B., and Harding, T., (2003). Huntington's disease: Do future physicians and lawyers think eugenically? *Clin. Genet.* 64:327–338.

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Genetics, Ethics, and Society essays provide synopses of ethical issues related to current findings in genetics that impact directly on society today. They include a section called *Your Turn*, which directs students to related resources of short readings and websites to support deeper investigation and discussion of the main topic of each essay.

Case Studies at the end of each chapter have been updated with new topics. Students can read and answer questions about a short scenario related to one of the chapter topics. Each Case Study links the coverage of formal genetic knowledge to everyday societal issues, and they include ethical considerations.

CASE STUDY To test or not to test

Thomas discovered a devastating piece of family history when he learned that his brother had been diagnosed with Huntington disease (HD) at age 49. This dominantly inherited autosomal condition usually begins around age 45 with progressive dementia, muscular rigidity, and seizures and ultimately leads to death when affected individuals are in their early 60s. There currently is no effective treatment or cure for this genetic disorder. Thomas, now 38, wonders what the chances are that he also has inherited the mutant allele for HD, leading him to discuss with his wife whether they should seek genetic counseling and whether he should undergo genetic testing. They have two teenage children, a boy and a girl.

1. If they seek genetic counseling, what issues would likely be discussed? Which of these pose grave ethical dilemmas?
2. If you were in Thomas's position, would you want to be tested and possibly learn that you were almost certain to develop the disorder sometime in the next 5–10 years?
3. If Thomas tests positive for the HD allele, should his children be told about the situation, and if so, at what age? Who should make the decision about having the son and daughter tested?

Fulda, K., and Lykens, K. (2006). Ethical issues in predictive genetic testing: A public health perspective. *J. Med. Ethics* 32:143–147.

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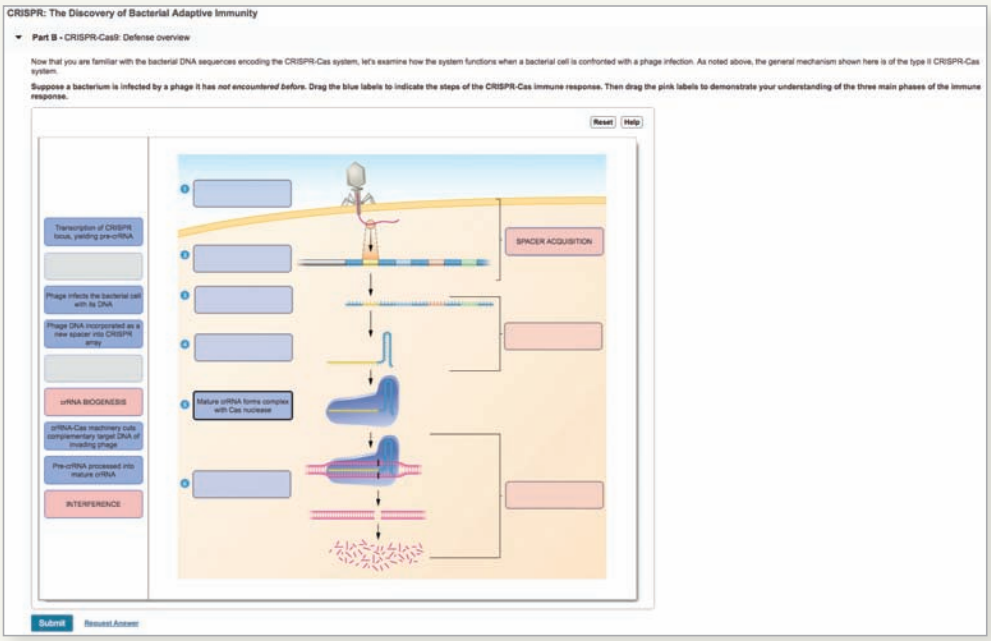
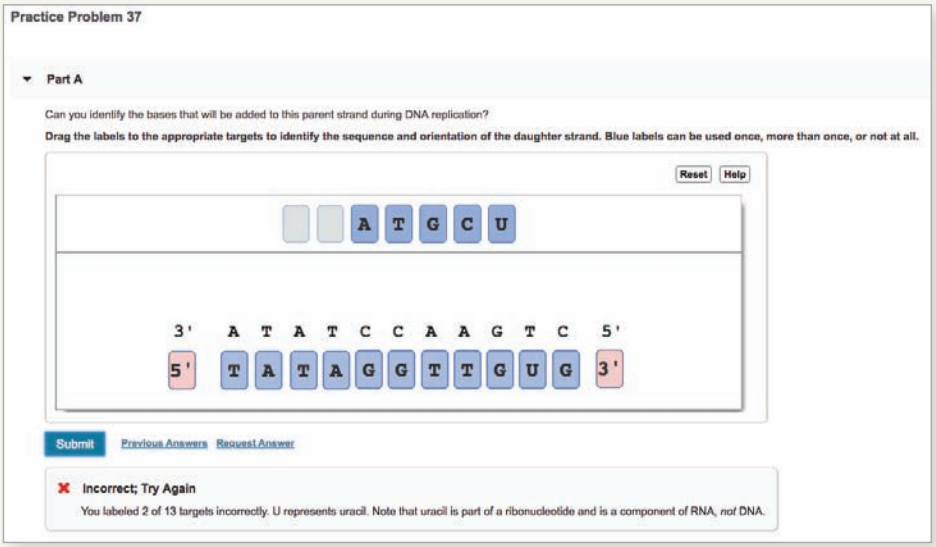
Learn genetics concepts and problem solving in Mastering Genetics



NEW! Tutorials have been added to the library on topics like CRISPR-Cas and epigenetics, to help students master important and challenging concepts.

A library of over 100 Practice Problems offers more opportunities to assign high quality problems for student homework or practice. These questions appear only in Mastering Genetics and include targeted wrong-answer feedback to help students learn from their mistakes. They are similar to end-of-chapter questions in terms of topic coverage and difficulty.



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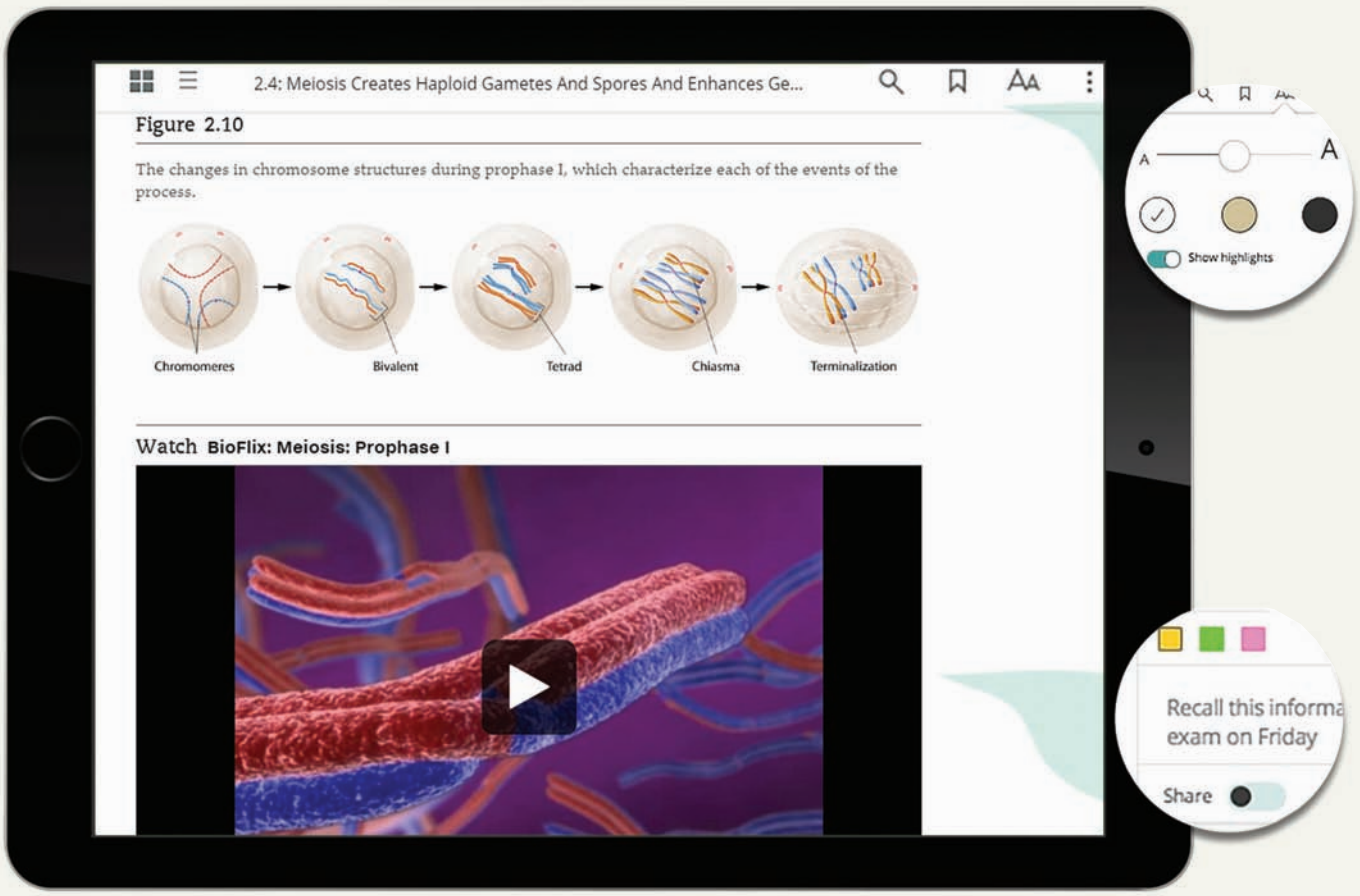

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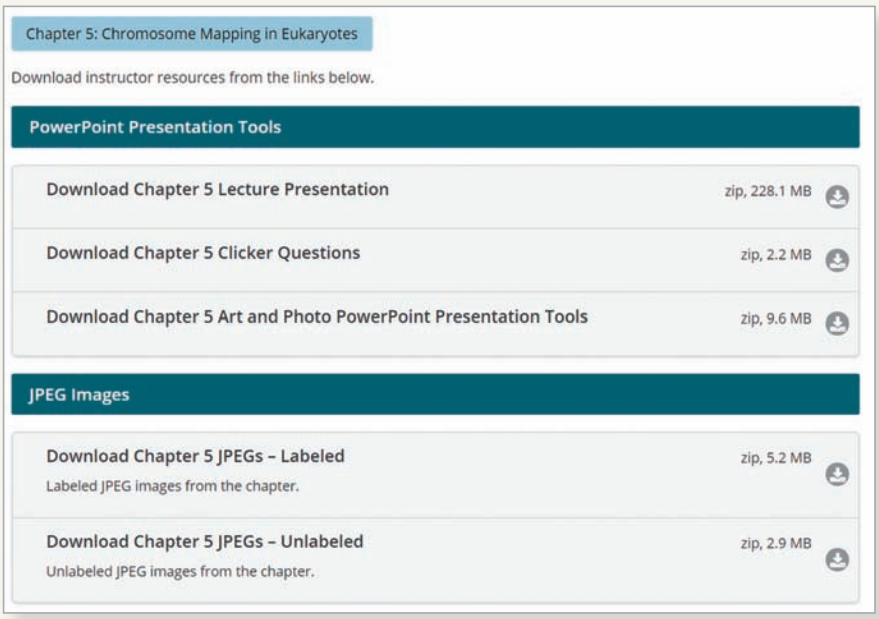
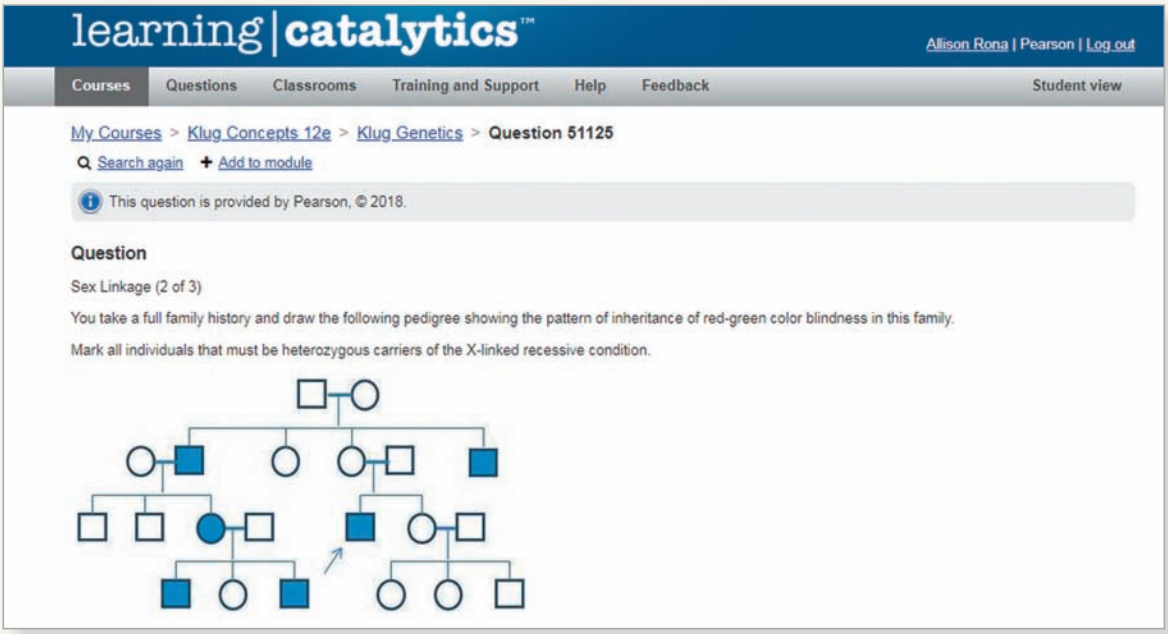


Essentials of Genetics includes a full suite of instructor support materials in the Instructor Resources area in Mastering Genetics. Resources include lecture presentations, clicker questions, and art and photos in PowerPoint®; labeled and unlabeled JPEGs of images from the text; and a test bank.



Instructors also have access to Learning Catalytics. With Learning Catalytics, you'll hear from every student when it matters most. You can pose a variety of questions in class that help students recall ideas, apply concepts, and develop critical-thinking skills. Your students respond using their own smartphones, tablets, or laptops. You can monitor responses with real-time analytics and find out what your students do—and don't—understand. Then, you can adjust your teaching accordingly and even facilitate peer-to-peer learning, helping students stay motivated and engaged. Write your own questions, pull from a shared library of community-generated questions, or use Pearson's content clusters, which pose 2-5 questions about a single data set or scenario.

About the Authors

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

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

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

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and the 2005 Caring Heart Award from the New Jersey Association for Biomedical Research. He is co-author of the undergraduate textbook *Introduction to Biotechnology*. He was Series Editor for the Benjamin Cummings *Special Topics in Biology* booklet series, and author of the first booklet in the series, *Understanding the Human Genome Project*. When away from the university or authoring textbooks, Dr. Palladino can often be found watching or playing soccer or attempting to catch most any species of fish in freshwater or saltwater.

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Dedication

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

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Preface

Essentials of Genetics is written for courses requiring a text that is briefer and less detailed than its more comprehensive companion, *Concepts of Genetics*. While coverage is thorough and modern, *Essentials* is written to be more accessible to biology majors, as well as to students majoring in a number of other disciplines, including agriculture, animal husbandry, chemistry, nursing, engineering, forestry, psychology, and wildlife management. Because *Essentials of Genetics* is shorter than many other texts, it is also more manageable in one-quarter and trimester courses.

Goals

In this edition of *Essentials of Genetics*, the two most important goals have been to introduce pedagogic innovations that enhance learning and to provide carefully updated, highly accessible coverage of genetic topics of both historical and modern significance. As new tools and findings of genetics research continue to emerge rapidly and grow in importance in the study of all subdisciplines of biology, instructors face tough choices about what content is truly essential as they introduce the discipline to novice students. We have thoughtfully revised each chapter in light of this challenge, by selectively scaling back the detail or scope of coverage in the more traditional chapters in order to provide expanded coverage and broader context for the more modern, cutting-edge topics. Our aim is to continue to provide efficient coverage of the fundamental concepts in transmission and molecular genetics that lay the groundwork for more in-depth coverage of emerging topics of growing importance—in particular, the many aspects of the genomic revolution that is already relevant to our day-to-day lives.

While we have adjusted this edition to keep pace with changing content and teaching practices, we remain dedicated to the core principles that underlie this book. Specifically, we seek to

- Emphasize concepts rather than excessive detail.
- Write clearly and directly to students in order to provide understandable explanations of complex analytical topics.
- Emphasize problem solving, thereby guiding students to think analytically and to apply and extend their knowledge of genetics.
- Provide the most modern and up-to-date coverage of this exciting field.
- Propagate the rich history of genetics that so beautifully elucidates how information is acquired as the discipline develops and grows.
- Create inviting, engaging, and pedagogically useful figures enhanced by meaningful photographs to support student understanding.
- Provide outstanding interactive media support to guide students in understanding important concepts through animations, tutorial exercises, and assessment tools.

The above goals serve as the cornerstone of *Essentials of Genetics*. This pedagogic foundation allows the book to accommodate courses with many different approaches and lecture formats. While the book presents a coherent table of contents that represents one approach to offering a course in genetics, chapters are nevertheless written to be independent of one another, allowing instructors to utilize them in various sequences.

New to This Edition

In addition to updating information with new findings in all chapters throughout the text, four chapters are new to this edition.

- **Two new chapters expand the coverage of the regulation of gene expression** The topic of genetic regulation was previously covered in a single chapter, but has now been split into two new chapters. The first (Chapter 15) involves regulation in bacteria, while the second (Chapter 16) focuses on eukaryotes. The bacterial coverage represents the pioneering work in this field and then concludes with an introduction to CRISPR-Cas. The eukaryotic coverage focuses on the regulation of gene expression first at the level of transcription, and then post-transcriptionally, where the expanded coverage focuses on mechanisms that regulate RNA. Research into posttranscriptional regulation in the past 15 years has highlighted the importance of topics such as alternative splicing, mRNA stability and decay, and regulatory noncoding RNAs. Collectively, the addition of these two new chapters provides students and instructors with a thorough, up-to-date presentation of these important aspects of genetics.
- **Two new Special Topics in Modern Genetics chapters** Special Topics chapters are focused and flexible, providing abbreviated, cohesive coverage of important topics in genetics. There are seven Special Topics chapters in this edition, two of which are new. Special Topics Chapter 2—*Genetic Testing* explores how genetic testing is becoming prominent in many contexts and how its use raises many questions and ethical concerns. Special Topics Chapter 4—*Advances in Neurogenetics: The Study of Huntington Disease* illustrates the many advances that have been made in the study of Huntington disease, a

monogenic human disorder that has been subjected to analysis using multiple approaches involving molecular genetics. As such, the chapter exemplifies the growing body of information that has accrued regarding the causes, symptoms, and future treatment of this disorder.

- **Expanded coverage of CRISPR-Cas** Since the previous edition was published, techniques for genome editing have vastly improved due to CRISPR-Cas technology. Thus, we have integrated information about CRISPR-Cas in several different locations within the text. The impact of genome editing with CRISPR-Cas is briefly introduced in Chapter 1. Then, in Chapter 15, students learn how CRISPR-Cas was originally discovered as a bacterial system that regulates the gene expression of bacterial viruses (bacteriophages), providing an immunity against infection. The mechanism and applications to biotechnology are subsequently covered in Chapter 17. Finally, the use of CRISPR-Cas genome editing for gene therapy and the production of genetically modified foods is discussed in Special Topics Chapter 3—*Gene Therapy* and Special Topics Chapter 6—*Genetically Modified Foods*.
- **Increased emphasis on ethics** We recognize in this edition the importance of providing an increased emphasis on ethical considerations that genetics is bringing into everyday life. Regarding this point, we have converted the essay feature previously called *Genetics, Technology, and Society* to one with added emphasis on ethics and renamed it *Genetics, Ethics, and Society*. Approximately half the chapters have new or revised essays. In each case, a synopsis is presented of an ethical issue related to a current finding in genetics that impacts directly on society today. The feature then includes a section called *Your Turn*, which directs students to related resources of short readings and Web sites to support deeper investigation and discussion of the main topic of each essay. In addition, another feature called *Case Study*, which appears near the end of all chapters, has been recast with an increased focus on ethics. Both of these features increase the opportunities for active and cooperative learning as well.

New and Updated Coverage

Below is a chapter-by-chapter list of the most significant new and updated coverage present in this edition.

Ch. 1: Introduction to Genetics • New chapter introduction vignette emphasizing the significance of the discovery of CRISPR-Cas9, a powerful genome-editing system.

Ch. 2: Mitosis and Meiosis • New information on microtubules and microfilaments • Revised Figure 2.9 on Meiotic Prophase I • New Exploring Genomics (EG) entry: PubMed: Exploring and Retrieving Biomedical Literature • New Case Study (CS): Timing Is Everything

Ch. 3: Mendelian Genetics • New Table 3.2 on Dominant and Recessive Human Traits • New Now Solve This (NST) 3.5 on pedigree analysis

Ch. 4: Modification of Mendelian Ratios • New information in the "Mitochondria, Human Health, and Aging" section • New information on the *MERFF* mutation • New Genetics, Ethics, and Society (GES) entry: Mitochondrial Replacement and Three-Parent Babies

Ch. 5: Sex Determination and Sex Chromosomes • New information on Klinefelter syndrome • New GES: A Question of Gender: Sex Selection in Humans

Ch. 6: Chromosome Mutations: Variation in Number and Arrangement • Updated information on copy number variation • New GES: Down Syndrome and Prenatal Testing—The New Eugenics? • A new end of chapter problem involving mapping analysis in *Drosophila*.

Ch. 8: Genetic Analysis and Mapping in Bacteria and Bacteriophages • New GES: Multidrug-Resistant Bacteria: Fighting with Phage

Ch. 10: DNA Replication and Recombination • New details about DNA unwinding during replication • New section entitled "Telomeres in Disease, Aging, and Cancer" • Two new end of chapter problems involving telomeres and telomerase

Ch. 12: The Genetic Code and Transcription • Revised coverage of transcription and RNA processing in eukaryotes • New information on termination of transcription in bacteria • New section entitled "Why Do Introns Exist?" • New GES: Treating Duchene Muscular Dystrophy

Ch. 13: Translation and Proteins • Revised coverage of ribosome and tRNA structure • Revised coverage of translation in bacteria • Expanded coverage of translation in eukaryotes including new information on closed-loop translation, illustrated in a new figure (Fig. 13.10)

Ch. 14: Gene Mutation, DNA Repair, and Transposition • Reorganization of the section on mutation classification, including new table summaries • New and expanded coverage of human germ-line and somatic mutation rates • New, reorganized, and revised coverage of transposable elements, focusing on the major characteristics of retrotransposons and DNA transposons, as well as on how transposons create mutations • Three new figures and one new table

Ch. 15: Regulation of Gene Expression in Bacteria • New chapter that focuses specifically on gene regulation in bacteria • Expanded coverage on the roles of RNA in bacterial gene regulation • New coverage of CRISPR-Cas-mediated regulation of invading viral DNA sequences

Ch. 16: Regulation of Gene Expression in Eukaryotes • New chapter that focuses specifically on gene regulation in eukaryotes • Revised and expanded coverage of alternative splicing, including a new figure, and its relevance to human disease • Expanded coverage on RNA stability and RNA decay including a new figure (Fig. 16.11) • Updated information on noncoding RNAs that regulate gene expression • Enriched coverage of ubiquitin-mediated protein degradation, including a new figure (Fig. 16.14)

Ch. 17: Recombinant DNA Technology • Updated content on modern sequencing technologies including a new figure (Fig. 17.12) on third-generation sequencing (single-strand DNA sequencing) • New section, "Genome Editing with CRISPR-Cas," describes this system as a genome editing tool and includes a new figure (Fig. 17.16)

Ch. 18: Genomics, Bioinformatics, and Proteomics • A new section, "DNA Sequence Analysis Relies on Bioinformatics Applications and Genome Databases," integrating applications of bioinformatics, genome databases, and functional genomics for analyzing and understanding gene function by sequence analysis • Reorganized and revised content on the Human Genome Project, including a new end of chapter problem citing the PANTHER database as part of the Human Genome Project • Updated content on personal genome projects • New content on diploid genomes, mosaicism, and reference genomes and the pangenome to emphasize human genetic variations, including a new figure (Fig. 18.8) • Incorporated coverage of the Human Microbiome Project into a new section, "Metagenomics," and expanded content to include a new Figure (Fig. 18.9) displaying microbiome results of patients with different human disease conditions • A new section titled "RNA Sequencing" • A new section, "Synthetic Genomes and the Emergence of Synthetic Biology," including a new figure (Fig. 18.13) • New GES: Privacy and Anonymity in the Era of Genomic Big Data • Several new and revised end of chapter problems

Ch. 19: The Genetics of Cancer • Extended coverage of environmental agents that contribute to human cancers, including more information about both natural and human-made carcinogens • New subsection entitled "Tobacco Smoke and Cancer" explaining how a well-studied carcinogen induces a wide range of genetic effects that may lead to mutations and cancer

Ch. 20: Quantitative Genetics and Multifactorial Traits • Revised coverage of Expression QTLs (eQTLs) in the regulation of gene expression • New GES: Rice, Genes, and the Second Green Revolution • New CS: A Chance Discovery

Ch. 21: Population and Evolutionary Genetics • New figure (Fig. 21.7) on the relationship between genotype and allele frequency • Important modifications to Figures 21.8 and 21.9 illustrating allele selection • New figure (Fig. 21.13) on the impact of selection types on the phenotypic mean and variance • Revised text and figure (Fig. 21.24) on molecular clocks • Updated information about the origins of the human genome • New figure (Fig. 21.26) on hominin contributions to the genome of modern humans

Special Topic 1: Epigenetics • Revised, updated, and expanded coverage of epigenetic topics, including histone modifications, noncoding RNAs, assisted reproductive technologies, and the heritability of stress-induced behaviors • Updated coverage of epigenetics and cancer • New section on "Epigenetics and Monoallelic Gene Expression" • New figures on DNA methylation, chemical modification of histones, genomic imprinting, random autosomal monoallelic gene expression, imprinting in germ cells, and maternal behavior and stress responses in rat pups

Special Topic 2: Genetic Testing • New Special Topics chapter emphasizing modern approaches to genetic testing including prenatal genetic testing, noninvasive procedures for testing fetal DNA, testing using allele-specific oligonucleotides, microarrays, and genetic analysis by DNA and RNA sequencing • Includes coverage of the recommended uniform screening panel, undiagnosed diseases network, and genetic analysis for pathogen identification during infectious disease outbreaks • Section on genome-wide association studies incorporates approaches for genomic analysis of disease conditions at the population level • A range of ethical, social, and legal considerations are discussed

Special Topic 3: Gene Therapy • Updated information on gene therapy trials that are under way • An expanded section "Genome Editing" highlighting the application of the CRISPR-Cas system and describing some of the most promising trials under way in humans and animals • New ethical considerations of CRISPR-Cas and germ-line and embryo editing • New section, "RNA-Based Therapeutics," that includes coverage of antisense RNA; RNA interference; and updated trials for RNA-based therapeutics, including Spinraza as an antisense RNA modifying splicing for the treatment of spinal muscular atrophy • Updated content on roles of stem cells in gene therapy • New content on combining genome editing with immunotherapy

Special Topic 4: Advances in Neurogenetics: The Study of Huntington Disease • New Special Topics chapter that surveys the study of Huntington Disease (HD) from 1970 to the present • Coverage includes the genetic basis and progression of HD, the mapping and isolation of the gene responsible for the disorder, and information on the mutant gene product • Discussions

include information on the molecular and cellular alterations caused by the mutant protein, the use of transgenic animal models of HD, and the molecular and cellular approaches to therapy

Special Topic 5: DNA Forensics • New section entitled "DNA Phenotyping," describing a controversial forensic method, including descriptions of how law-enforcement agencies currently use this new technology

Special Topic 6: Genetically Modified Foods • New section, entitled "Gene Editing and GM Foods," describing how scientists are using the new techniques of gene editing (including ZFN, TALENS, and CRISPR-Cas) to create GM food plants and animals, and how these methods are changing the way in which GM foods are being regulated • A new box, "The New CRISPR Mushroom," describing the development and regulatory approval of the first CRISPR-created GM food to be cleared for human consumption

Special Topic 7: Genomics and Precision Medicine • New section, entitled "Precision Oncology," describing two targeted cancer immunotherapies: adoptive cell transfer and engineered T-cell therapy • Updated section, "Pharmacogenomics," including a discussion of new trends in preemptive gene screening for pharmacogenomic variants • New box, "Preemptive Pharmacogenomic Screening: The pGEN-4Kids Program," discussing preemptive gene screening that integrates DNA analysis into patient electronic health records

Emphasis on Concepts

Essentials of Genetics focuses on conceptual issues in genetics and uses problem solving to develop a deep understanding of them. We consider a concept to be a cognitive unit of meaning that encompasses a related set of scientifically derived findings and ideas. As such, a concept provides broad mental imagery, which we believe is a very effective way to teach science, in this case, genetics. Details that might be memorized, but soon forgotten, are instead subsumed within a conceptual framework that is more easily retained. Such a framework may be expanded in content as new information is acquired and may interface with other concepts, providing a useful mechanism to integrate and better understand related processes and ideas. An extensive set of concepts may be devised and conveyed to eventually encompass and represent an entire discipline—and this is our goal in this genetics textbook.

To aid students in identifying the conceptual aspects of a major topic, each chapter begins with a section called ***Chapter Concepts***, which identifies the most important ideas about to be presented. Then, throughout each chapter, ***Essential Points*** are provided that establish the key issues that have been discussed. And in the ***How Do We Know?*** question that starts each chapter's problem set, students are asked to identify the experimental basis of important genetic findings presented in the chapter. As an extension of the learning approach in biology called "Science as a Way of Knowing," this feature enhances students' understanding of many key concepts covered in each chapter. Finally, the second entry in each chapter's problem set is labeled as a **Concepts Question**, which asks the student to review and comment on specific aspects of the Chapter Concepts found at the beginning of each chapter.

Collectively, these features help to ensure that students easily become aware of and understand the major conceptual issues as they confront the extensive vocabulary and the many important details of genetics. Carefully designed figures also support this approach throughout the book.

Emphasis on Problem Solving

Helping students develop effective problem-solving skills is one of the greatest challenges of a genetics course. The feature called ***Now Solve This***, integrated throughout each chapter, asks students to link conceptual understanding in a more immediate way to problem solving. Each entry provides a problem for the student to solve that is closely related to the current text discussion. A pedagogic hint is then provided to aid in arriving at the correct solution. All chapters conclude with ***Insights and Solutions***, a popular and highly useful section that provides sample problems and solutions that demonstrate approaches useful in genetic analysis. These help students develop analytical thinking and experimental reasoning skills. Digesting the information in *Insights and Solutions* primes students as they move on to the lengthier ***Problems and Discussion Questions*** section that concludes each chapter. Here, we present questions that review topics in the chapter and problems that ask students to think in an analytical and applied way about genetic concepts. The addition of Mastering Genetics extends our focus on problem solving online, and it allows students to get help and guidance while practicing how to solve problems.

Continuing Features

The Tenth Edition has maintained several popular features that are pedagogically useful for students as they study genetics. Together, these create a platform that seeks to challenge students to think more deeply about, and thus understand more comprehensively, the information he or she has just finished studying.

- **Exploring Genomics** Appearing in numerous chapters, this feature illustrates the pervasiveness of genomics in the current study of genetics. Each entry asks students to access one or more genomics-related Web sites that collectively are among the best publicly available resources and databases. Students work through interactive exercises that ensure their familiarity with the type of

genomic or proteomic information available. Exercises instruct students on how to explore specific topics and how to access significant data. Questions guide student exploration and challenge them to further explore the sites on their own. Importantly, *Exploring Genomics* integrates genomics information throughout the text, as this emerging field is linked to chapter content. This feature provides the basis for individual or group assignments in or out of the classroom.

- **Case Studies** This feature, with an increased emphasis on ethical considerations, appears at the end of each chapter and provides the basis for enhanced classroom interactions. In each entry, a short scenario related to one of the chapter topics is presented, followed by several questions. These ask students to apply their newly acquired knowledge to real-life issues that may be explored in small-group discussions or serve as individual assignments.

For the Instructor

Mastering Genetics
http://www.masteringgenetics.com

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

- In-depth tutorials that coach students with hints and feedback specific to their misconceptions.
- A new, robust library of **Practice Problems** offers more opportunities to assign challenging problems for student homework or practice. These questions include targeted wrong answer feedback to help students learn from their mistakes. They appear only in Mastering Genetics.
- An item library of assignable questions including end of chapter problems, test bank questions, and reading quizzes. You can use publisher-created prebuilt assignments to get started quickly. Each question can be easily edited to match the precise language you use.
- A gradebook that provides you with quick results and easy-to-interpret insights into student performance.

Instructor Resources

The Instructor Resources, available for download in the Instructor area of Mastering Genetics, offer adopters of the text convenient access to a comprehensive and innovative set of lecture presentation and teaching tools. Developed to meet the needs of veteran and newer instructors alike, these resources include:

- The JPEG files of all text line drawings with labels individually enhanced for optimal projection results (as well as unlabeled versions) and all text tables.
- Most of the text photos, including all photos with pedagogical significance, as JPEG files.
- The JPEG files of line drawings, photos, and tables preloaded into comprehensive PowerPoint presentations for each chapter.
- A second set of PowerPoint presentations consisting of a thorough lecture outline for each chapter augmented by key text illustrations.
- An impressive series of concise instructor animations adding depth and visual clarity to the most important topics and dynamic processes described in the text.
- The instructor animations preloaded into PowerPoint presentation files for each chapter.
- PowerPoint presentations containing a comprehensive set of in-class Classroom Response System (CRS) questions for each chapter.
- In Word files, a complete set of the assessment materials and study questions and answers from the test bank, the text's in-chapter text questions, and the student media practice questions.

TestGen EQ Computerized Testing Software

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

Mastering Genetics
http://www.masteringgenetics.com

Used by over a million science students, the Mastering platform is the most effective and widely used online tutorial, homework, and assessment system for the sciences. Perform better on exams with Mastering Genetics. As an instructor-assigned homework system, Mastering Genetics is designed to provide students with a variety of assessments to help them understand key topics and concepts and to build problem-solving skills. Mastering Genetics tutorials guide students through the toughest topics in genetics with self-paced tutorials that provide individualized coaching with hints and feedback specific to a student's individual misconceptions. Students can also explore Mastering Genetics' Study Area, which includes animations, the eText, *Exploring Genomics* exercises, and other study aids. The interactive eText 2.0 allows students to access their text on mobile devices, highlight text, add study notes, review instructor's notes, and search throughout the text, 24/7.

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

Editorial and Production Input

At Pearson, we express appreciation and high praise for the editorial guidance of Michael Gillespie, whose ideas and efforts have helped to shape and refine the features of this edition of the text. Brett Coker, our Content Producer, has worked tirelessly to keep the project on schedule and to maintain our standards of high quality. In addition, our editorial team—Ginnie Simione Jutson, Executive Director of Development, Robert Johnson, Rich Media Content Producer, and Sarah Jensen, Director of Editorial Content for Mastering Genetics—have provided valuable input into the current edition. They have worked creatively to ensure that the pedagogy and design of the book and media package are at the cutting edge of a rapidly changing discipline. Brett Coker and Heidi Aguiar supervised all of the production intricacies with great attention to detail and perseverance. Outstanding copyediting was performed by Lucy Mullins, for which we are most grateful. Allison Rona, Alysun Estes, and Kelly Galli have professionally and enthusiastically managed the marketing of the text. Finally, the beauty and consistent presentation of the art work are the product of Imagineering of Toronto. Without the work ethic and dedication of the above individuals, the text would never have come to fruition.

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1

Introduction to Genetics

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

CHAPTER CONCEPTS

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

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

Although gene editing was first made possible with other methods, the CRISPR-Cas system is now the method of choice for gene modification because it is more accurate, more efficient, more versatile, and easier to use. CRISPR-Cas was initially discovered as a "seek and destroy" mechanism that bacteria use to fight off viral infection. CRISPR (clustered regularly interspersed short palindromic repeats) refers to part of the bacterial genome that produces RNA molecules, and Cas (CRISPR-associated) refers to a nuclease, or DNA-cutting enzyme. The CRISPR RNA binds to a matching sequence in the viral DNA (seek) and recruits the Cas nuclease to cut it (destroy). Researchers have harnessed this technology by synthesizing CRISPR RNAs that direct Cas nucleases to any chosen DNA sequence. In laboratory experiments, CRISPR-Cas has already been used to repair mutations in cells derived from individuals with genetic disorders, such as cystic fibrosis, Huntington disease,

sickle-cell disease, and muscular dystrophy. In the United States a clinical trial using CRISPR-Cas for genome editing in cancer therapy is recruiting participants, while proposals for treating a genetic form of blindness and genetic blood disorders are in preparation. In China, at least 86 patients have already started receiving treatments in CRISPR-Cas clinical trials for cancer.

The application of this remarkable system goes far beyond developing treatments for human genetic disorders. In organisms of all kinds, wherever genetic modification may benefit human existence and our planet, the use of CRISPR-Cas will find many targets. For example, one research group edited a gene in mosquitoes, which prevents them from carrying the parasite that causes malaria in humans. Other researchers have edited the genome of algae to double their output for biofuel production. The method has also been used to create disease-resistant strains of wheat and rice.

The power of this system, like any major technological advance, has already raised ethical concerns. For example, genetic modification of human embryos would change the genetic information carried by future generations. These modifications may have unintended and significant negative consequences for our species. In 2017, an international panel of experts discussed the science, ethics, and governance of human genome editing. The panel recommended caution, but not a ban, stating that human embryo modification should "only be permitted for compelling reasons and under strict oversight."

CRISPR-Cas may turn out to be one of the most exciting genetic advances in decades. We will return later in the text to discuss its discovery in bacteria (Chapter 15), its development as a gene-editing tool (Chapter 17), its potential for gene therapy (Special Topic Chapter 3 Gene Therapy), and its uses in genetically edited foods (Special Topic Chapter 6 Genetically Modified Foods).

For now, we hope that this short introduction has stimulated your curiosity, interest, and enthusiasm for the study of genetics. The remainder of this chapter provides an overview of many important concepts of genetics and a survey of the major turning points in the history of the discipline.

1.1 Genetics Has an Interesting Early History

While as early as 350 B.C., Aristotle proposed that active "humors" served as bearers of hereditary traits, it was not until the 1600s that initial strides were made to understand the biological basis of life. In that century, the physician and anatomist William Harvey proposed the theory of **epigenesis,** which states that an organism develops from the fertilized egg by a succession of developmental events that eventually transform the egg into an adult. The theory of epigenesis directly conflicted with the theory of **preformationism,** which stated that the fertilized egg contains a complete miniature adult, called a **homunculus** (**Figure 1.1**). Around 1830, Matthias Schleiden and Theodor Schwann proposed the **cell theory,** stating that all organisms are composed of basic structural units called cells, which are derived from preexisting cells. The idea of **spontaneous generation,** the creation of living organisms from nonliving components, was disproved by Louis Pasteur later in the century, and living organisms were then considered to be derived from preexisting organisms and to consist of cells.

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

Darwin and Mendel

In 1859, Darwin published *On the Origin of Species*, describing his ideas about evolution. Darwin's geological, geographical, and biological observations convinced him that existing species arose by descent with modification from ancestral species. Greatly influenced by his voyage on the HMS *Beagle* (1831–1836), Darwin's thinking led him to formulate the theory of **natural selection,** which presented an explanation of the mechanism of evolutionary change. Formulated and proposed independently by Alfred Russel Wallace, natural selection is based on the observation

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

that populations tend to produce more offspring than the environment can support, leading to a struggle for survival among individuals. Those individuals with heritable traits that allow them to adapt to their environment are better able to survive and reproduce than those with less adaptive traits. Over time, advantageous variations, even very slight ones, will accumulate. If a population carrying these inherited variations becomes reproductively isolated, a new species may result.

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

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

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

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

Mendel's Work on Transmission of Traits

Gregor Mendel, an Augustinian monk, conducted a decade-long series of experiments using pea plants. He applied quantitative data analysis to his results and showed that traits are passed from parents to offspring in predictable ways. He further concluded that each trait in pea plants is controlled by a pair of factors (which we now call genes) and that members of a gene pair separate from each other during gamete formation (the formation of egg cells and sperm). Mendel's findings explained the transmission of traits in pea plants and all other higher organisms. His work forms the foundation for **genetics,** the branch of biology concerned with the study of heredity and variation. Mendelian genetics will be discussed later in the text (see Chapters 3 and 4).

The Chromosome Theory of Inheritance: Uniting Mendel and Meiosis

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

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

Early in the twentieth century, Walter Sutton and Theodor Boveri independently noted that the behavior of chromosomes during meiosis is identical to the behavior of genes

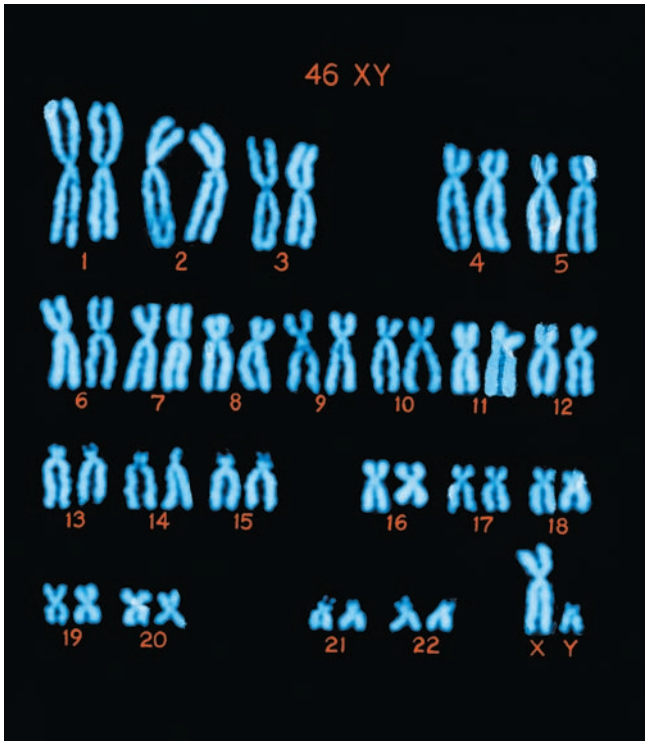


FIGURE 1.2 A colorized image of a replicated set of human male chromosomes. Arranged in this way, the set is called a karyotype.

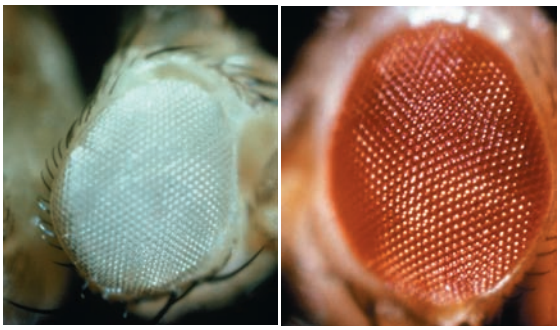


FIGURE 1.3 The white-eyed mutation in *D. melanogaster* (left) and the normal red eye color (right).

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

ESSENTIAL POINT

The chromosome theory of inheritance explains how genetic information is transmitted from generation to generation. ■

Genetic Variation

About the same time that the chromosome theory of inheritance was proposed, scientists began studying the inheritance of traits in the fruit fly, *Drosophila melanogaster*. Early in this work, a white-eyed fly (**Figure 1.3**) was discovered among normal (wild-type) red-eyed flies. This variation was produced by a **mutation** in one of the genes controlling eye color. Mutations are defined as any heritable change in the DNA sequence and are the source of all genetic variation.

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

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

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

In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty, researchers at the Rockefeller Institute in New York, published experiments showing that DNA was the carrier of genetic information in bacteria. This evidence, though clear-cut, failed to convince many influential scientists. Additional evidence for the role of DNA as a carrier of genetic information came from Alfred Hershey and Martha Chase who worked with viruses. This evidence that DNA carries genetic information, along with other research over the next few years, provided solid proof that DNA, not protein, is the genetic material, setting the stage for work to establish the structure of DNA.

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

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

The Structure of DNA and RNA

One of the great discoveries of the twentieth century was made in 1953 by James Watson and Francis Crick, who described the structure of DNA. DNA is a long, ladder-like macromolecule that twists to form a double helix (**Figure 1.4**). Each linear strand of the helix is made up of subunits called **nucleotides.** In DNA, there are four different nucleotides, each of which contains a nitrogenous base, abbreviated A (adenine), G (guanine), T (thymine),

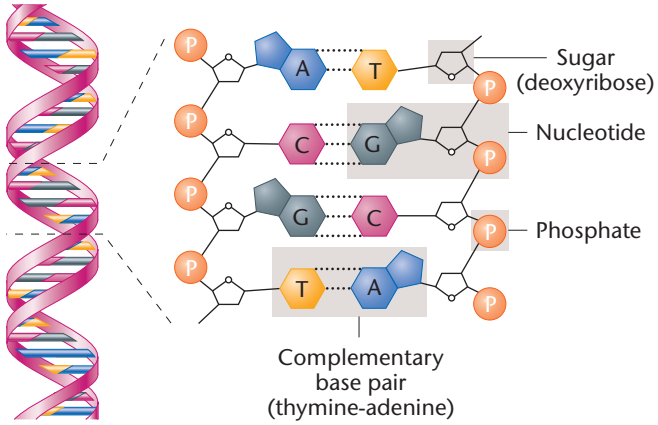


FIGURE 1.4 The structure of DNA showing the arrangement of the double helix (on the left) and the chemical components making up each strand (on the right). The dotted lines on the right represent weak chemical bonds, called hydrogen bonds, which hold together the two strands of the DNA helix.

or C (cytosine). These four bases, in various sequence combinations, ultimately encode genetic information. The two strands of DNA are exact complements of one another, so that the rungs of the ladder in the double helix always consist of A=T and G=C base pairs. Along with Maurice Wilkins, Watson and Crick were awarded a Nobel Prize in 1962 for their work on the structure of DNA. We will discuss the structure of DNA later in the text (see Chapter 9).

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

Gene Expression: From DNA to Phenotype

The genetic information encoded in the order of nucleotides in DNA is expressed in a series of steps that results in the formation of a functional gene product. In the majority of cases, this product is a protein. In eukaryotic cells, the process leading to protein production begins in the nucleus with **transcription,** in which the nucleotide sequence in one strand of DNA is used to construct a complementary RNA sequence (top part of **Figure 1.5**). Once an RNA molecule is produced, it moves to the cytoplasm, where the RNA—called **messenger RNA,** or **mRNA** for short—binds to a **ribosome.** The synthesis of proteins under the direction of mRNA is called **translation** (center part of Figure 1.5). The information encoded in mRNA (called the **genetic code**) consists of a linear series of nucleotide triplets. Each triplet, called a **codon,** is complementary to the information stored in DNA and specifies the insertion of a specific amino acid into a protein. Proteins (lower part of Figure 1.5) are polymers made up of amino acid monomers. There are 20 different amino acids commonly found in proteins.

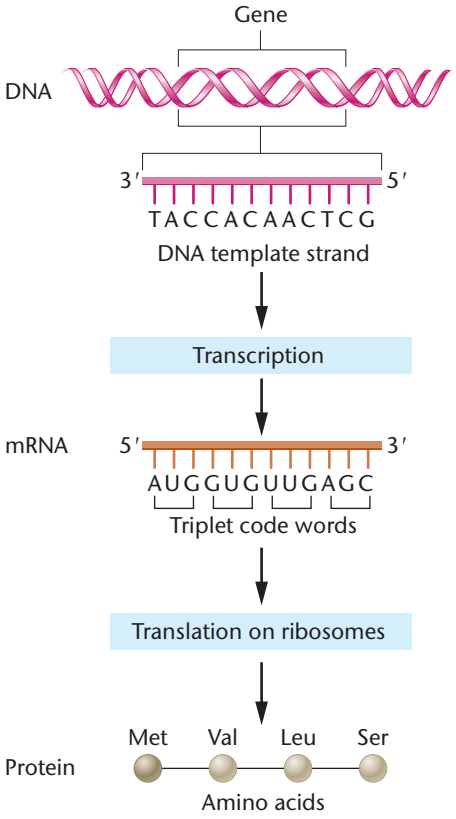


FIGURE 1.5 Gene expression consists of transcription of DNA into mRNA (top) and the translation (center) of mRNA (with the help of a ribosome) into a protein (bottom).

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

We now know that gene expression can be more complex than outlined here. Some of these complexities will be discussed later in the text (see Chapters 15 and 16).

Proteins and Biological Function

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

$$20^{100}$$

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

Enzymes form the largest category of proteins. These molecules serve as biological catalysts, lowering the energy

of activation in reactions and allowing cellular metabolism to proceed at body temperature.

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

Linking Genotype to Phenotype: Sickle-Cell Anemia

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

Sickle-cell anemia is caused by a mutant form of hemoglobin, the protein that transports oxygen from the lungs to cells in the body. Hemoglobin is a composite molecule made up of two different proteins, α-globin and β-globin, each encoded by a different gene. In sickle-cell anemia, a mutation in the gene encoding β-globin causes an amino acid substitution in 1 of the 146 amino acids in the protein. **Figure 1.6** shows the DNA sequence, the corresponding mRNA codons, and the amino acids occupying positions 4–7 for the normal and mutant forms of β-globin. Notice that the mutation in sickle-cell anemia consists of a change in one DNA nucleotide, which leads to a change in codon 6 in mRNA from GAG to GUG, which in turn changes amino acid number 6 in β-globin from glutamic acid to valine. The other 145 amino acids in the protein are not changed by this mutation.

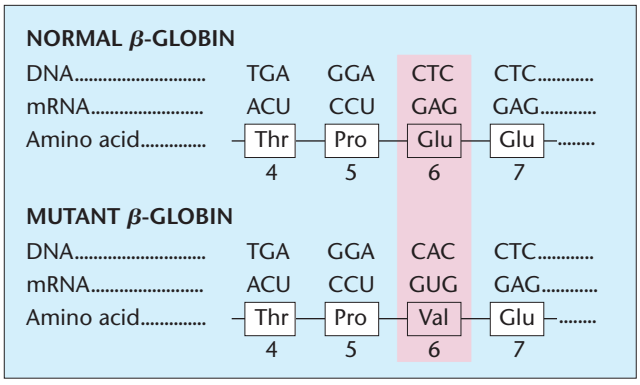


FIGURE 1.6 A single-nucleotide change in the DNA encoding β-globin (CTC → CAC) leads to an altered mRNA codon (GAG → GUG) and the insertion of a different amino acid (Glu → Val), producing the altered version of the β-globin protein that is responsible for sickle-cell anemia.

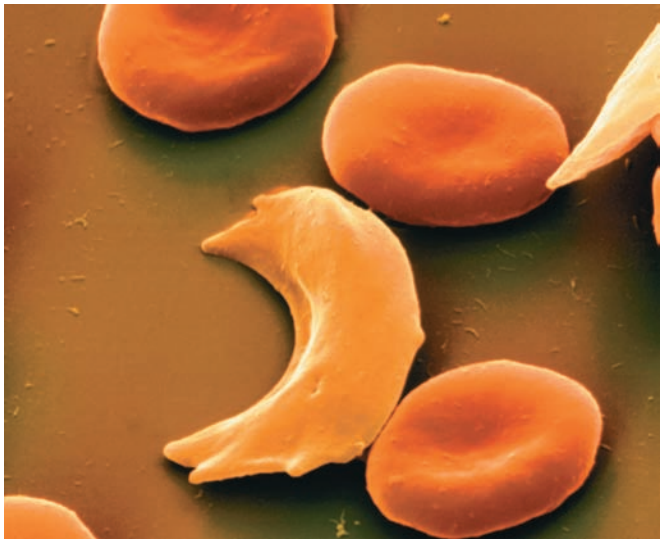


FIGURE 1.7 Normal red blood cells (round) and sickled red blood cells. The sickled cells block capillaries and small blood vessels.

ESSENTIAL POINT

The central dogma of molecular biology -- that DNA is a template for making RNA, which in turn directs the synthesis of proteins -- explains how genes control phenotype. ■

Individuals with two mutant copies of the β-globin gene have sickle-cell anemia. Their mutant β-globin proteins cause hemoglobin molecules in red blood cells to polymerize when the blood's oxygen concentration is low, forming long chains of hemoglobin that distort the shape of red blood cells (**Figure 1.7**). Deformed cells are fragile and break easily, reducing the number of circulating red blood cells (anemia is an insufficiency of red blood cells). Sickle-shaped cells block blood flow in capillaries and small blood vessels, causing severe pain and damage to the heart, brain, muscles, and kidneys. All the symptoms of this disorder are caused by a change in a single nucleotide in a gene that changes one amino acid out of 146 in the β-globin molecule, demonstrating the close relationship between genotype and phenotype.

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

The era of recombinant DNA began in the early 1970s, when researchers discovered that **restriction enzymes,** used by bacteria to cut and inactivate the DNA of invading viruses, could be used to cut any organism's DNA at

specific nucleotide sequences, producing a reproducible set of fragments.

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

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

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

FIGURE 1.8 Dolly, a Finn Dorset sheep cloned from the genetic material of an adult mammary cell, shown next to her first-born lamb, Bonnie.

1.5 The Impact of Biotechnology Is Continually Expanding

The use of recombinant DNA technology and other molecular techniques to make products is called **biotechnology.** In the United States, biotechnology has quietly revolutionized many aspects of everyday life; products made by biotechnology are now found in the supermarket, in health care, in agriculture, and in the court system. A later chapter (see Chapter 18) contains a detailed discussion of biotechnology, but for now, let's look at some everyday examples of biotechnology's impact.

Plants, Animals, and the Food Supply

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

We will discuss the most recent findings involving genetically modified organisms later in the text. (Special Topics Chapter 6—Genetically Modified Foods).

New methods of cloning livestock such as sheep and cattle have changed the way we use these animals. In 1996, Dolly the sheep (**Figure 1.8**) was cloned by nuclear transfer, a method in which the nucleus of an adult cell is transferred into an egg that has had its nucleus removed. This makes it possible to produce dozens or hundreds of genetically identical offspring with desirable traits with many applications in agriculture and medicine.

Biotechnology has also changed the way human proteins for medical use are produced. Through use of gene transfer, transgenic animals now synthesize these therapeutic proteins. In 2009, an anticlotting protein derived from the milk of transgenic goats was approved by the U.S. Food and Drug Administration for use in the United States. Other human proteins from transgenic animals are now being used in clinical trials to treat several diseases. The biotechnology revolution will continue to expand as gene editing by CRISPR/Cas and other new methods are used to develop an increasing array of products.

Biotechnology in Genetics and Medicine

More than 10 million children or adults in the United States suffer from some form of genetic disorder, and every childbearing couple faces an approximately 3 percent risk of having a child with a genetic anomaly. The molecular basis for hundreds of genetic disorders is now known, and most of these genes have been mapped, isolated, and cloned. Biotechnology-derived genetic testing is now available to perform prenatal diagnosis of heritable disorders and to test parents for their status as heterozygous carriers of more than 100 inherited disorders. Newer methods now offer the possibility of scanning an entire genome to establish an

individual's risk of developing a genetic disorder or having an affected child. The use of genetic testing and related technologies raises ethical concerns that have yet to be resolved.

ESSENTIAL POINT

Biotechnology has revolutionized agriculture and the pharmaceutical industry, while genetic testing has had a profound impact on the diagnosis of genetic diseases. ■

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

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

One such project, the Human Genome Project (HGP), began in 1990 as an international effort to sequence the human genome. By 2003, the publicly funded HGP and a private, industry-funded genome project completed sequencing of the gene-containing portion of the genome.

As more genome sequences were acquired, several new biological disciplines arose. One, called **genomics** (the study of genomes), studies the structure, function, and evolution of genes and genomes. A second field, **proteomics,** identifies the set of proteins present in a cell under a given set of conditions, and studies their functions and interactions. To store, retrieve, and analyze the massive amount of data generated by genomics and proteomics, a specialized subfield of information technology called **bioinformatics** was created to develop hardware and software for processing nucleotide and protein data.

Geneticists and other biologists now use information in databases containing nucleic acid sequences, protein sequences, and gene-interaction networks to answer experimental questions in a matter of minutes instead of months and years. A feature called "Exploring Genomics," located at the end of many of the chapters in this textbook, gives you the opportunity to explore these databases for yourself while completing an interactive genetics exercise.

Modern Approaches to Understanding Gene Function

Historically, an approach referred to as **classical** or **forward genetics** was essential for studying and understanding gene function. In this approach geneticists relied on the use of naturally occurring mutations or intentionally induced mutations (using chemicals, X-rays, or UV light as examples) to cause altered phenotypes in model organisms, and then worked through the labor-intensive and time-consuming process of identifying the genes that caused these new phenotypes. Such characterization often led to the identification of the gene or genes of interest, and once the technology advanced, the gene sequence could be determined.

Classical genetics approaches are still used, but as whole genome sequencing has become routine, molecular approaches to understanding gene function have changed considerably in genetic research. These modern approaches are what we will highlight in this section.

For the past two decades or so, geneticists have relied on the use of molecular techniques incorporating an approach referred to as **reverse genetics.** In reverse genetics, the DNA sequence for a particular gene of interest is known, but the role and function of the gene are typically not well understood. For example, molecular biology techniques such as **gene knockout** render targeted genes nonfunctional in a model organism or in cultured cells, allowing scientists to investigate the fundamental question of "what happens if this gene is disrupted?" After making a knockout organism, scientists look for both apparent phenotype changes, as well as those at the cellular and molecular level. The ultimate goal is to determine the function of the gene being studied.

ESSENTIAL POINT

Recombinant DNA technology gave rise to several new fields, including genomics, proteomics, and bioinformatics, which allow scientists to explore the structure and evolution of genomes and the proteins they encode. ■

1.7 Genetic Studies Rely on the Use of Model Organisms

After the rediscovery of Mendel's work in 1900, research using a wide range of organisms confirmed that the principles of inheritance he described were of universal significance among plants and animals. Geneticists gradually came to focus attention on a small number of organisms, including the fruit fly (*Drosophila melanogaster*) and the mouse (*Mus musculus*) (**Figure 1.9**). This trend developed for two main reasons: First, it was clear that genetic mechanisms were the same in most organisms, and second, these organisms had characteristics that made them especially suitable for genetic research. They were easy to grow, had relatively short life cycles, produced many offspring, and their genetic analysis was fairly straightforward. Over time, researchers created a large catalog of mutant strains for these species,

(a) (b)

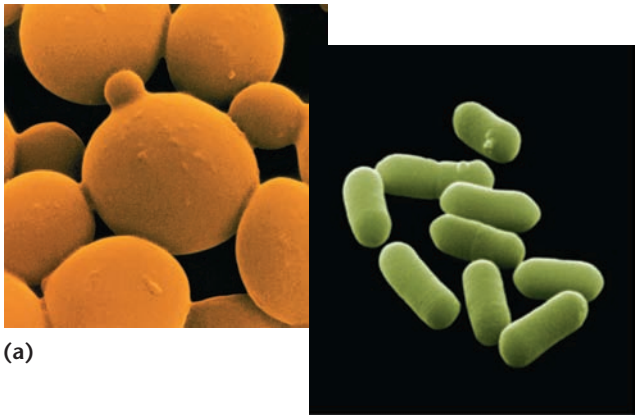
FIGURE 1.9 The first generation of model organisms in genetic analysis included (a) the mouse, *Mus musculus,* and (b) the fruit fly, *Drosophila melanogaster*.

and the mutations were carefully studied, characterized, and mapped. Because of their well-characterized genetics, these species became **model organisms,** defined as organisms used for the study of basic biological processes. In later chapters, we will see how discoveries in model organisms are shedding light on many aspects of biology, including aging, cancer, and behavior.

The Modern Set of Genetic Model Organisms

Gradually, geneticists added other species to their collection of model organisms: viruses (such as the T phages and lambda phage) and microorganisms (the bacterium *Escherichia coli* and the yeast *Saccharomyces cerevisiae*) (**Figure 1.10**).

More recently, additional species have been developed as model organisms, three of which are shown in the chapter opening photograph. Each species was chosen to allow study of some aspect of embryonic development. The nematode *Caenorhabditis elegans* was chosen as a model system to study the development and function of the nervous system because its nervous system contains only a few hundred cells and the developmental fate of these and all other cells in the body has been mapped out. *Arabidopsis thaliana*, a small plant with a short life cycle, has become a model organism for the study of many aspects of plant biology. The zebrafish, *Danio rerio*, is used to study vertebrate development: it is small, it reproduces rapidly, and its egg, embryo, and larvae are all transparent.



(a) (b)

FIGURE 1.10 Microbes that have become model organisms for genetic studies include (a) the yeast *Saccharomyces cerevisiae* and (b) the bacterium *Escherichia coli*.

Model Organisms and Human Diseases

The development of recombinant DNA technology and the results of genome sequencing have confirmed that all life has a common origin. Because of this, genes with similar functions in different organisms tend to be similar or identical in structure and nucleotide sequence. Much of what scientists learn by studying the genetics of model organisms can therefore be applied to humans as the basis for understanding and treating human diseases. In addition, the ability to create transgenic organisms by transferring genes between species has enabled scientists to develop models of human diseases in organisms ranging from bacteria to fungi, plants, and animals (**Table 1.1**).

The idea of studying a human disease such as colon cancer by using *E. coli* may strike you as strange, but the basic steps of DNA repair (a process that is defective in some forms of colon cancer) are the same in both organisms, and a gene involved in DNA repair (*mutL* in *E. coli* and *MLH1* in humans) is found in both organisms. More importantly, *E. coli* has the advantage of being easier to grow (the cells divide every 20 minutes), and researchers can easily create and study new mutations in the bacterial *mutL* gene in order to figure out how it works. This knowledge may eventually lead to the development of drugs and other therapies to treat colon cancer in humans.

The fruit fly, *Drosophila melanogaster*, is also being used to study a number of human diseases. Mutant genes

TABLE 1.1 Model Organisms Used to Study Some Human Diseases

Organism	Human Diseases
E. coli	Colon cancer and other cancers
S. cerevisiae	Cancer, Werner syndrome
D. melanogaster	Disorders of the nervous system, cancer
C. elegans	Diabetes
D. rerio	Cardiovascular disease
M. musculus	Lesch–Nyhan syndrome, cystic fibrosis, fragile-X syndrome, and many other diseases

have been identified in *D. melanogaster* that produce phenotypes with structural abnormalities of the nervous system and adult-onset degeneration of the nervous system. The information from genome-sequencing projects indicates that almost all these genes have human counterparts. For example, genes involved in a complex human disease of the retina called retinitis pigmentosa are identical to *Drosophila* genes involved in retinal degeneration. Study of these mutations in *Drosophila* is helping to dissect this complex disease and identify the function of the genes involved.

Another approach to studying diseases of the human nervous system is to transfer mutant human disease genes into *Drosophila* using recombinant DNA technology. The transgenic flies are then used for studying the mutant human genes themselves, other genes that affect the expression of the human disease genes, and the effects of therapeutic drugs on the action of those genes—all studies that are difficult or impossible to perform in humans. This gene transfer approach is being used to study almost a dozen human neurodegenerative disorders, including Huntington disease, Machado–Joseph disease, myotonic dystrophy, and Alzheimer disease.

Throughout the following chapters, you will encounter these model organisms again and again. Remember each time you meet them that they not only have a rich history in basic genetics research but are also at the forefront in the study of human genetic disorders and infectious diseases.

ESSENTIAL POINT

The study of model organisms for understanding human health and disease is one of the many ways genetics and biotechnology are changing everyday life. ■

1.8 Genetics Has Had a Profound Impact on Society

Mendel described his decade-long project on inheritance in pea plants in an 1865 paper presented at a meeting of the Natural History Society of Brünn in Moravia. Less than 100 years later, the 1962 Nobel Prize was awarded to James Watson, Francis Crick, and Maurice Wilkins for their work on the structure of DNA. This time span encompassed the years leading up to the acceptance of Mendel's work, the discovery that genes are on chromosomes, the experiments that proved DNA encodes genetic information, and the elucidation of the molecular basis for DNA replication. The rapid development of genetics from Mendel's monastery garden to the Human Genome Project and beyond is summarized in a timeline in **Figure 1.11**.

The Nobel Prize and Genetics

No other scientific discipline has experienced the explosion of information and the level of excitement generated by the discoveries in genetics. This impact is especially apparent in the list of Nobel Prizes related to genetics, beginning with those awarded in the early and mid-twentieth century and continuing into the present (see inside back cover). Nobel Prizes in Medicine or Physiology and Chemistry have been consistently awarded for work in genetics and related fields. The first such prize awarded was given to Thomas H. Morgan in 1933 for his research on the chromosome theory of inheritance. That award was followed by many others, including prizes for the discovery of genetic recombination, the relationship between genes and proteins, the structure of DNA, and the genetic code. This trend has continued throughout

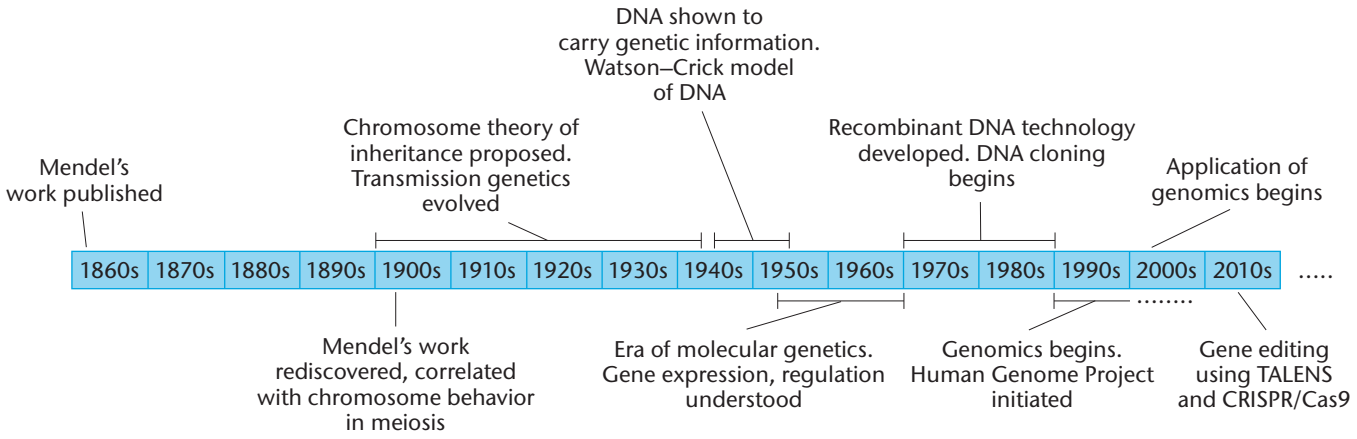


FIGURE 1.11 A timeline showing the development of genetics from Gregor Mendel's work on pea plants to the current era of genomics and its many applications in research, medicine, and society. Having a sense of the history of discovery in genetics should provide you with a useful framework as you proceed through this textbook.

the twentieth and twenty-first centuries. The advent of genomic studies and the applications of such findings will most certainly lead the way for future awards.

Genetics, Ethics, and Society

Just as there has never been a more exciting time to study genetics, the impact of this discipline on society has never been more profound. Genetics and its applications in biotechnology are developing much faster than the social conventions, public policies, and laws required to regulate their use. As a society, we are grappling with a host of sensitive genetics-related issues, including concerns about prenatal testing, genetic discrimination, ownership of genes, access to and safety of gene therapy, and genetic privacy. Two features appearing at the end of most chapters, "Case Study" and "Genetics, Ethics, and Society," consider ethical issues raised by the use of genetic technology. This emphasis on ethics reflects the growing concern and dilemmas that advances in genetics pose to our society and the future of our species. It is our hope that upon the completion of your study of genetics, you will become an informed, active participant in future debates that arise.

ESSENTIAL POINT

Genetic technology is having a profound effect on society, while raising many ethical dilemmas. ■

Problems and Discussion Questions

Mastering Genetics Visit for instructor-assigned tutorials and problems.

1. How does Mendel's work relate to our understanding of the transmission of traits?
2. **CONCEPT QUESTION** Review the Chapter Concepts list on p. 25. Most of these are related to the discovery of DNA as the genetic material and the subsequent development of recombinant DNA technology. Write a brief essay that discusses the impact of recombinant DNA technology on genetics as we perceive the discipline today.
3. What is the chromosome theory of inheritance, and how is it related to Mendel's findings?
4. Define genotype and phenotype. Describe how they are related and how alleles fit into your definitions.
5. Given the state of knowledge at the time of the Avery, MacLeod, and McCarty experiment, why was it difficult for some scientists to accept that DNA is the carrier of genetic information?
6. What is a gene?
7. What is the structure of DNA? How does it differ from that of RNA?
8. Describe the central dogma of molecular genetics and how it serves as the basis of modern genetics.
9. Until the mid-1940s, many scientists considered protein to be the likely candidate for genetic material. Why?
10. Outline the roles played by restriction enzymes and vectors in cloning DNA.
11. What are the impacts of biotechnology on human genetics?
12. Summarize the arguments for and against patenting genetically modified organisms.
13. We all carry about 20,000 genes in our genome. So far, patents have been issued for more than 6000 of these genes. Do you think that companies or individuals should be able to patent human genes? Why or why not?
14. How is it possible to study certain aspects of diseases such as cancer in simple model organisms like the *E. coli* bacteria?
15. If you knew that a devastating late-onset inherited disease runs in your family (in other words, a disease that does not appear until later in life) and you could be tested for it at the age of 20, would you want to know whether you are a carrier? Would your answer be likely to change when you reach age 40?
16. Why do you think discoveries in genetics have been recognized with so many Nobel Prizes?

2

Mitosis and Meiosis

Chromosomes in the prometaphase stage of mitosis, derived from a cell in the flower of *Haemanthus*.

CHAPTER CONCEPTS

- Genetic continuity between generations of cells and between generations of sexually reproducing organisms is maintained through the processes of mitosis and meiosis, respectively.
- Diploid eukaryotic cells contain their genetic information in pairs of homologous chromosomes, with one member of each pair being derived from the maternal parent and one from the paternal parent.
- Mitosis provides a mechanism by which chromosomes, having been duplicated, are distributed into progeny cells during cell reproduction.
- Mitosis converts a diploid cell into two diploid daughter cells.
- Meiosis provides a mechanism by which one member of each homologous pair of chromosomes is distributed into each gamete or spore, thus reducing the diploid chromosome number to the haploid chromosome number.
- Meiosis generates genetic variability by distributing various combinations of maternal and paternal members into gametes or spores.
- During the stages of mitosis and meiosis, the genetic material is condensed into discrete structures called chromosomes.

Every living thing contains a substance described as the genetic material. Except in certain viruses, this material is composed of the nucleic acid DNA. DNA has an underlying linear structure possessing segments called genes, the products of which direct the metabolic activities of cells. An organism's DNA, with its arrays of genes, is organized into structures called **chromosomes,** which serve as vehicles for transmitting genetic information. The manner in which chromosomes are transmitted from one generation of cells to the next and from organisms to their descendants must be exceedingly precise. In this chapter we consider exactly how genetic continuity is maintained between cells and organisms.

Two major processes are involved in the genetic continuity of nucleated cells: **mitosis** and **meiosis.** Although the mechanisms of the two processes are similar in many ways, the outcomes are quite different. Mitosis leads to the production of two cells, each with the same number of chromosomes as the parent cell. In contrast, meiosis reduces the genetic content and the number of chromosomes by precisely half. This reduction is essential if sexual reproduction is to occur without doubling the amount of genetic material in each new generation. Strictly speaking, mitosis is that portion of the cell cycle during which the hereditary components are equally partitioned into daughter cells. Meiosis is part of a special type of cell division that leads to the production of sex cells: **gametes** or **spores.** This process is an essential step in the transmission of genetic information from an organism to its offspring.

Normally, chromosomes are visible only during mitosis and meiosis. When cells are not undergoing division, the genetic material making up chromosomes unfolds and uncoils into a diffuse network within the nucleus, generally referred to as **chromatin.** Before describing mitosis and meiosis, we will briefly review the structure of cells, emphasizing components that are of particular significance to genetic function. We will also compare the structural differences between the nonnucleated cells of bacteria and the eukaryotic cells of higher organisms. We then devote the remainder of the chapter to the behavior of chromosomes during cell division.

2.1 Cell Structure Is Closely Tied to Genetic Function

Before 1940, our knowledge of cell structure was limited to what we could see with the light microscope. Around 1940, the transmission electron microscope was in its early stages of development, and by 1950, many details of cell ultrastructure had emerged. Under the electron microscope, cells were seen as highly varied, highly organized structures whose form and function are dependent on specific genetic expression by each cell type. A new world of whorled membranes, organelles, microtubules, granules, and filaments was revealed. These discoveries revolutionized thinking in the entire field of biology. Many cell components, such as the nucleolus, ribosome, and centriole, are involved directly or indirectly with genetic processes. Other components—the mitochondria and chloroplasts—contain their own unique genetic information. Here, we will focus primarily on those aspects of cell structure that relate to genetic study. The generalized animal cell shown in **Figure 2.1** illustrates most of the structures we will discuss.

All cells are surrounded by a *plasma membrane,* an outer covering that defines the cell boundary and delimits the cell from its immediate external environment. This membrane is not passive but instead actively controls the

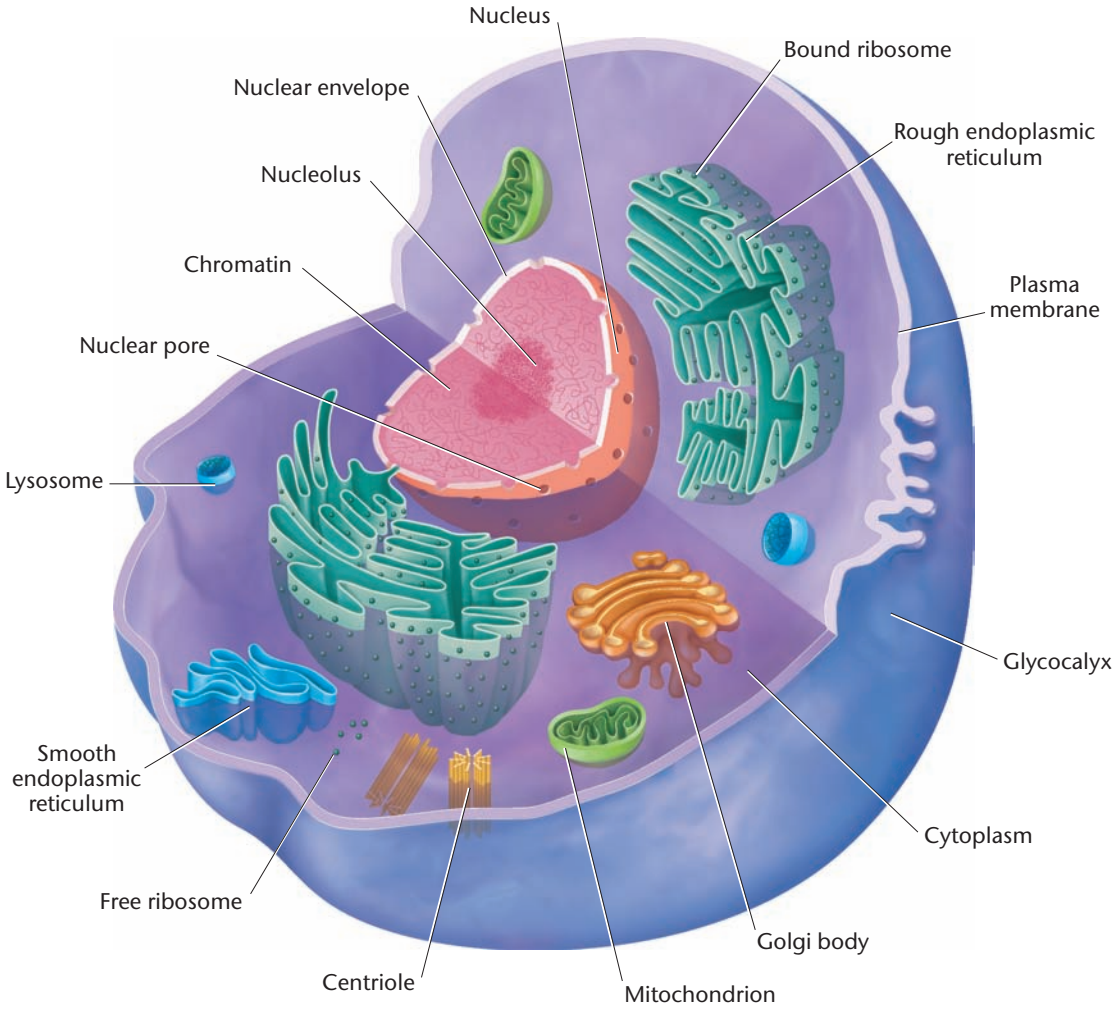


FIGURE 2.1 A generalized animal cell. The cellular components discussed in the text are emphasized here.

movement of materials into and out of the cell. In addition to this membrane, plant cells have an outer covering called the *cell wall* whose major component is a polysaccharide called *cellulose*.

Many, if not most, animal cells have a covering over the plasma membrane, referred to as the *glycocalyx*, or *cell coat*. Consisting of glycoproteins and polysaccharides, this covering has a chemical composition that differs from comparable structures in either plants or bacteria. The glycocalyx, among other functions, provides biochemical identity at the surface of cells, and the components of the coat that establish cellular identity are under genetic control. For example, various cell-identity markers that you may have heard of—the AB, Rh, and MN antigens—are found on the surface of red blood cells, among other cell types. On the surface of other cells, histocompatibility antigens, which elicit an immune response during tissue and organ transplants, are present. Various *receptor molecules* are also found on the surfaces of cells. These molecules act as recognition sites that transfer specific chemical signals across the cell membrane into the cell.

Living organisms are categorized into two major groups depending on whether or not their cells contain a nucleus. The presence of a nucleus and other membranous organelles is the defining characteristic of **eukaryotes.** The **nucleus** in eukaryotic cells is a membrane-bound structure that houses the genetic material, DNA, which is complexed with an array of acidic and basic proteins into thin fibers. During nondivisional phases of the cell cycle, the fibers are uncoiled and dispersed into chromatin (as mentioned above). During mitosis and meiosis, chromatin fibers coil and condense into chromosomes. Also present in the nucleus is the **nucleolus,** an amorphous component where ribosomal RNA (rRNA) is synthesized and where the initial stages of ribosomal assembly occur. The portions of DNA that encode rRNA are collectively referred to as the **nucleolus organizer region,** or the **NOR.**

Prokaryotes, of which there are two major groups, lack a nuclear envelope and membranous organelles. For the purpose of our brief discussion here, we will consider the *eubacteria,* the other group being the more ancient bacteria referred to as *archaea.* In eubacteria, such as *Escherichia coli,* the genetic material is present as a long, circular DNA molecule that is compacted into an unenclosed region called the **nucleoid.** Part of the DNA may be attached to the cell membrane, but in general the nucleoid extends through a large part of the cell. Although the DNA is compacted, it does not undergo the extensive coiling characteristic of the stages of mitosis, during which the chromosomes of eukaryotes become visible. Nor is the DNA associated as extensively with proteins as is eukaryotic DNA. **Figure 2.2**, which shows two bacteria forming by cell division, illustrates the nucleoid regions containing the bacterial chromosomes. Prokaryotic cells do not have a distinct nucleolus but do contain genes that specify rRNA molecules.

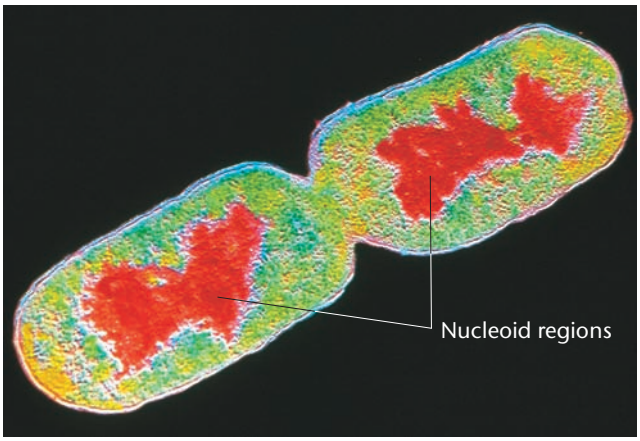


FIGURE 2.2 Color-enhanced electron micrograph of *E. coli* undergoing cell division. Particularly prominent are the two chromosomal areas (shown in red), called nucleoids, that have been partitioned into the daughter cells.

The remainder of the eukaryotic cell within the plasma membrane, excluding the nucleus, is referred to as *cytoplasm* and includes a variety of extranuclear cellular organelles. In the cytoplasm, a nonparticulate, colloidal material referred to as the *cytosol* surrounds and encompasses the cellular organelles. The cytoplasm also includes an extensive system of tubules and filaments, comprising the cytoskeleton, which provides a lattice of support structures within the cell. Consisting primarily of *microtubules*, which are made of the protein *tubulin*, and *microfilaments*, which derive from the protein *actin*, this structural framework maintains cell shape, facilitates cell mobility, and anchors the various organelles.

One organelle, the membranous *endoplasmic reticulum (ER)*, compartmentalizes the cytoplasm, greatly increasing the surface area available for biochemical synthesis. The ER appears smooth in places where it serves as the site for synthesizing fatty acids and phospholipids; in other places, it appears rough because it is studded with ribosomes. **Ribosomes** serve as sites where genetic information contained in messenger RNA (mRNA) is translated into proteins.

Three other cytoplasmic structures are very important in the eukaryotic cell's activities: mitochondria, chloroplasts, and centrioles. **Mitochondria** are found in most eukaryotes, including both animal and plant cells, and are the sites of the oxidative phases of cell respiration. These chemical reactions generate large amounts of the energy-rich molecule adenosine triphosphate (ATP). **Chloroplasts,** which are found in plants, algae, and some protozoans, are associated with photosynthesis, the major energy-trapping process on Earth. Both mitochondria and chloroplasts contain DNA in a form distinct from that found in the nucleus. They are able to duplicate themselves and transcribe and translate their own genetic information.

Animal cells and some plant cells also contain a pair of complex structures called **centrioles.** These cytoplasmic

bodies, each located in a specialized region called the **centrosome,** are associated with the organization of spindle fibers that function in mitosis and meiosis. In some organisms, the centriole is derived from another structure, the basal body, which is associated with the formation of cilia and flagella (hair-like and whip-like structures for propelling cells or moving materials).

The organization of **spindle fibers** by the centrioles occurs during the early phases of mitosis and meiosis. These fibers play an important role in the movement of chromosomes as they separate during cell division. They are composed of arrays of microtubules consisting of polymers of the protein tubulin.

ESSENTIAL POINT

Most components of cells are involved directly or indirectly with genetic processes. ■

2.2 Chromosomes Exist in Homologous Pairs in Diploid Organisms

As we discuss the processes of mitosis and meiosis, it is important that you understand the concept of homologous chromosomes. Such an understanding will also be of critical importance in our future discussions of Mendelian genetics. Chromosomes are most easily visualized during mitosis. When they are examined carefully, distinctive lengths and shapes are apparent. Each chromosome contains a constricted region called the **centromere,** whose location establishes the general appearance of each chromosome. **Figure 2.3** shows chromosomes with centromere placements at different distances along their length. Extending from either side of the centromere are the arms of the chromosome. Depending on the position of the centromere, different arm ratios are produced. As Figure 2.3 illustrates, chromosomes are classified as **metacentric, submetacentric, acrocentric,** or **telocentric** on the basis of the centromere location. The shorter arm, by convention, is shown above the centromere and is called the **p arm** (p, for "petite"). The longer arm is shown below the centromere and is called the **q arm** (q because it is the next letter in the alphabet).

In the study of mitosis, several other observations are of particular relevance. First, all somatic cells derived from members of the same species contain an identical number of chromosomes. In most cases, this represents what is referred to as the **diploid number (2*n*).** When the lengths and centromere placements of all such chromosomes are examined, a second general feature is apparent. With the exception of sex chromosomes, they exist in pairs with regard to these two properties, and the members of each pair are called **homologous chromosomes.** So, for each chromosome exhibiting a specific length and centromere placement, another exists with identical features.

There are exceptions to this rule. Many bacteria and viruses have but one chromosome, and organisms such as yeasts and molds, and certain plants such as bryophytes (mosses), spend the predominant phase of their life cycle in the haploid stage. That is, they contain only one member of each homologous pair of chromosomes during most of their lives.

Figure 2.4 illustrates the physical appearance of different pairs of homologous chromosomes. There, the human mitotic chromosomes have been photographed, cut out of the print, and matched up, creating a display called a **karyotype.** As you can see, humans have a 2*n* number of 46 chromosomes, which on close examination exhibit a diversity of sizes and centromere placements. Note also that each of the 46 chromosomes in this karyotype is clearly a

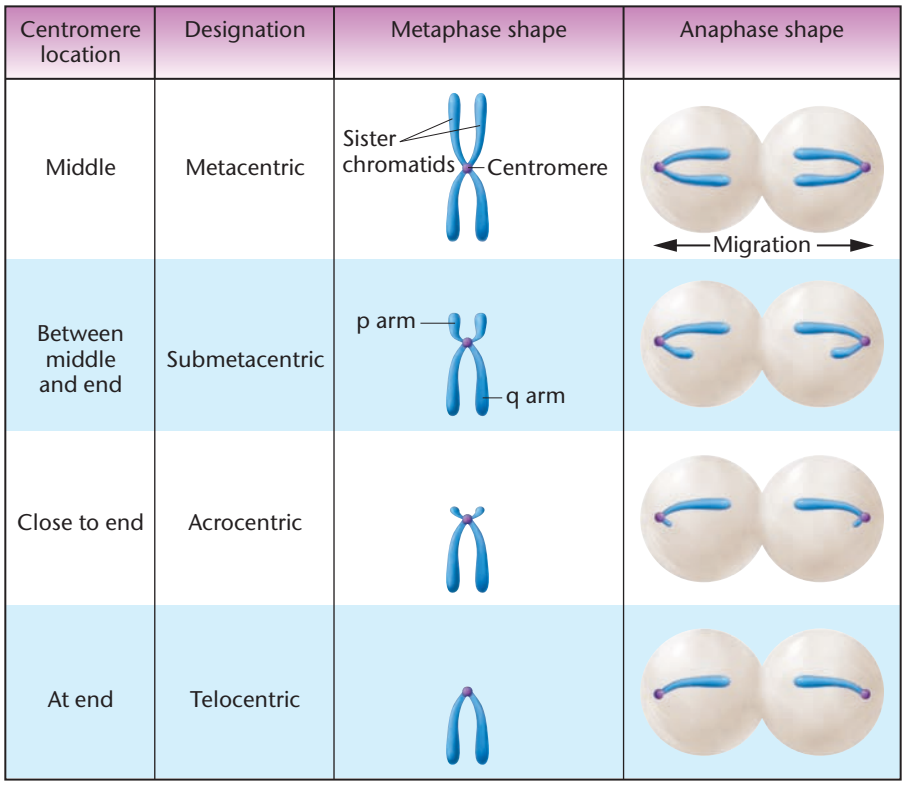


FIGURE 2.3 Centromere locations and the chromosome designations that are based on them. Note that the shape of the chromosome during anaphase is determined by the position of the centromere during metaphase.

double structure consisting of two parallel *sister chromatids* connected by a common centromere. Had these chromosomes been allowed to continue dividing, the sister chromatids, which are replicas of one another, would have separated into the two new cells as division continued.

The **haploid number (*n*)** of chromosomes is equal to one-half the diploid number. Collectively, the genetic information contained in a haploid set of chromosomes constitutes the **genome** of the species. This, of course, includes copies of all genes as well as a large amount of noncoding DNA. The examples listed in **Table 2.1** demonstrate the wide range of *n* values found in plants and animals.

Homologous chromosomes have important genetic similarities. They contain identical gene sites along their lengths; each site is called a **locus** (pl. loci). Thus, they are identical in the traits that they influence and in their genetic potential. In sexually reproducing organisms, one member of each pair is derived from the maternal parent (through the ovum) and the other member is derived from the paternal parent (through the sperm). Therefore, each diploid organism contains two copies of each gene as a consequence of **biparental inheritance,** inheritance from two parents. As we shall see during our discussion of transmission genetics (Chapters 3 and 4), the members of each pair of genes, while influencing the same characteristic or trait, need not be identical. In a population of members of the same species, many different alternative forms of the same gene, called **alleles,** can exist.

FIGURE 2.4 A metaphase preparation of chromosomes derived from a dividing cell of a human male (right), and the karyotype derived from the metaphase preparation (left). All but the X and Y chromosomes are present in homologous pairs. Each chromosome is clearly a double structure consisting of a pair of sister chromatids joined by a common centromere.

TABLE 2.1 The Haploid Number of Chromosomes for a Variety of Organisms

Common Name	Scientific Name	Haploid Number
Black bread mold	*Aspergillus nidulans*	8
Broad bean	*Vicia faba*	6
Chimpanzee	*Pan troglodytes*	24
Corn	*Zea mays*	10
Cotton	*Gossypium hirsutum*	26
Fruit fly	*Drosophila melanogaster*	4
Garden pea	*Pisum sativum*	7
House mouse	*Mus musculus*	20
Human	*Homo sapiens*	23
Pink bread mold	*Neurospora crassa*	7
Roundworm	*Caenorhabditis elegans*	6
Yeast	*Saccharomyces cerevisiae*	16
Zebrafish	*Danio rerio*	25

The concepts of haploid number, diploid number, and homologous chromosomes are important for understanding the process of meiosis. During the formation of gametes or spores, meiosis converts the diploid number of chromosomes to the haploid number. As a result, haploid gametes or spores contain precisely one member of each homologous pair of chromosomes—that is, one complete haploid set. Following fusion of two gametes at fertilization, the diploid number is reestablished; that is, the zygote contains two complete haploid sets of chromosomes. The constancy of genetic material is thus maintained from generation to generation.

There is one important exception to the concept of homologous pairs of chromosomes. In many species, one pair, consisting of the *sex-determining chromosomes,* is often not homologous in size, centromere placement, arm ratio, or genetic content. For example, in humans, while females carry two homologous X chromosomes, males carry one Y chromosome in addition to one X chromosome (Figure 2.4). These X and Y chromosomes are not strictly homologous. The Y is considerably smaller and lacks most of the gene loci contained on the X. Nevertheless, they contain homologous regions and behave as homologs in meiosis so that gametes produced by males receive either one X or one Y chromosome.

ESSENTIAL POINT

In diploid organisms, chromosomes exist in homologous pairs, where each member is identical in size, centromere placement, and gene sites. One member of each pair is derived from the maternal parent, and one is derived from the paternal parent. ■

2.3 Mitosis Partitions Chromosomes into Dividing Cells

The process of mitosis is critical to all eukaryotic organisms. In some single-celled organisms, such as protozoans and some fungi and algae, mitosis (as a part of cell division) provides the basis for asexual reproduction. Multicellular diploid organisms begin life as single-celled fertilized eggs called **zygotes.** The mitotic activity of the zygote and the subsequent daughter cells is the foundation for the development and growth of the organism. In adult organisms, mitotic activity is the basis for wound healing and other forms of cell replacement in certain tissues. For example, the epidermal cells of the skin and the intestinal lining of humans are continuously sloughed off and replaced. Cell division also results in the continuous production of reticulocytes that eventually shed their nuclei and replenish the supply of red blood cells in vertebrates. In abnormal situations, somatic cells may lose control of cell division and form a tumor.

The genetic material is partitioned into daughter cells during nuclear division, or **karyokinesis.** This process is quite complex and requires great precision. The chromosomes must first be exactly replicated and then accurately partitioned. The end result is the production of two daughter nuclei, each with a chromosome composition identical to that of the parent cell.

Karyokinesis is followed by cytoplasmic division, or **cytokinesis.** This less complex process requires a mechanism that partitions the volume into two parts and then encloses each new cell in a distinct plasma membrane. As the cytoplasm is reconstituted, organelles replicate themselves, arise from existing membrane structures, or are synthesized *de novo* (anew) in each cell.

Following cell division, the initial size of each new daughter cell is approximately one-half the size of the parent cell. However, the nucleus of each new cell is not appreciably smaller than the nucleus of the original cell. Quantitative measurements of DNA confirm that there is an amount of genetic material in the daughter nuclei equivalent to that in the parent cell.

Interphase and the Cell Cycle

Many cells undergo a continuous alternation between division and nondivision. The events that occur from the completion of one division until the completion of the next division constitute the **cell cycle** (Figure 2.5). We will consider **interphase,** the initial stage of the cell cycle, as the interval between divisions. It was once thought that the biochemical activity during interphase was devoted solely to the cell's growth and its normal function. However, we now know that another biochemical step critical to the ensuing mitosis occurs during interphase: *the replication of the DNA of each chromosome.* This period, during which DNA is synthesized, occurs before

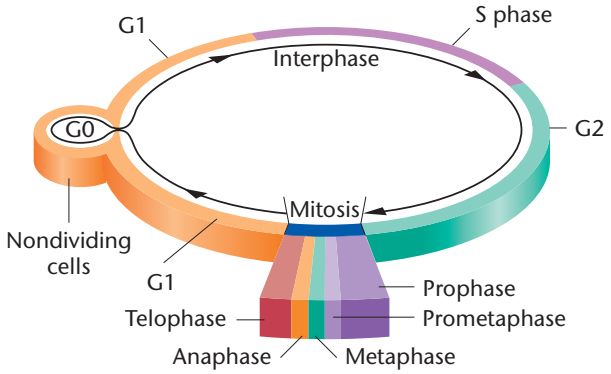


FIGURE 2.5 The stages comprising an arbitrary cell cycle. Following mitosis, cells enter the G1 stage of interphase, initiating a new cycle. Cells may become nondividing (G0) or continue through G1, where they become committed to begin DNA synthesis (S) and complete the cycle (G2 and mitosis). Following mitosis, two daughter cells are produced, and the cycle begins anew for both of them.

the cell enters mitosis and is called the **S phase.** The initiation and completion of synthesis can be detected by monitoring the incorporation of radioactive precursors into DNA.

Investigations of this nature demonstrate two periods during interphase when no DNA synthesis occurs, one before and one after the S phase. These are designated **G1 (gap I)** and **G2 (gap II),** respectively. During both of these intervals, as well as during S, intensive metabolic activity, cell growth, and cell differentiation are evident. By the end of G2, the volume of the cell has roughly doubled, DNA has been replicated, and mitosis (M) is initiated. Following mitosis, continuously dividing cells then repeat this cycle (G1, S, G2, M) over and over, as shown in Figure 2.5.

Much is known about the cell cycle based on *in vitro* (literally, "in glass") studies. When grown in culture, many cell types in different organisms traverse the complete cycle in about 16 hours. The actual process of mitosis occupies only a small part of the overall cycle, often less than an hour. The lengths of the S and G2 phases of interphase are fairly consistent in different cell types. Most variation is seen in the length of time spent in the G1 stage. **Figure 2.6** shows the relative length of these intervals as well as the length of the stages of mitosis in a human cell in culture.

Interphase			Mitosis
G1	S	G2	M
5	7	3	1

Hours

Pro	Met	Ana	Tel
36	3	3	18

Minutes

FIGURE 2.6 The time spent in each interval of one complete cell cycle of a human cell in culture. Times vary according to cell types and conditions.

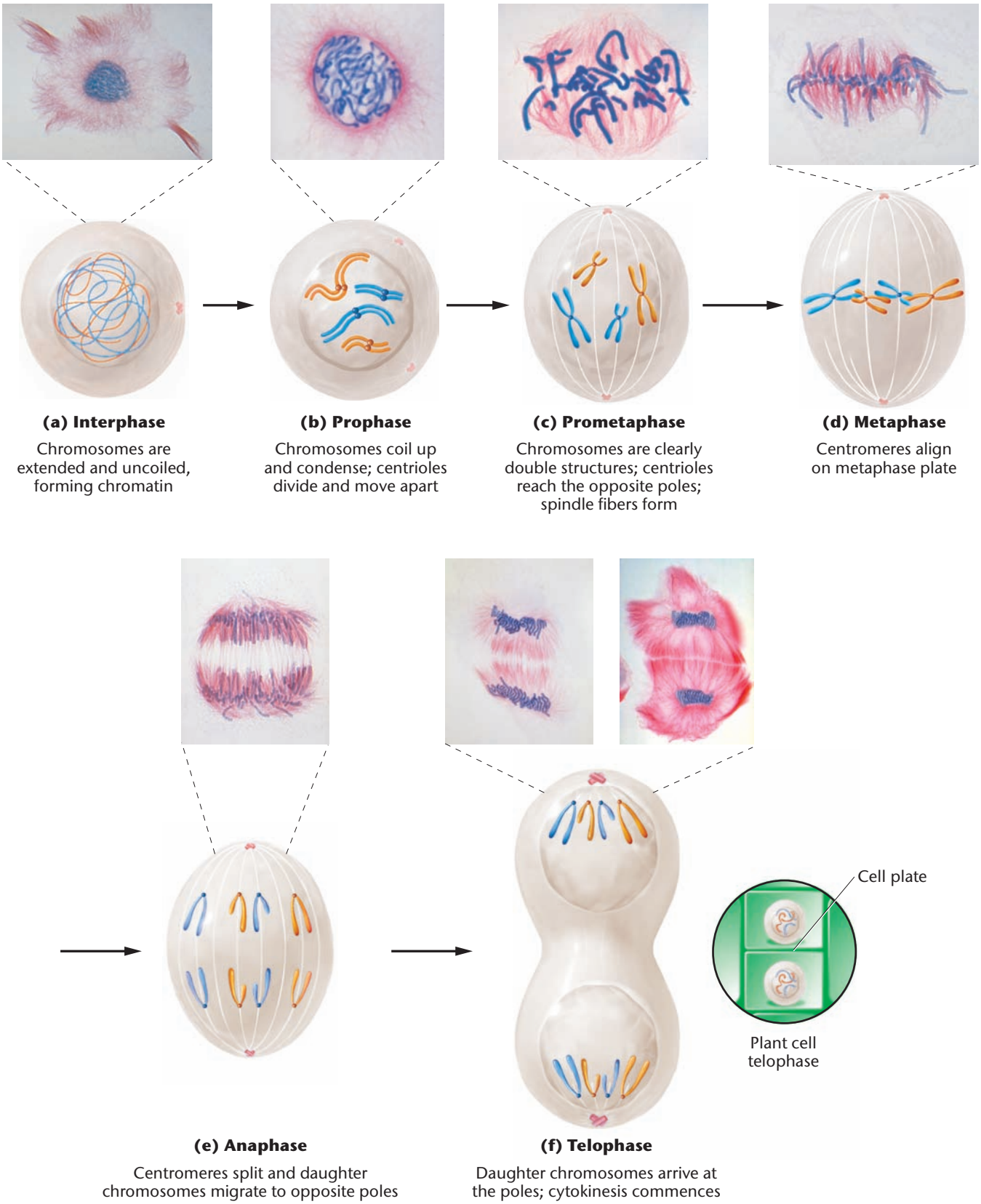


FIGURE 2.7 Drawings depicting mitosis in an animal cell with a diploid number of 4. The events occurring in each stage are described in the text. Of the two homologous pairs of chromosomes, one pair consists of longer, metacentric members and the other of shorter, submetacentric members. The maternal chromosome and the paternal chromosome of each pair are shown in different colors. To the right of (f), a drawing of late telophase in a plant cell shows the formation of the cell plate and lack of centrioles. The cells shown in the light micrographs came from the flower of *Haemanthus,* a plant that has a diploid number of 8.

G1 is of great interest in the study of cell proliferation and its control. At a point during G1, all cells follow one of two paths. They either withdraw from the cycle, become quiescent, and enter the **G0 stage** (see Figure 2.5), or they become committed to proceed through G1, initiating DNA synthesis, and completing the cycle. Cells that enter G0 remain viable and metabolically active but are not proliferative. Cancer cells apparently avoid entering G0 or pass through it very quickly. Other cells enter G0 and never reenter the cell cycle. Still other cells in G0 can be stimulated to return to G1 and thereby reenter the cell cycle.

Cytologically, interphase is characterized by the absence of visible chromosomes. Instead, the nucleus is filled with chromatin fibers that are formed as the chromosomes uncoil and disperse after the previous mitosis [**Figure 2.7(a)**]. Once G1, S, and G2 are completed, mitosis is initiated. Mitosis is a dynamic period of vigorous and continual activity. For discussion purposes, the entire process is subdivided into discrete stages, and specific events are assigned to each one. These stages, in order of occurrence, are prophase, prometaphase, metaphase, anaphase, and telophase.

Prophase

Often, over half of mitosis is spent in **prophase** [**Figure 2.7(b)**], a stage characterized by several significant occurrences. One of the early events in prophase of all animal cells is the migration of two pairs of centrioles to opposite ends of the cell. These structures are found just outside the nuclear envelope in an area of differentiated cytoplasm called the centrosome (introduced in Section 2.1). It is believed that each pair of centrioles consists of one mature unit and a smaller, newly formed daughter centriole.

The centrioles migrate and establish poles at opposite ends of the cell. After migration, the centrosomes, in which the centrioles are localized, are responsible for organizing cytoplasmic microtubules into the spindle fibers that run between these poles, creating an axis along which chromosomal separation occurs. Interestingly, the cells of most plants (there are a few exceptions), fungi, and certain algae seem to lack centrioles. Spindle fibers are nevertheless apparent during mitosis.

As the centrioles migrate, the nuclear envelope begins to break down and gradually disappears. In a similar fashion, the nucleolus disintegrates within the nucleus. While these events are taking place, the diffuse chromatin fibers have begun to condense, until distinct thread-like structures, the chromosomes, become visible. It becomes apparent near the end of prophase that each chromosome is actually a double structure split longitudinally except at a single point of constriction, the centromere. The two parts of each chromosome are called **sister chromatids** because the DNA contained in each of them is genetically identical, having formed from a single replicative event. Sister chromatids are held together by a multi-subunit protein complex called **cohesin.** This molecular complex is originally formed between them during the S phase of the cell cycle when the DNA of each chromosome is replicated. Thus, even though we cannot see chromatids in interphase because the chromatin is uncoiled and dispersed in the nucleus, the chromosomes are already double structures, which becomes apparent in late prophase. In humans, with a diploid number of 46, a cytological preparation of late prophase reveals 46 chromosomes randomly distributed in the area formerly occupied by the nucleus.

Prometaphase and Metaphase

The distinguishing event of the two ensuing stages is the migration of every chromosome, led by its centromeric region, to the equatorial plane. The equatorial plane, also referred to as the *metaphase plate,* is the midline region of the cell, a plane that lies perpendicular to the axis established by the spindle fibers. In some descriptions, the term **prometaphase** refers to the period of chromosome movement [**Figure 2.7(c)**], and the term **metaphase** is applied strictly to the chromosome configuration following migration.

Migration is made possible by the binding of spindle fibers to the chromosome's **kinetochore,** an assembly of multilayered plates of proteins associated with the centromere. This structure forms on opposite sides of each paired centromere, in intimate association with the two sister chromatids. Once properly attached to the spindle fibers, cohesin is degraded by an enzyme, appropriately named *separase,* and the sister chromatid arms disjoin, except at the centromere region. A unique protein family called **shugoshin** (from the Japanese meaning "guardian spirit") protects cohesin from being degraded by separase at the centromeric regions. The involvement of the cohesin and shugoshin complexes with a pair of sister chromatids during mitosis is depicted in **Figure 2.8**.

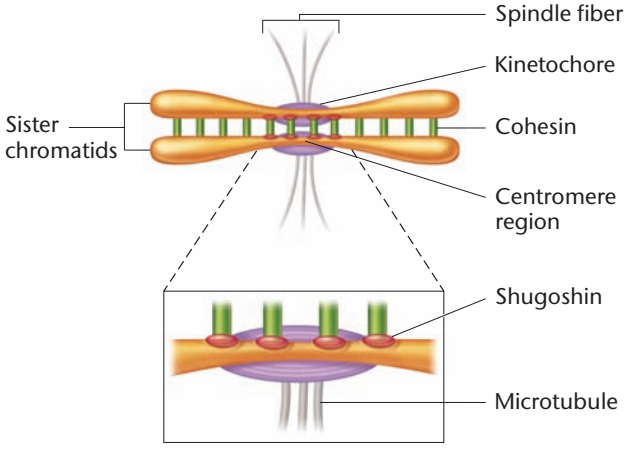


FIGURE 2.8 The depiction of the alignment, pairing, and disjunction of sister chromatids during mitosis, involving the molecular complexes cohesin and shugoshin and the enzyme separase.

We know a great deal about the molecular interactions involved in kinetechore assembly along the centromere. This is of great interest because of the consequences when mutations alter the proteins that make up the kinetechore complex. Altered kinetechore function potentially leads to errors during chromosome migration, altering the diploid content of daughter cells. A more detailed account will be presented later in the text, once we have provided more information about DNA and the proteins that make up chromatin (see Chapter 11).

We also know a great deal about spindle fibers and the mechanism responsible for their attachment to the kinetechore. Spindle fibers consist of microtubules, which themselves consist of molecular subunits of the protein tubulin. Microtubules seem to originate and "grow" out of the two centrosome regions at opposite poles of the cell. They are dynamic structures that lengthen and shorten as a result of the addition or loss of polarized tubulin subunits. The microtubules most directly responsible for chromosome migration make contact with, and adhere to, kinetochores as they grow from the centrosome region. They are referred to as *kinetochore microtubules* and have one end near the centrosome region (at one of the poles of the cell) and the other end anchored to the kinetochore. The number of microtubules that bind to the kinetochore varies greatly between organisms. Yeast (*Saccharomyces*) has only a single microtubule bound to each plate-like structure of the kinetochore. Mitotic cells of mammals, at the other extreme, reveal 30 to 40 microtubules bound to each portion of the kinetochore.

At the completion of metaphase, each centromere is aligned at the metaphase plate with the chromosome arms extending outward in a random array. This configuration is shown in **Figure 2.7(d)**.

Anaphase

Events critical to chromosome distribution during mitosis occur during **anaphase,** the shortest stage of mitosis. During this phase, sister chromatids of each chromosome, held together only at their centromere regions, *disjoin* (separate) from one another—an event described as **disjunction**—and are pulled to opposite ends of the cell. For complete disjunction to occur: (1) shugoshin must be degraded, reversing its protective role; (2) the cohesin complex holding the centromere region of each sister chromosome is then cleaved by separase; and (3) sister chromatids of each chromosome are pulled toward the opposite poles of the cell (Figure 2.8). As these events proceed, each migrating chromatid is now referred to as a *daughter chromosome*.

The location of the centromere determines the shape of the chromosome during separation, as you saw in Figure 2.3. The steps that occur during anaphase are critical in providing each subsequent daughter cell with an identical set of chromosomes. In human cells, there would now be 46 chromosomes at each pole, one from each original sister pair. **Figure 2.7(e)** shows anaphase prior to its completion.

Telophase

Telophase is the final stage of mitosis and is depicted in **Figure 2.7(f)**. At its beginning, two complete sets of chromosomes are present, one set at each pole. The most significant event of this stage is cytokinesis, the division or partitioning of the cytoplasm. Cytokinesis is essential if two new cells are to be produced from one cell. The mechanism of cytokinesis differs greatly in plant and animal cells, but the end result is the same: Two new cells are produced. In plant cells, a *cell plate* is synthesized and laid down across the region of the metaphase plate. Animal cells, however, undergo a constriction of the cytoplasm, much as a loop of string might be tightened around the middle of a balloon.

It is not surprising that the process of cytokinesis varies in different organisms. Plant cells, which are more regularly shaped and structurally rigid, require a mechanism for depositing new cell wall material around the plasma membrane. The cell plate laid down during telophase becomes a structure called the *middle lamella*. Subsequently, the primary and secondary layers of the cell wall are deposited between the cell membrane and middle lamella in each of the resulting daughter cells. In animals, complete constriction of the cell membrane produces the *cell furrow* characteristic of newly divided cells.

Other events necessary for the transition from mitosis to interphase are initiated during late telophase. They generally constitute a reversal of events that occurred during prophase. In each new cell, the chromosomes begin to uncoil and become diffuse chromatin once again, while the nuclear envelope re-forms around them, the spindle fibers disappear, and the nucleolus gradually re-forms and becomes visible in the nucleus during early interphase. At the completion of telophase, the cell enters interphase.

Cell-Cycle Regulation and Checkpoints

The cell cycle, culminating in mitosis, is fundamentally the same in all eukaryotic organisms. This similarity in many diverse organisms suggests that the cell cycle is governed by a genetically regulated program that has been conserved throughout evolution. Because disruption of this regulation may underlie the uncontrolled cell division characterizing malignancy, interest in how genes regulate the cell cycle is particularly strong.

A mammoth research effort over the past 20 years has paid high dividends, and we now have knowledge of many genes involved in the control of the cell cycle. This work

was recognized by the awarding of the 2001 Nobel Prize in Medicine or Physiology to Lee Hartwell, Paul Nurse, and Tim Hunt. As with other studies of genetic control over essential biological processes, investigation has focused on the discovery of mutations that interrupt the cell cycle and on the effects of those mutations. As we shall return to this subject in much greater detail later in the text during our consideration of the molecular basis of cancer (see Chapter 19), what follows is a very brief overview.

Many mutations are now known that exert an effect at one or another stage of the cell cycle. First discovered in yeast, but now evident in all organisms, including humans, such mutations were originally designated as *cell division cycle (cdc) mutations*. The normal products of many of the mutated genes are enzymes called **kinases** that can add phosphates to other proteins. They serve as "master control" molecules functioning in conjunction with proteins called **cyclins.** Cyclins bind to these kinases (creating *cyclin-dependent kinases*), activating them at appropriate times during the cell cycle. Activated kinases then phosphorylate other target proteins that regulate the progress of the cell cycle. The study of *cdc* mutations has established that the cell cycle contains at least three **cell-cycle checkpoints,** where the processes culminating in normal mitosis are monitored, or "checked," by these master control molecules before the next stage of the cycle is allowed to commence.

The importance of cell-cycle control and these checkpoints can be demonstrated by considering what happens when this regulatory system is impaired. Let's assume, for example, that the DNA of a cell has incurred damage leading to one or more mutations impairing cell-cycle control. If allowed to proceed through the cell cycle, this genetically altered cell would divide uncontrollably—a key step in the development of a cancer cell. If, instead, the cell cycle is arrested at one of the checkpoints, the cell can repair the DNA damage or permanently stop the cell from dividing, thereby preventing its potential malignancy.

ESSENTIAL POINT

Mitosis is subdivided into discrete stages that initially depict the condensation of chromatin into the diploid number of chromosomes, each of which is initially a double structure, each composed of a pair of sister chromatids. During mitosis, sister chromatids are pulled apart and directed toward opposite poles, after which cytoplasmic division creates two new cells with identical genetic information. ■

NOW SOLVE THIS

2.1 With the initial appearance of the feature we call "Now Solve This," a short introduction is in order. The feature occurs several times in this and all ensuing chapters, each time providing a problem related to the discussion just presented. A "Hint" is then offered that may help you solve the problem. Here is the first problem:

(a) If an organism has a diploid number of 16, how many chromatids are visible at the end of mitotic prophase?
(b) How many chromosomes are moving to each pole during anaphase of mitosis?

■ **HINT:** *This problem involves an understanding of what happens to each pair of homologous chromosomes during mitosis, asking you to apply your understanding of chromosome behavior to an organism with a diploid number of 16. The key to its solution is your awareness that throughout mitosis, the members of each homologous pair do not pair up, but instead behave independently.*

2.4 Meiosis Creates Haploid Gametes and Spores and Enhances Genetic Variation in Species

Whereas in diploid organisms, mitosis produces two daughter cells with full diploid complements, **meiosis** produces gametes or spores that are characterized by only one haploid set of chromosomes. During sexual reproduction, haploid gametes then combine at fertilization to reconstitute the diploid complement found in parental cells. Meiosis must be highly specific since haploid gametes or spores must contain precisely one member of each homologous pair of chromosomes. When successfully completed, meiosis provides the basis for maintaining genetic continuity from generation to generation.

Another major accomplishment of meiosis is to ensure that during sexual reproduction an enormous amount of genetic variation is produced among members of a species. Such variation occurs in two forms. First, meiosis produces haploid gametes with many unique combinations of maternally and paternally derived chromosomes. As we will see (Chapter 3), this process is the underlying basis of Mendel's principles of segregation and independent assortment. The second source of variation is created by the meiotic event referred to as **crossing over,** which results in genetic exchange between members of each homologous pair of chromosomes prior to one or the other finding its way into a haploid gamete or spore. This creates intact chromosomes that are mosaics of the maternal and paternal homologs. Sexual reproduction therefore significantly reshuffles the genetic material, producing highly diverse offspring.

Meiosis: Prophase I

As in mitosis, the process in meiosis begins with a diploid cell duplicating its genetic material in the interphase stage preceding chromosome division. To achieve haploidy, two divisions are thus required. The meiotic achievements are largely dependent on the behavior of chromosomes during the initial stage of the first division, called *prophase I*. Recall

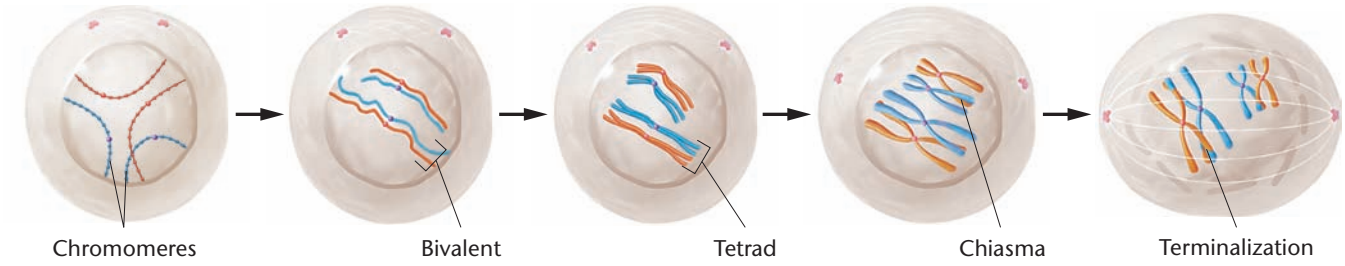


FIGURE 2.9 The events characterizing meiotic prophase I. In the first two frames, illustrating chromomeres and bivalents, each chromatid is actually a double structure, consisting of sister chromatids, which first becomes apparent in the ensuing tetrad stage.

that in mitosis the paternally and maternally derived members of each homologous pair of chromosomes behave autonomously during division. Each chromosome is duplicated, creating genetically identical **sister chromatids,** and subsequently, one chromatid of each pair is distributed to each new cell. The major difference in meiosis is that once the chromatin characterizing interphase has condensed into visible structures, the homologous chromosomes are not autonomous but are instead seen to be paired up, having undergone the process called **synapsis.** **Figure 2.9** illustrates this process as well as the ensuing events of prophase I. Each synapsed pair of homologs is initially called a **bivalent,** and the number of bivalents is equal to the haploid number. In Figure 2.9, we have

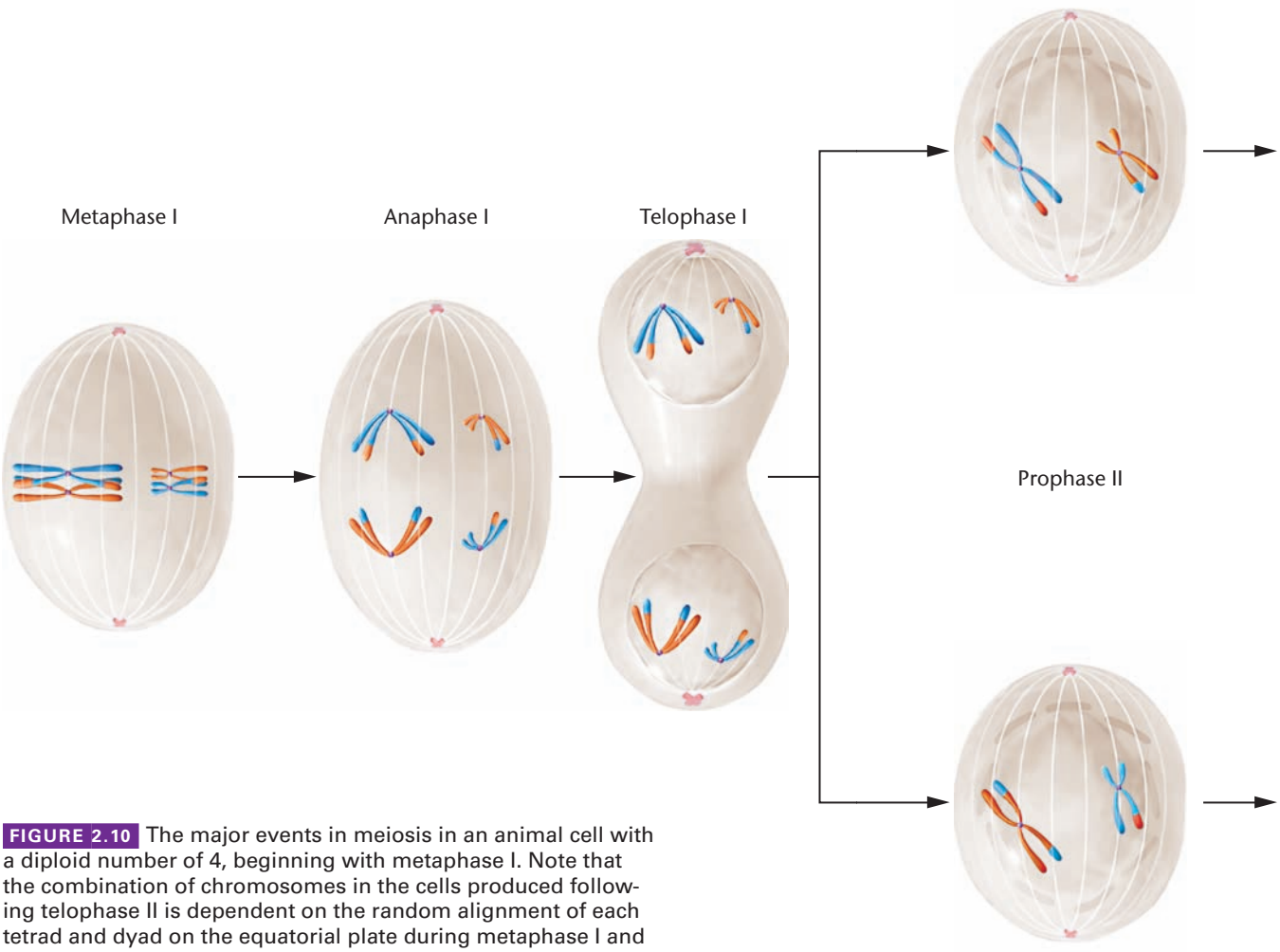
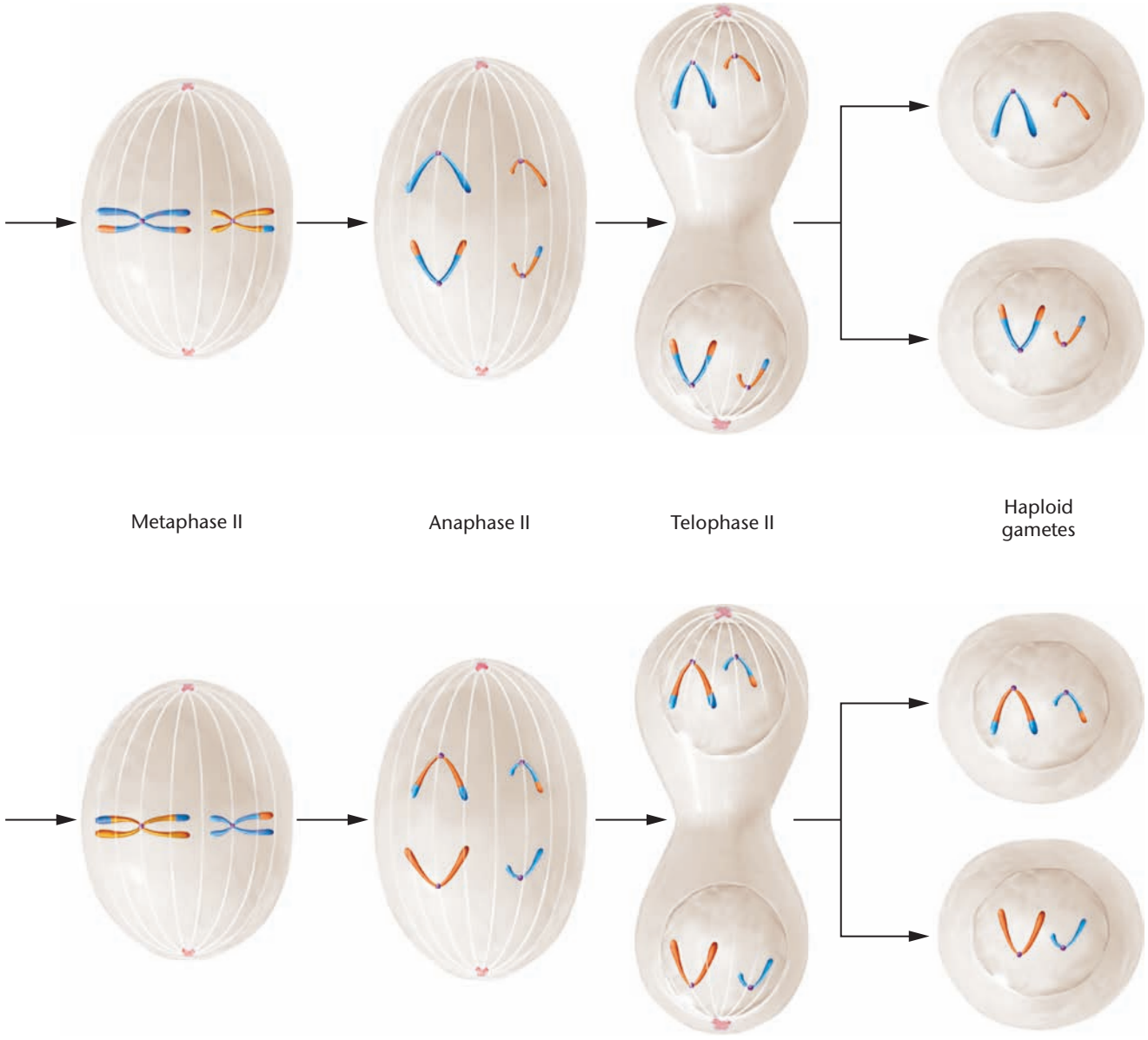


FIGURE 2.10 The major events in meiosis in an animal cell with a diploid number of 4, beginning with metaphase I. Note that the combination of chromosomes in the cells produced following telophase II is dependent on the random alignment of each tetrad and dyad on the equatorial plate during metaphase I and metaphase II. Several other combinations, which are not shown, can also be formed. The events depicted here are described in the text.

depicted two homologous pairs of chromosomes and thus two bivalents. As the homologs condense and shorten, each bivalent gives rise to a unit called a **tetrad,** consisting of two pairs of sister chromatids, each of which is joined at a common centromere. Remember that one pair of sister chromatids is maternally derived, and the other pair paternally derived. The presence of tetrads is visible evidence that *both* homologs have, in fact, duplicated. As prophase progresses within each tetrad, each pair of sister chromatids is seen to pull apart. However, one or more areas remain in contact where chromatids are intertwined. Each such area, called a **chiasma** (pl. chiasmata), is thought to represent a point where **nonsister chromatids** (one paternal and one maternal chromatid) have undergone genetic exchange through the process of crossing over. Since crossing over is thought to occur one or more times in each tetrad, mosaic chromosomes are routinely created during every meiotic event. During the final period of prophase I, the nucleolus and nuclear envelope break down, and the two centromeres of each tetrad attach to the recently formed spindle fibers.

Metaphase I, Anaphase I, and Telophase I

The remainder of the meiotic process is depicted in **Figure 2.10**. After meiotic prophase I, steps similar to those of mitosis occur. In the first division, *metaphase I,* the chromosomes have maximally shortened and thickened. The terminal chiasmata of each tetrad are visible and appear to be the only factor holding the nonsister chromatids together. Each tetrad interacts with spindle fibers, facilitating movement to the metaphase plate. The alignment of each tetrad prior to the first anaphase is random. Half of each tetrad is pulled randomly to one or the other pole, and the other half then moves to the opposite pole.



During the stages of meiosis I, a single centromere holds each pair of sister chromatids together. It does *not* divide. At *anaphase I,* one-half of each tetrad (the dyad) is pulled toward each pole of the dividing cell. This separation process is the physical basis of **disjunction,** the separation of chromosomes from one another. Occasionally, errors in meiosis occur and separation is not achieved. The term **nondisjunction** describes such an error. At the completion of a normal anaphase I, a series of dyads equal to the haploid number is present at each pole.

In many organisms, *telophase I* reveals a nuclear membrane forming around the dyads. Next, the nucleus enters into a short interphase period. If interphase occurs, the chromosomes do not replicate since they already consist of two chromatids. In other organisms, the cells go directly from anaphase I to meiosis II. In general, meiotic telophase is much shorter than the corresponding stage in mitosis.

The Second Meiotic Division

A second division, *meiosis II,* is essential if each gamete or spore is to receive only one chromatid from each original tetrad. The stages characterizing meiosis II are shown in the right half of Figure 2.10. During *prophase II,* each dyad is composed of one pair of sister chromatids attached by a common centromere. During *metaphase II,* the centromeres are positioned on the metaphase plate. When they divide, *anaphase II* is initiated, and the sister chromatids of each dyad are pulled to opposite poles. Because the number of dyads is equal to the haploid number, *telophase II* reveals one member of each pair of homologous chromosomes at each pole. Each chromosome is now a monad. Following cytokinesis in telophase II, four haploid gametes may result from a single meiotic event. At the conclusion of meiosis II, not only has the haploid state been achieved, but if crossing over has occurred, each monad is also a combination of maternal and paternal genetic information. As a result, the offspring produced by any gamete receives a mixture of genetic information originally present in his or her grandparents. Meiosis thus significantly increases the level of genetic variation in each ensuing generation.

ESSENTIAL POINT

Meiosis converts a diploid cell into a haploid gamete or spore, making sexual reproduction possible. As a result of chromosome duplication and two subsequent meiotic divisions, each haploid cell receives one member of each homologous pair of chromosomes. ■

NOW SOLVE THIS

2.2 An organism has a diploid number of 16 in a primary oocyte. (a) How many tetrads are present in prophase I? (b) How many dyads are present in prophase II? (c) How many monads migrate to each pole during anaphase II?

■ **HINT:** *This problem involves an understanding of what happens to the maternal and paternal members of each pair of homologous chromosomes during meiosis, asking you to extrapolate your understanding to chromosome behavior in an organism with a diploid number of 16. The major insight needed to solve this problem is to understand that maternal and paternal homologs synapse during meiosis. Once it is evident that each chromatid has duplicated, creating a tetrad in the early phases of meiosis, each original pair behaves as a unit and leads to two dyads during anaphase I.*

2.5 The Development of Gametes Varies in Spermatogenesis Compared to Oogenesis

Although events that occur during the meiotic divisions are similar in all cells participating in gametogenesis in most animal species, there are certain differences between the production of a male gamete (spermatogenesis) and a female gamete (oogenesis). **Figure 2.11** summarizes these processes.

Spermatogenesis takes place in the testes, the male reproductive organs. The process begins with the enlargement of an undifferentiated diploid germ cell called a *spermatogonium.* This cell grows to become a *primary spermatocyte,* which undergoes the first meiotic division. The products of this division, called *secondary spermatocytes,* contain a haploid number of dyads. The secondary spermatocytes then undergo meiosis II, and each of these cells produces two haploid *spermatids.* Spermatids go through a series of developmental changes, *spermiogenesis,* to become highly specialized, motile *spermatozoa,* or *sperm.* All sperm cells produced during spermatogenesis contain the haploid number of chromosomes and equal amounts of cytoplasm.

Spermatogenesis may be continuous or may occur periodically in mature male animals; its onset is determined by the species' reproductive cycles. Animals that reproduce year-round produce sperm continuously, whereas those whose breeding period is confined to a particular season produce sperm only during that time.

In animal *oogenesis,* the formation of *ova* (sing. *ovum*), or eggs, occurs in the ovaries, the female reproductive organs. The daughter cells resulting from the two meiotic divisions of this process receive equal amounts of genetic material, but they do *not* receive equal amounts of cytoplasm. Instead, during each division, almost all the cytoplasm of the *primary oocyte,* itself derived from the *oogonium,* is concentrated in one of the two daughter cells. The concentration of cytoplasm is necessary because a major function of the mature ovum is to nourish the developing embryo following fertilization.

During anaphase I in oogenesis, the tetrads of the primary oocyte separate, and the dyads move toward opposite poles. During telophase I, the dyads at one pole are pinched off with very little surrounding cytoplasm to form the *first polar body.* The first polar body may or may not divide again

to produce two small haploid cells. The other daughter cell produced by this first meiotic division contains most of the cytoplasm and is called the *secondary oocyte*. The mature ovum will be produced from the secondary oocyte during the second meiotic division. During this division, the cytoplasm of the secondary oocyte again divides unequally, producing an *ootid* and a *second polar body*. The ootid then differentiates into the mature ovum.

Unlike the divisions of spermatogenesis, the two meiotic divisions of oogenesis may not be continuous. In some animal species, the second division may directly follow the first. In others, including humans, the first division of all oocytes begins in the embryonic ovary but arrests in prophase I. Many years later, meiosis resumes in each oocyte just prior to its ovulation. The second division is completed only after fertilization.

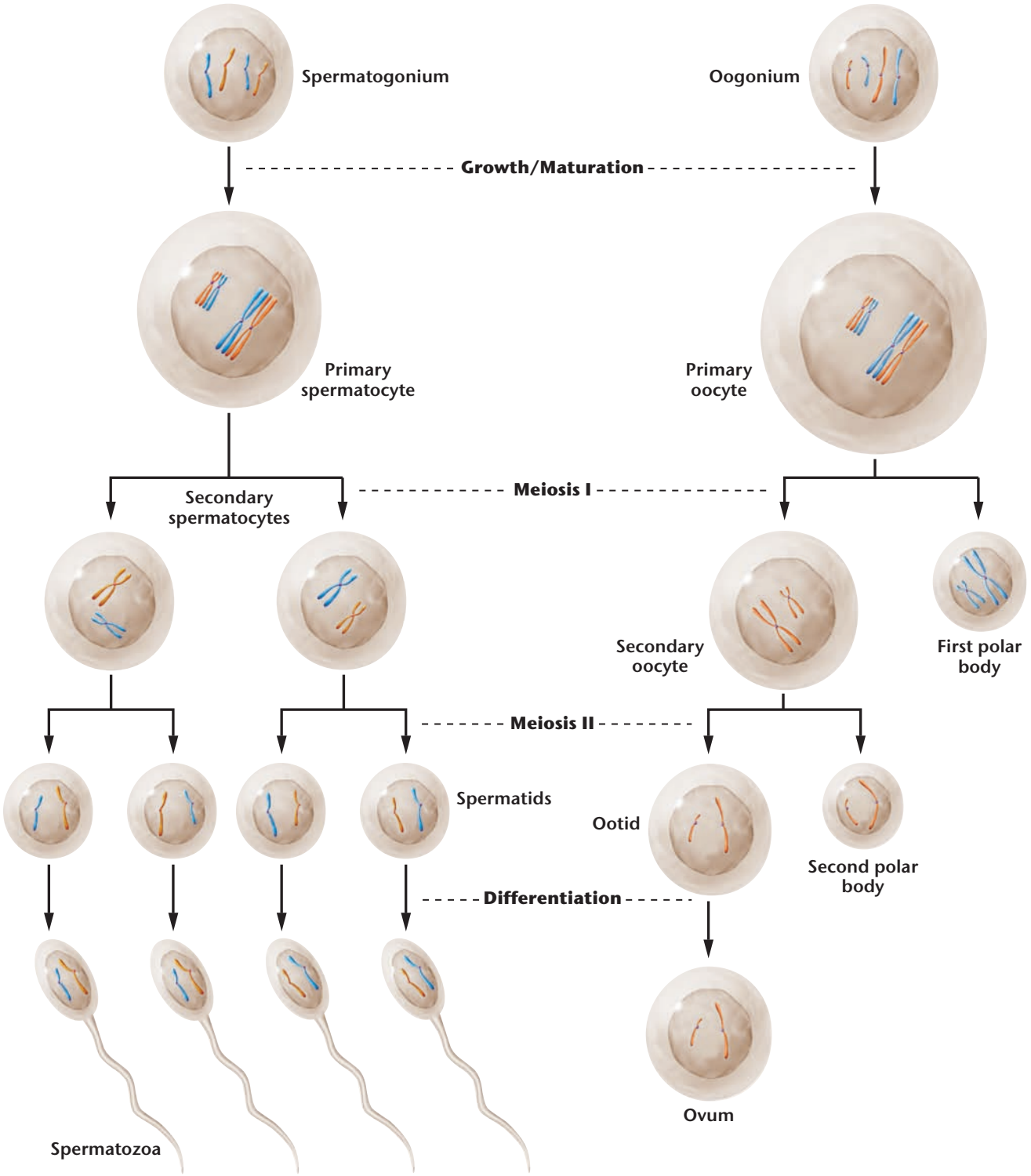


FIGURE 2.11 Spermatogenesis and oogenesis in animal cells.

ESSENTIAL POINT

There is a major difference between meiosis in males and in females. On the one hand, spermatogenesis partitions the cytoplasmic volume equally and produces four haploid sperm cells. Oogenesis, on the other hand, collects the bulk of cytoplasm in one egg cell and reduces the other haploid products to polar bodies. The extra cytoplasm in the egg contributes to zygote development following fertilization. ■

NOW SOLVE THIS

2.3 Examine Figure 2.11, which shows oogenesis in animal cells. Will the genotype of the second polar body (derived from meiosis II) always be identical to that of the ootid? Why or why not?

■ **HINT:** *This problem involves an understanding of meiosis during oogenesis, asking you to demonstrate your knowledge of polar bodies. The key to its solution is to take into account that crossing over occurred between each pair of homologs during meiosis I.*

2.6 Meiosis Is Critical to Sexual Reproduction in All Diploid Organisms

The process of meiosis is critical to the successful sexual reproduction of all diploid organisms. It is the mechanism by which the diploid amount of genetic information is reduced to the haploid amount. In animals, meiosis leads to the formation of gametes, whereas in plants haploid spores are produced, which in turn lead to the formation of haploid gametes.

Each diploid organism stores its genetic information in the form of homologous pairs of chromosomes. Each pair consists of one member derived from the maternal parent and one from the paternal parent. Following meiosis, haploid cells potentially contain either the paternal or the maternal representative of every homologous pair of chromosomes. However, the process of crossing over, which occurs in the first meiotic prophase, further reshuffles the alleles between the maternal and paternal members of each homologous pair, which then segregate and assort independently into gametes. These events result in the great amount of genetic variation present in gametes.

It is important to touch briefly on the significant role that meiosis plays in the life cycles of fungi and plants. In many fungi, the predominant stage of the life cycle consists of haploid vegetative cells. They arise through meiosis and proliferate by mitotic cell division. In multicellular plants, the life cycle alternates between the diploid *sporophyte stage* and the haploid *gametophyte stage*. While one or the other predominates in different plant groups during this "alternation of generations," the processes of meiosis and fertilization constitute the "bridges" between the sporophyte and gametophyte stages. Therefore, meiosis is an essential component of the life cycle of plants.

ESSENTIAL POINT

Meiosis results in extensive genetic variation by virtue of the exchange during crossing over between maternal and paternal chromatids and their random segregation into gametes. In addition, meiosis plays an important role in the life cycles of fungi and plants, serving as the bridge between alternating generations. ■

2.7 Electron Microscopy Has Revealed the Physical Structure of Mitotic and Meiotic Chromosomes

Thus far in this chapter, we have focused on mitotic and meiotic chromosomes, emphasizing their behavior during cell division and gamete formation. An interesting question is why chromosomes are invisible during interphase but visible during the various stages of mitosis and meiosis. Studies using electron microscopy clearly show why this is the case.

Recall that, during interphase, only dispersed chromatin fibers are present in the nucleus [**Figure 2.12(a)**]. Once mitosis begins, however, the fibers coil and fold, condensing into typical mitotic chromosomes [**Figure 2.12(b)**]. If the fibers comprising a mitotic chromosome are loosened, the

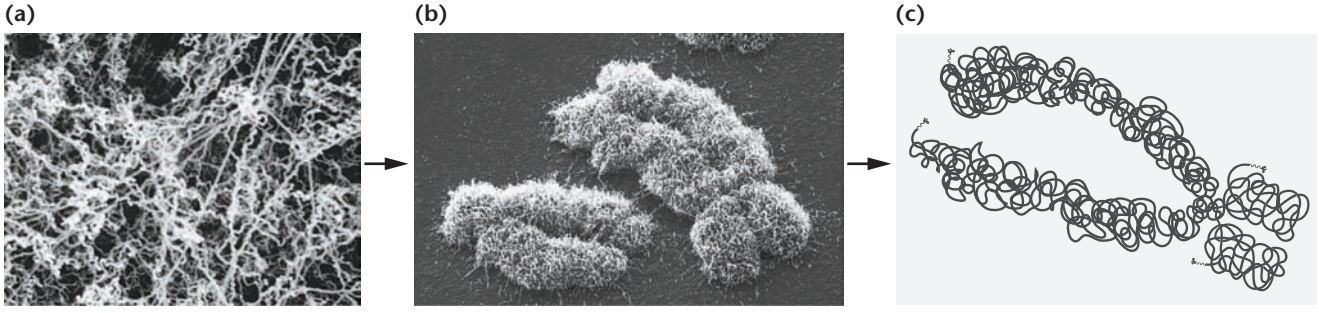


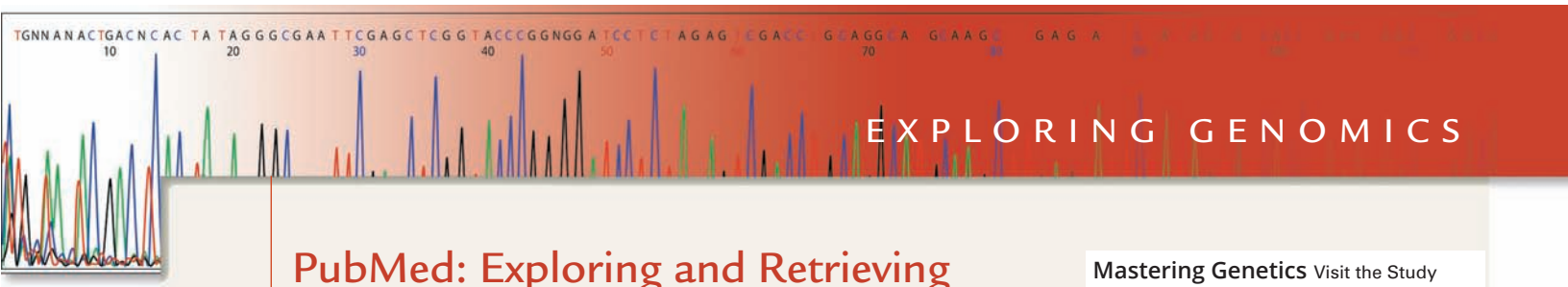
FIGURE 2.12 Comparison of (a) the chromatin fibers characteristic of the interphase nucleus with (b) metaphase chromosomes that are derived from chromatin during mitosis. Part (c) diagrams a mitotic chromosome, showing how chromatin is condensed to produce it. Part (a) is a transmission electron micrograph, and part (b) is a scanning electron micrograph.

areas of greatest spreading reveal individual fibers similar to those seen in interphase chromatin [**Figure 2.12(c)**]. Very few fiber ends seem to be present, and in some cases, none can be seen. Instead, individual fibers always seem to loop back into the interior. Such fibers are obviously twisted and coiled around one another, forming the regular pattern of folding in the mitotic chromosome. Starting in late telophase of mitosis and continuing during G1 of interphase, chromosomes unwind to form the long fibers characteristic of chromatin, which consist of DNA and associated proteins, particularly proteins called *histones*. It is in this physical arrangement that DNA can most efficiently function during transcription and replication.

Electron microscopic observations of metaphase chromosomes in varying degrees of coiling led Ernest DuPraw to postulate the **folded-fiber model,** shown in Figure 2.12(c). During metaphase, each chromosome consists of two sister chromatids joined at the centromeric region. Each arm of the chromatid appears to be a single fiber wound much like a skein of yarn. The fiber is composed of tightly coiled double-stranded DNA and protein. An orderly coiling–twisting–condensing process appears to facilitate the transition of the interphase chromatin into the more condensed mitotic chromosomes. Geneticists believe that during the transition from interphase to prophase, a 5000-fold compaction occurs in the length of DNA within the chromatin fiber! This process must be extremely precise given the highly ordered and consistent appearance of mitotic chromosomes in all eukaryotes. Note particularly in the micrographs the clear distinction between the sister chromatids constituting each chromosome. They are joined only by the common centromere that they share prior to anaphase. We will return to this general topic later in the text when we consider chromosome structure in further detail (see Chapter 11).

ESSENTIAL POINT

Mitotic chromosomes are produced as a result of the coiling and condensation of chromatin fibers characteristic of interphase and are thus visible only during cell division. ■



EXPLORING GENOMICS

PubMed: Exploring and Retrieving Biomedical Literature

Mastering Genetics Visit the Study Area: Exploring Genomics

PubMed is an Internet-based search system developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine. Using PubMed, one can access over 26 million citations for publications in over 5600 biomedical journals. The full text of many of the articles can be obtained electronically through college or university libraries, and some journals (such as *Proceedings of the National Academy of Sciences USA; Genome Biology;* and *Science*) provide free public access to articles within certain time frames.

In this exercise, we will explore PubMed to answer questions about relationships between tubulin, cancer, and cancer therapies.

■ Exercise I – Tubulin, Cancer, and Cancer Therapies

In this chapter we were introduced to tubulin and the dynamic behavior of microtubules during mitosis. Cancer cells are characterized by continuous and uncontrolled mitotic divisions.

Is it possible that tubulin and microtubules contribute to the development of cancer? Could these important structures be targets for cancer therapies?

1. To begin your search for the answers, access the PubMed site at http://www.ncbi.nlm.nih.gov/pubmed/.
2. In the search box, type "tubulin cancer" and then click the "Search" button to perform the search.
3. Select several research papers and read the abstracts.

To answer the question about tubulin's association with cancer, you may want to limit your search to fewer papers, perhaps those that are review articles. To do this, click the "Review" link under the Article Types category on the left side of the page.

Explore some of the articles, as abstracts or as full text, available in your library or by free public access. Prepare a brief report or verbally share your experiences with your class. Describe two of the most important things you learned during your exploration, and identify the information sources you encountered during the search.

CASE STUDY Timing is everything

Over a period of two years, a man in his early 20s received a series of intermittent chemotherapy and radiotherapy treatments for Hodgkin disease. During this therapy, he and his wife were unable to initiate a pregnancy. The man had a series of his semen samples examined at a fertility clinic. The findings revealed that shortly after each treatment very few mature sperm were present, and abnormal chromosome numbers were often observed in developing spermatocytes. However, such chromosome abnormalities disappeared about 40 days after treatment, and normal sperm reappeared about 74 days posttreatment.

1. How might a genetic counselor explain the time-related differences in sperm production and the appearance and subsequent disappearance of chromosomal abnormalities?
2. Do you think that exposure to chemotherapy and radiotherapy would cause more problems to spermatocytes than to mature sperm?
3. Prior to treatment, should the physician(s) involved have been ethically obligated to recommend genetic counseling? What advice regarding fertility might have been suggested?

For further reading, see: Harel, S., et al., (2011). Management of fertility in patients treated for Hodgkin's lymphoma. *Haematologica*. 96: 1692–1699.

INSIGHTS AND SOLUTIONS

This appearance of "Insights and Solutions" begins a feature that will have great value to you as a student. From this point on, "Insights and Solutions" precedes the "Problems and Discussion Questions" at each chapter's end to provide sample problems and solutions that demonstrate approaches you will find useful in genetic analysis. The insights you gain by working through the sample problems will improve your ability to solve the ensuing problems in each chapter.

1. In an organism with a diploid number of $2n = 6$, how many individual chromosomal structures will align on the metaphase plate during (a) mitosis, (b) meiosis I, and (c) meiosis II? Describe each configuration.

Solution:

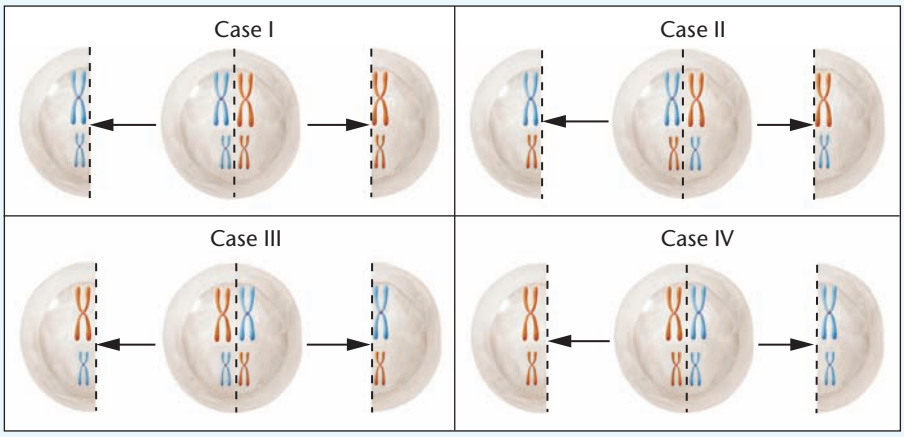
(a) Remember that in mitosis, homologous chromosomes do not synapse, so there will be six double structures, each consisting of a pair of sister chromatids. In other words, the number of structures is equivalent to the diploid number.

(b) In meiosis I, the homologs have synapsed, reducing the number of structures to three. Each is called a tetrad and consists of two pairs of sister chromatids.

(c) In meiosis II, the same number of structures exist (three), but in this case they are called dyads. Each dyad is a pair of sister chromatids. When crossing over has occurred, each chromatid may contain parts of one of its nonsister chromatids, obtained during exchange in prophase I.

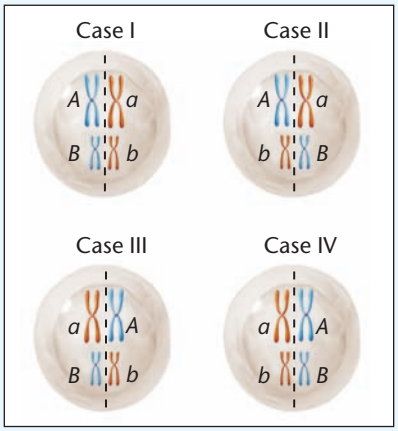
2. Disregarding crossing over, draw all possible alignment configurations that can occur during metaphase for the chromosomes shown in Figure 2.10.

Solution: As shown in the diagram below, four configurations are possible when $n = 2$.



Solution for #2

3. For the chromosomes in Problem 2, assume that each of the larger chromosomes has a different allele for a given gene, *A* or *a*, as shown in the diagram below. Also assume that each of the smaller chromosomes has a different allele for a second gene, *B* or *b*. Calculate the probability of generating each possible combination of these alleles (*AB*, *Ab*, *aB*, *ab*) following meiosis I.



Solution:

Case I	*AB* and *ab*	**Total:**	$AB = 2\,(p = 1/4)$
Case II	*Ab* and *aB*		$Ab = 2\,(p = 1/4)$
Case III	*aB* and *Ab*		$aB = 2\,(p = 1/4)$
Case IV	*ab* and *AB*		$ab = 2\,(p = 1/4)$

Problems and Discussion Questions

Mastering Genetics Visit for instructor-assigned tutorials and problems.

1. **HOW DO WE KNOW?** In this chapter, we focused on how chromosomes are distributed during cell division, both in dividing somatic cells (mitosis) and in gamete- and spore-forming cells (meiosis). We found many opportunities to consider the methods and reasoning by which much of this information was acquired. From the explanations given in the chapter, answer the following questions.
   (a) How do we know that chromosomes exist in homologous pairs?
   (b) How do we know that DNA replication occurs during interphase, not early in mitosis?
   (c) How do we know that mitotic chromosomes are derived from chromatin?
2. **CONCEPT QUESTION** Review the Chapter Concepts list on page 36. All of these pertain to conceptual issues involving mitosis or meiosis. Based on these concepts, write a short essay that contrasts mitosis and meiosis, including their respective roles in organisms, the mechanisms by which they achieve their respective outcomes, and the consequences should either process fail to be executed with absolute fidelity. ■
3. What role do the following cellular components play in the storage, expression, or transmission of genetic information: (a) chromatin, (b) nucleolus, (c) ribosome, (d) mitochondrion, (e) centriole, (f) centromere?
4. Discuss the concepts of homologous chromosomes, diploidy, and haploidy. What characteristics do two homologous chromosomes share?
5. If two chromosomes of a species are the same length and have similar centromere placements and yet are not homologous, what is different about them?
6. Describe the events that characterize each stage of mitosis.
7. How are spindle fibers formed and how do chromosomes separate in animal cells?
8. Compare chromosomal separation in plant and animal cells.
9. Why might different cells of the same organism have cell cycles of different durations?
10. Define and discuss these terms: (a) synapsis, (b) bivalents, (c) chiasmata, (d) crossing over, (e) sister chromatids, (f) tetrads, (g) dyads, (h) monads.
11. A diploid organism has the alleles *T* and *t* for the same gene on a pair of homologous chromosomes. In what circumstances might both alleles segregate? At what stage of cell division would this occur?
12. Given the end results of the two types of division, why is it necessary for homologs to pair during meiosis and not desirable for them to pair during mitosis?
13. Contrast spermatogenesis and oogenesis. What is the significance of the formation of polar bodies?
14. How do the stages of mitosis and meiosis occur in a specific order and never alternate?
15. A diploid cell contains three pairs of homologous chromosomes designated C1 and C2, M1 and M2, and S1 and S2. No crossing over occurs. What combinations of chromosomes are possible in (a) daughter cells following mitosis, (b) cells undergoing the first meiotic metaphase, (c) haploid cells following both divisions of meiosis?
16. Predict the number of unique haploid gametes that could be produced through meiosis in an organism with a diploid number of $2n = 16$. Assume that crossing over does not occur.

17. To test the quality of eggs, polar bodies are routinely extracted from them. In a study, the first polar body dyads for all chromosomes were identified, but they were absent in Chromosome 13.
    (a) Provide a possible reason behind this oddity.
    (b) What chromosomal configuration would you expect in the secondary oocyte?
    (c) What would the consequences be in a zygote if it were fertilized?
18. Humans have a diploid number of 46. What is the probability that a sperm will be formed that contains all chromosomes whose centromeres are derived from maternal homologs?
19. Cattle (*Bos taurus*) have a diploid number of 60, and their haploid DNA content per cell is approximately 3.2 picogram. What would be the DNA content of a somatic cell (non-sex cell) at anaphase? What would be the nuclear DNA content of a secondary spermatocyte? What would be the nuclear DNA content of a spermatozoon?
20. Describe the role of meiosis in the life cycle of a vascular plant.
21. How many sister chromatids are seen in the metaphase for a single chromosome? How different are these structures from the interphase chromatin?
22. What is the significance of checkpoints in the cell cycle?
23. A metaphase chromosome preparation from an unknown organism clearly shows 40 chromosomes that can be easily paired. However, there are two unmatched chromosomes that differ from each other in size and centromere placement. What can you say about the chromosomes and the ploidy of this organism?
24. If one follows 50 primary oocytes in an animal through their various stages of oogenesis, how many secondary oocytes would be formed? How many first polar bodies would be formed? How many ootids would be formed? If one follows 50 primary spermatocytes in an animal through their various stages of spermatogenesis, how many secondary spermatocytes would be formed? How many spermatids would be formed?

For Problems **25–30,** consider a diploid cell that contains three pairs of chromosomes designated AA, BB, and CC. Each pair contains a maternal and a paternal member (e.g., A^m and A^p). Using these designations, demonstrate your understanding of mitosis and meiosis by drawing chromatid combinations as requested. Be sure to indicate when chromatids are paired as a result of replication and/or synapsis. You may wish to use a large piece of brown manila wrapping paper or a cut-up paper grocery bag for this project and to work in partnership with another student. We recommend cooperative learning as an efficacious way to develop the skills you will need for solving the problems presented throughout this text.

25. In mitosis, what chromatid combination(s) will be present during metaphase? What combination(s) will be present at each pole at the completion of anaphase?
26. During meiosis I, assuming no crossing over, what chromatid combination(s) will be present at the completion of prophase I? Draw all possible alignments of chromatids as migration begins during early anaphase.
27. Are there any possible combinations present during prophase of meiosis II other than those that you drew in Problem 26? If so, draw them.
28. Draw all possible combinations of chromatids during the early phases of anaphase in meiosis II.
29. Assume that during meiosis I none of the *C* chromosomes disjoin at metaphase, but they separate into dyads (instead of monads) during meiosis II. How would this change the alignments that you constructed during the anaphase stages in meiosis I and II? Draw them.
30. A normal gamete fuses with another that has undergone nondisjunction of B chromosome dyads into the secondary oocyte during meiosis I, but segregates into the daughter cells during meiosis II. What combinations could be obtained in the zygote?

3

Mendelian Genetics

Gregor Johann Mendel, who in 1866 put forward the major postulates of transmission genetics as a result of experiments with the garden pea.

CHAPTER CONCEPTS

- Inheritance is governed by information stored in discrete unit factors called genes.
- Genes are transmitted from generation to generation on vehicles called chromosomes.
- Chromosomes, which exist in pairs in diploid organisms, provide the basis of biparental inheritance.
- During gamete formation, chromosomes are distributed according to postulates first described by Gregor Mendel, based on his nineteenth-century research with the garden pea.
- Mendelian postulates prescribe that homologous chromosomes segregate from one another and assort independently with other segregating homologs during gamete formation.
- Genetic ratios, expressed as probabilities, are subject to chance deviation and may be evaluated statistically.
- The analysis of pedigrees allows predictions concerning the genetic nature of human traits.

Although inheritance of biological traits has been recognized for thousands of years, the first significant insights into how it takes place only occurred about 150 years ago. In 1866, Gregor Johann Mendel published the results of a series of experiments that would lay the foundation for the formal discipline of genetics. Mendel's work went largely unnoticed until the turn of the twentieth century, but eventually, the concept of the gene as a distinct hereditary unit was established. Since then, the ways in which genes, as segments of chromosomes, are transmitted to offspring and control traits have been clarified. Research continued unabated throughout the twentieth century and into the present—indeed, studies in genetics, most recently at the molecular level, have remained at the forefront of biological research since the early 1900s.

When Mendel began his studies of inheritance using *Pisum sativum,* the garden pea, chromosomes and the role and mechanism of meiosis were totally unknown. Nevertheless, he determined that discrete units of inheritance exist and predicted their behavior in the formation of gametes. Subsequent investigators, with access to cytological data, were able to relate their own observations of chromosome behavior during meiosis and Mendel's principles of inheritance. Once this correlation was recognized, Mendel's postulates were accepted as the basis for the study of what is known as **transmission genetics**—how genes are transmitted from parents to offspring. These principles were derived directly from Mendel's experimentation.

3.1 Mendel Used a Model Experimental Approach to Study Patterns of Inheritance

Johann Mendel was born in 1822 to a peasant family in the Central European village of Heinzendorf. An excellent student in high school, he studied philosophy for several years afterward and in 1843, taking the name Gregor, was admitted to the Augustinian Monastery of St. Thomas in Brno, now part of the Czech Republic. In 1849, he was relieved of pastoral duties, and from 1851 to 1853, he attended the University of Vienna, where he studied physics and botany. He returned to Brno in 1854, where he taught physics and natural science for the next 16 years. Mendel received support from the monastery for his studies and research throughout his life.

In 1856, Mendel performed his first set of hybridization experiments with the garden pea, launching the research phase of his career. His experiments continued until 1868, when he was elected abbot of the monastery. Although he retained his interest in genetics, his new responsibilities demanded most of his time. In 1884, Mendel died of a kidney disorder. The local newspaper paid him the following tribute:

> His death deprives the poor of a benefactor, and mankind at large of a man of the noblest character, one who was a warm friend, a promoter of the natural sciences, and an exemplary priest.

Mendel first reported the results of some simple genetic crosses between certain strains of the garden pea in 1865. Although his findings went unappreciated until the turn of the century, well after his death, his work was not the first attempt to provide experimental evidence pertaining to inheritance. Mendel's success where others had failed can be attributed, at least in part, to his elegant experimental design and analysis.

Mendel showed remarkable insight into the methodology necessary for good experimental biology. First, he chose an organism that was easy to grow and to hybridize artificially. The pea plant is self-fertilizing in nature, but it is easy to cross-breed experimentally. It reproduces well and grows to maturity in a single season. Mendel followed seven visible features (we refer to them as characters, or characteristics), each represented by two contrasting forms, or **traits** (**Figure 3.1**). For the character stem height, for example,

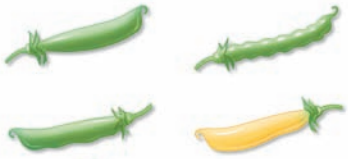
Character	Contrasting traits		F_1 results	F_2 results	F_2 ratio
Seed shape	round/wrinkled		all round	5474 round 1850 wrinkled	2.96:1
Seed color	yellow/green		all yellow	6022 yellow 2001 green	3.01:1
Pod shape	full/constricted		all full	882 full 299 constricted	2.95:1
Pod color	green/yellow		all green	428 green 152 yellow	2.82:1
Flower color	violet/white		all violet	705 violet 224 white	3.15:1
Flower position	axial/terminal		all axial	651 axial 207 terminal	3.14:1
Stem height	tall/dwarf		all tall	787 tall 277 dwarf	2.84:1

FIGURE 3.1 Seven pairs of contrasting traits and the results of Mendel's seven monohybrid crosses of the garden pea (*Pisum sativum*). In each case, pollen derived from plants exhibiting one trait was used to fertilize the ova of plants exhibiting the other trait. In the F_1 generation, one of the two traits was exhibited by all plants. The contrasting trait reappeared in approximately 1/4 of the F_2 plants.

he experimented with the traits *tall* and *dwarf.* He selected six other contrasting pairs of traits involving seed shape and color, pod shape and color, and flower color and position. From local seed merchants, Mendel obtained true-breeding strains, those in which each trait appeared unchanged generation after generation in self-fertilizing plants.

There were several other reasons for Mendel's success. In addition to his choice of a suitable organism, he restricted his examination to one or very few pairs of contrasting traits in each experiment. He also kept accurate quantitative records, a necessity in genetic experiments. From the analysis of his data, Mendel derived certain postulates that have become the principles of transmission genetics.

3.2 The Monohybrid Cross Reveals How One Trait Is Transmitted from Generation to Generation

Mendel's simplest crosses involved only one pair of contrasting traits. Each such experiment is called a **monohybrid cross.** A monohybrid cross is made by mating true-breeding individuals from two parent strains, each exhibiting one of the two contrasting forms of the character under study. Initially, we examine the first generation of offspring of such a cross, and then we consider the offspring of **selfing,** that is, of self-fertilization of individuals from this first generation. The original parents constitute the **P_1,** or **parental generation;** their offspring are the **F_1,** or **first filial generation;** the individuals resulting from the selfed F_1 generation are the **F_2,** or **second filial generation;** and so on.

The cross between true-breeding pea plants with tall stems and dwarf stems is representative of Mendel's monohybrid crosses. *Tall* and *dwarf* are contrasting traits of the character of stem height. Unless tall or dwarf plants are crossed together or with another strain, they will undergo self-fertilization and breed true, producing their respective traits generation after generation. However, when Mendel crossed tall plants with dwarf plants, the resulting F_1 generation consisted of only tall plants. When members of the F_1 generation were selfed, Mendel observed that 787 of 1064 F_2 plants were tall, while 277 of 1064 were dwarf. Note that in this cross (Figure 3.1), the dwarf trait disappeared in the F_1 generation, only to reappear in the F_2 generation.

Genetic data are usually expressed and analyzed as ratios. In this particular example, many identical P_1 crosses were made and many F_1 plants—all tall—were produced. As noted, of the 1064 F_2 offspring, 787 were tall and 277 were dwarf—a ratio of approximately 2.8:1.0, or about 3:1.

Mendel made similar crosses between pea plants exhibiting each of the other pairs of contrasting traits; the results of these crosses are shown in Figure 3.1. In every case, the outcome was similar to the tall/dwarf cross just described. For the character of interest, all F_1 offspring expressed the same trait exhibited by one of the parents, but in the F_2 offspring, an approximate ratio of 3:1 was obtained. That is, three-fourths looked like the F_1 plants, while one-fourth exhibited the contrasting trait, which had disappeared in the F_1 generation.

We note one further aspect of Mendel's monohybrid crosses. In each cross, the F_1 and F_2 patterns of inheritance were similar regardless of which P_1 plant served as the source of pollen (sperm) and which served as the source of the ovum (egg). The crosses could be made either way—pollination of dwarf plants by tall plants, or vice versa. Crosses made in both these ways are called **reciprocal crosses.** Therefore, the results of Mendel's monohybrid crosses were not sex dependent.

To explain these results, Mendel proposed the existence of particulate *unit factors* for each trait. He suggested that these factors serve as the basic units of heredity and are passed unchanged from generation to generation, determining various traits expressed by each individual plant. Using these general ideas, Mendel proceeded to hypothesize precisely how such factors could account for the results of the monohybrid crosses.

Mendel's First Three Postulates

Using the consistent pattern of results in the monohybrid crosses, Mendel derived the following three postulates, or principles, of inheritance.

1. UNIT FACTORS IN PAIRS

Genetic characters are controlled by unit factors existing in pairs in individual organisms.

In the monohybrid cross involving tall and dwarf stems, a specific **unit factor** exists for each trait. Each diploid individual receives one factor from each parent. Because the factors occur in pairs, three combinations are possible: two factors for tall stems, two factors for dwarf stems, or one of each factor. Every individual possesses one of these three combinations, which determines stem height.

2. DOMINANCE/RECESSIVENESS

When two unlike unit factors responsible for a single character are present in a single individual, one unit factor is dominant to the other, which is said to be recessive.

In each monohybrid cross, the trait expressed in the F_1 generation is controlled by the dominant unit factor. The trait not expressed is controlled by the recessive unit factor. The terms dominant and recessive are also used to designate traits. In this case, tall stems are said to be dominant over recessive dwarf stems.

3. SEGREGATION

During the formation of gametes, the paired unit factors separate, or segregate, randomly so that each gamete receives one or the other with equal likelihood.

If an individual contains a pair of like unit factors (e.g., both specific for tall), then all its gametes receive one of that same kind of unit factor (in this case, tall). If an individual contains unlike unit factors (e.g., one for tall and one for dwarf), then each gamete has a 50 percent probability of receiving either the tall or the dwarf unit factor.

These postulates provide a suitable explanation for the results of the monohybrid crosses. Let's use the tall/dwarf cross to illustrate. Mendel reasoned that P_1 tall plants contained identical paired unit factors, as did the P_1 dwarf plants. The gametes of tall plants all receive one tall unit factor as a result of segregation. Similarly, the gametes of dwarf plants all receive one dwarf unit factor. Following fertilization, all F_1 plants receive one unit factor from each parent—a tall factor from one and a dwarf factor from the other—reestablishing the paired relationship, but because tall is dominant to dwarf, all F_1 plants are tall.

When F_1 plants form gametes, the postulate of segregation demands that each gamete randomly receives either the tall *or* dwarf unit factor. Following random fertilization events during F_1 selfing, four F_2 combinations will result with equal frequency:

1. tall/tall
2. tall/dwarf
3. dwarf/tall
4. dwarf/dwarf

Combinations (1) and (4) will clearly result in tall and dwarf plants, respectively. According to the postulate of dominance/recessiveness, combinations (2) and (3) will both yield tall plants. Therefore, the F_2 is predicted to consist of 3/4 tall and 1/4 dwarf, or a ratio of 3:1. This is approximately what Mendel observed in his cross between tall and dwarf plants. A similar pattern was observed in each of the other monohybrid crosses (Figure 3.1).

ESSENTIAL POINT

Mendel's postulates help describe the basis for the inheritance of phenotypic traits. He hypothesized that unit factors exist in pairs and exhibit a dominant/recessive relationship in determining the expression of traits. He further postulated that unit factors segregate during gamete formation, such that each gamete receives one or the other factor, with equal probability. ■

Modern Genetic Terminology

To analyze the monohybrid cross and Mendel's first three postulates, we must first introduce several new terms as well as a symbol convention for the unit factors. Traits such as tall or dwarf are physical expressions of the information contained in unit factors. The physical expression of a trait is the **phenotype** of the individual. Mendel's unit factors represent units of inheritance called **genes** by modern geneticists. For any given character, such as plant height, the phenotype is determined by alternative forms of a single gene, called **alleles.** For example, the unit factors representing tall and dwarf are alleles determining the height of the pea plant.

Geneticists have several different systems for using symbols to represent genes. Later in the text (see Chapter 4), we will review a number of these conventions, but for now, we will adopt one to use consistently throughout this chapter. According to this convention, the first letter of the recessive trait symbolizes the character in question; in lowercase italic, it designates the allele for the recessive trait, and in uppercase italic, it designates the allele for the dominant trait. Thus for Mendel's pea plants, we use *d* for the *d*warf allele and *D* for the tall allele. When alleles are written in pairs to represent the two unit factors present in any individual (*DD*, *Dd*, or *dd*), the resulting symbol is called the **genotype.** The genotype designates the genetic makeup of an individual for the trait or traits it describes, whether the individual is haploid or diploid. By reading the genotype, we know the phenotype of the individual: *DD* and *Dd* are tall, and *dd* is dwarf. When both alleles are the same (*DD* or *dd*), the individual is **homozygous** for the trait, or a **homozygote;** when the alleles are different (*Dd*), we use the terms **heterozygous** and **heterozygote.** These symbols and terms are used in **Figure 3.2** to describe the monohybrid cross.

Punnett Squares

The genotypes and phenotypes resulting from combining gametes during fertilization can be easily visualized by constructing a diagram called a **Punnett square,** named after the person who first devised this approach, Reginald C. Punnett. **Figure 3.3** illustrates this method of analysis for our $F_1 \times F_1$ monohybrid cross. Each of the possible gametes is assigned a column or a row; the vertical columns represent those of the female parent, and the horizontal rows represent those of the male parent. After assigning the gametes to the rows and columns, we predict the new generation by entering the male and female gametic information into each box and thus producing every possible resulting genotype. By filling out the Punnett square, we are listing all possible random fertilization events. The genotypes and phenotypes

of all potential offspring are ascertained by reading the combinations in the boxes.

The Punnett square method is particularly useful when you are first learning about genetics and how to solve genetics problems. Note the ease with which the 3:1 phenotypic ratio and the 1:2:1 genotypic ratio may be derived for the F_2 generation in Figure 3.3.

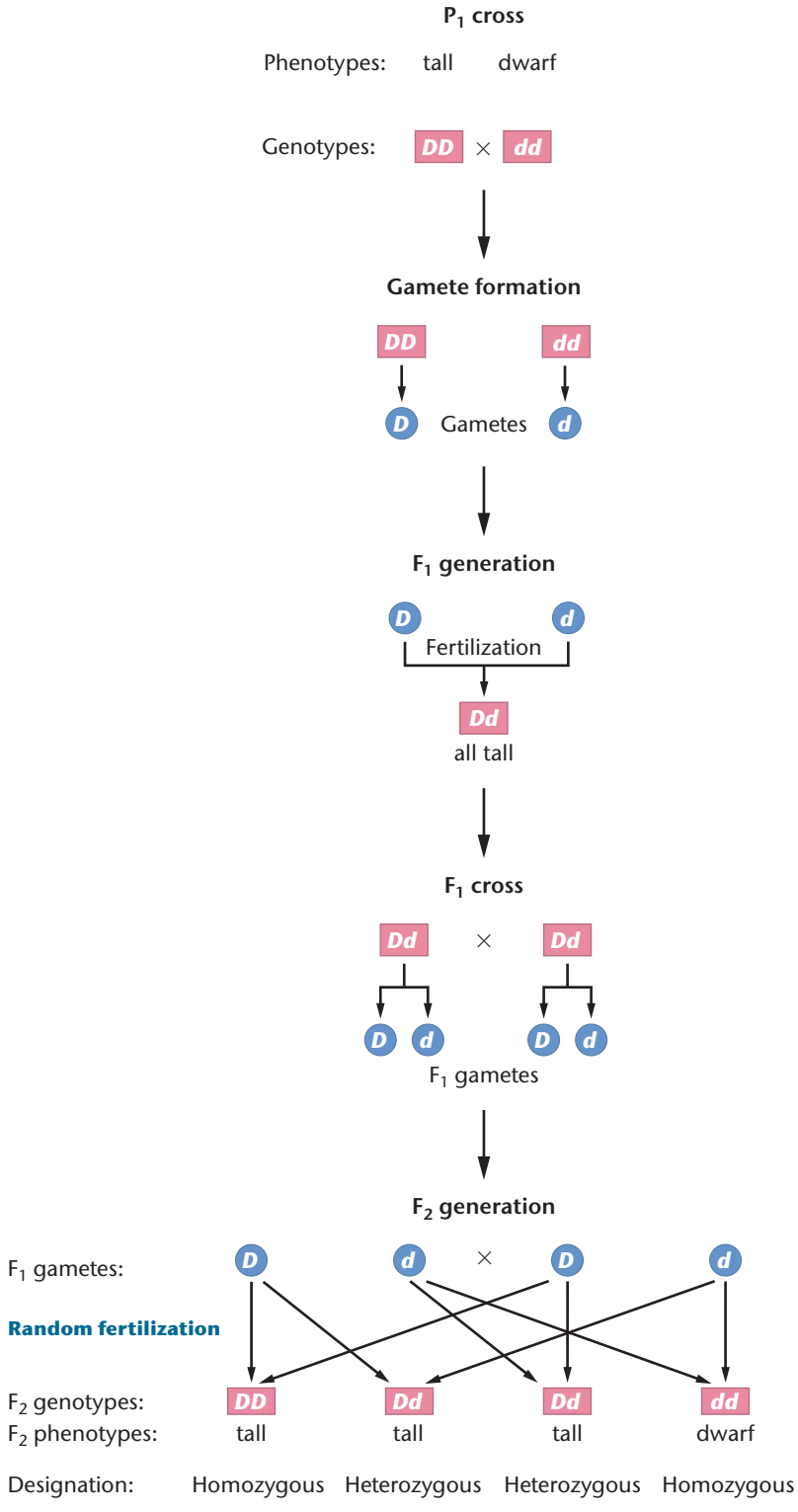


FIGURE 3.2 The monohybrid cross between tall (*D*) and dwarf (*d*) pea plants. Individuals are shown in rectangles, and gametes are shown in circles.

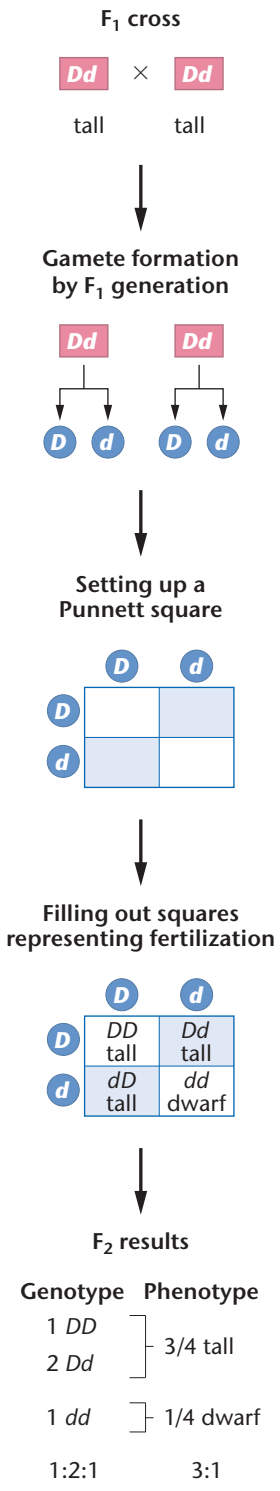


FIGURE 3.3 A Punnett square generating the F_2 ratio of the $F_1 \times F_1$ cross shown in Figure 3.2.

NOW SOLVE THIS

3.1 Pigeons may exhibit a checkered or plain color pattern. In a series of controlled matings, the following data were obtained.

	F_1 Progeny	
P_1 Cross	Checkered	Plain
(a) checkered × checkered	36	0
(b) checkered × plain	38	0
(c) plain × plain	0	35

Then F_1 offspring were selectively mated with the following results. (The P_1 cross giving rise to each F_1 pigeon is indicated in parentheses.)

	F_2 Progeny	
F_1 × F_1 Crosses	Checkered	Plain
(d) checkered (a) × plain (c)	34	0
(e) checkered (b) × plain (c)	17	14
(f) checkered (b) × checkered (b)	28	9
(g) checkered (a) × checkered (b)	39	0

How are the checkered and plain patterns inherited? Select and assign symbols for the genes involved, and determine the genotypes of the parents and offspring in each cross.

■ **HINT:** *This problem asks you to analyze the data produced from several crosses involving pigeons and to determine the mode of inheritance and the genotypes of the parents and offspring in a number of instances. The key to its solution is to first determine whether or not this is a monohybrid cross. To do so, convert the data to ratios that are characteristic of Mendelian crosses. In the case of this problem, ask first whether any of the F_2 ratios match Mendel's 3:1 monohybrid ratio. If so, the second step is to determine which trait is dominant and which is recessive.*

The Testcross: One Character

Tall plants produced in the F_2 generation are predicted to have either the *DD* or the *Dd* genotype. You might ask if there is a way to distinguish the genotype. Mendel devised a rather simple method that is still used today to discover the genotype of plants and animals: the **testcross.** The organism expressing the dominant phenotype but having an unknown genotype is crossed with a known *homozygous recessive individual.* For example, as shown in **Figure 3.4(a)**, if a tall plant of genotype *DD* is testcrossed with a dwarf plant, which must have the *dd* genotype, all offspring will be tall phenotypically and *Dd* genotypically. However, as shown in **Figure 3.4(b)**, if a tall plant is *Dd* and is crossed with a dwarf plant (*dd*), then one-half of the offspring will be tall (*Dd*) and the other half will be dwarf (*dd*). Therefore, a 1:1 tall/dwarf ratio demonstrates the heterozygous nature of the tall plant of unknown genotype. The results of the testcross reinforced Mendel's conclusion that separate unit factors control traits.

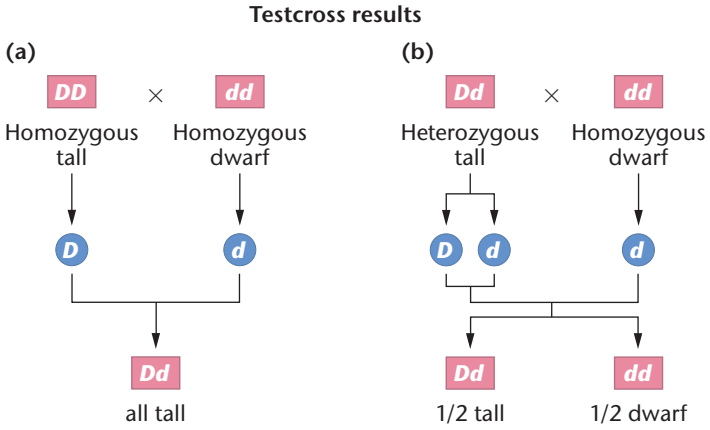


FIGURE 3.4 Testcross of a single character. In (a), the tall parent is homozygous, but in (b), the tall parent is heterozygous. The genotype of each tall P_1 plant can be determined by examining the offspring when each is crossed with the homozygous recessive dwarf plant.

3.3 Mendel's Dihybrid Cross Generated a Unique F_2 Ratio

As a natural extension of the monohybrid cross, Mendel also designed experiments in which he examined two characters simultaneously. Such a cross, involving two pairs of contrasting traits, is a **dihybrid cross,** or a *two-factor cross.* For example, if pea plants having yellow seeds that are round were bred with those having green seeds that are wrinkled, the results shown in **Figure 3.5** would occur: the F_1 offspring would all be yellow and round. It is therefore apparent that yellow is dominant to green and that round is dominant to wrinkled. When the F_1 individuals are selfed, approximately 9/16 of the F_2 plants express the yellow and round traits, 3/16 express yellow and wrinkled, 3/16 express green and round, and 1/16 express green and wrinkled.

A variation of this cross is also shown in Figure 3.5. Instead of crossing one P_1 parent with both dominant traits (yellow, round) to one with both recessive traits (green, wrinkled), plants with yellow, wrinkled seeds are crossed with those with green, round seeds. In spite of the change in the P_1 phenotypes, both the F_1 and F_2 results remain unchanged. Why this is so will become clear below.