GENETICS

From Genes to Genomes

Third
Edition

Leland H. Hartwell
Leroy Hood
Michael L. Goldberg
Ann E. Reynolds
Lee M. Silver
Ruth C. Veres

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Fred Hutchinson Cancer Research Center

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The Institute for Systems Biology

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Cornell University

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Princeton University

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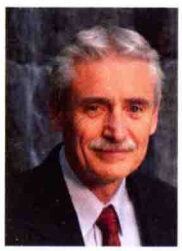
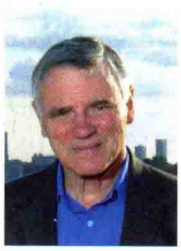
About the Authors



Dr. Leland Hartwell is President and Director of Seattle's Fred Hutchinson Cancer Research Center and Professor of Genome Sciences at the University of Washington.

Dr. Hartwell's primary research contributions were in identifying genes that control cell division in yeast including those necessary for the division process as well as those necessary for the fidelity of genome reproduction. Subsequently many of these same genes have been found to control cell division in humans and often to be the site of alteration in cancer cells.

Dr. Hartwell is a member of the National Academy of Sciences and has received the Albert Lasker Basic Medical Research Award, the Gairdner Foundation International Award, the Alfred P. Sloan Award in Cancer Research, and the 2001 Nobel Prize in Physiology or Medicine.



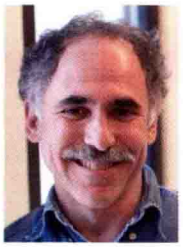
Dr. Lee Hood received an M.D. from the Johns Hopkins Medical School and a Ph.D. in biochemistry from the California Institute of Technology. His research interests include immunology, cancer biology, development, and the development of biological instrumentation (for example, the protein sequencer and the automated fluorescent DNA sequencer). His early research played a key role in unraveling the mysteries of antibody diversity. More recently he has pioneered systems approaches to biology and medicine.

Dr. Hood has taught molecular evolution, immunology, molecular biology, genomics and biochemistry and has co-authored textbooks in biochemistry, molecular biology, and immunology, as well as *The Code of Codes*—a monograph about the Human Genome Project. He was one of the first advocates for the Human Genome Project and directed one of the federal genome centers that sequenced the human genome. Dr. Hood is currently the president (and co-founder) of the cross-disciplinary Institute for Systems Biology in Seattle, Washington.

Dr. Hood has received a variety of awards, including the Albert Lasker Award for Medical Research (1987), the Distinguished Service Award from the National Association of Teachers (1998) and the Lemelson/MIT Award for Invention (2003). He is the 2002 recipient of the Kyoto Prize in Advanced Biotechnology—an award recognizing his pioneering work in developing the protein and DNA synthesizers and sequencers that provide the technical foundation of modern biology. He is deeply involved in K-12 science education. His hobbies include running, mountain climbing, and reading.

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

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



Dr. Lee M. Silver received B.A. and M.S. degrees in physics from the University of Pennsylvania, and a Ph.D. in biophysics from Harvard University. He obtained further training at New York's Memorial Sloan-Kettering Cancer Center, Cold Spring Harbor Laboratory, and the Pasteur Institute in Paris, France. Since 1984, he has been a professor at Princeton University, currently in the Department of Molecular Biology and the Woodrow Wilson School of Public and International Affairs. He also has joint appointments in the Program in Science, Technology, and Environmental Policy, the Center for Health and Wellbeing, the Office of Population Research, and the Princeton Environmental Institute, all at Princeton University.

Dr. Silver has published over 200 articles in the fields of mammalian genetics, evolution, reproduction, embryology, computer modeling, and behavioral science, and other scholarly papers on topics at the interfaces among biotechnology, law, politics, and religion. He has been elected to the governing boards of the Genetics Society of America and the International Mammalian Genome Society, and was a member of the New Jersey Bioethics Commission Task Force formed to recommend reproductive policy for the New Jersey State Legislature. Silver has been elected a lifetime fellow of the American Association for the Advancement of Science (AAAS) and he received a prestigious MERIT Award for outstanding research in genetics from the National Institutes of Health.

Dr. Silver's other books include *Remaking Eden: How Genetic Engineering and Cloning will Transform the American Family,* published in 16 languages, *Mouse Genetics,* and *Challenging Nature: The Clash of Science and Spirituality at the New Frontiers of Life.* He has also written popular articles for *The New York Times, Washington Post, Time Magazine,* and *Newsweek International.* Further information about Dr. Silver is available at www.leemsilver.net.

Ruth C. Veres is a science writer and editor with 35 years of experience in textbook publishing. She received her B.A. from Swarthmore College, obtained M.A. degrees from Columbia University and Tufts University, and taught writing and languages at the University of California at Berkeley.

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

Contributors

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

Ian Duncan, *Washington University, St. Louis*
Sylvia Fromherz, *University of Colorado at Boulder*
Gail E. Gasparich, *Towson University*
Bernadette Holdener, *State University of New York, Stony Brook*
Nancy M. Hollingsworth, *State University of New York, Stony Brook*
Kari Beth Krieger, *University of Wisconsin, Green Bay*
Debra Nero, *Cornell University*
Eric Richards, *Washington University, St. Louis*
Kenneth Shull, *Appalachian State University*

Preface

A Note from the Authors

The science of genetics is less than 150 years old, but its accomplishments within that short time have been astonishing. Gregor Mendel first described genes as abstract units of inheritance in 1865; his work was ignored and then "rediscovered" in 1900. Thomas Hunt Morgan and his students provided experimental verification of the idea that genes reside within chromosomes during the years 1910-1920. By 1944, Oswald Avery and his coworkers had established that genes are made of DNA. James Watson and Francis Crick published their pathbreaking structure of DNA in 1953. Remarkably, less than 50 years later (in 2001), an international consortium of investigators deciphered the sequence of the 3 billion nucleotides in the human genome. Twentieth-century genetics made it possible to identify individual genes and to understand a great deal about their functions.

Today, scientists are able to access the enormous amounts of genetic data generated by the sequencing of many organisms' genomes. Analysis of these data will result in a deeper understanding of the complex molecular interactions within and among vast networks of genes, proteins, and other molecules that help bring organisms to life. Finding new methods and tools for analyzing these data will be a significant part of genetics in the twenty-first century.

Our third edition of *Genetics: From Genes to Genomes* emphasizes both the core concepts of genetics and the cutting-edge discoveries, modern tools, and analytic methods that will keep the science of genetics moving forward.

Our Focus—An Integrated Approach

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

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

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

The Genetic Way of Thinking

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

Genetic portrait chapters on the website (www.mhhe.com/hartwell3) contain detailed discussions of model organisms, which clarify that their use in the study of human biology is possible only because of the genetic relatedness of all organisms. Throughout our book, we present the scientific reasoning of some of the ingenious researchers who have carried out genetic analysis, from Mendel, to Watson and Crick, to the collaborators on the Human Genome Project.

Student-Friendly Features

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

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

New to the Third Edition

- The **End-of-Chapter Problem Sets Have Been Extensively Revised** and include over 100 new problems. The problems are now organized by chapter section and in order of increasing difficulty within each section for ease of use by instructors and students. Each chapter contains a variety of problem types including: *Social & Ethical Issues* which prompt the student to apply problem-solving skills to real-world situations that scientific breakthroughs have forced us to face as a society; *Solved Problems* which cover topical material with complete answers to aid the student in understanding the problem solving process; and *Problems & Questions* that allow students to develop their own problem-solving skills. Answers to selected problems are in the back of the book.
- **New Chapter: Chapter 12** ***Systems Biology and Proteomics*** provides a framework for thinking about what a biological system is and describes tools for analyzing the genes and proteins of a system, as well as computational tools for integrating and modeling this information to begin to explain a system's emergent properties.
- **Content Updates** throughout make this the most current and modern book available. Every chapter reflects the updated information generated by the breakthroughs of the past few years. For example,
  - Chapter 18, *Gene Regulation in Eukaryotes,* discusses the latest on RNAi technology.
  - Chapter 22, *Evolution at the Molecular Level,* includes information on network evolution and comparative genome evolution.
- **"Tools of Genetics" boxed essays are new** to this edition. They explain various techniques geneticists use to look at DNA, genes, other aspects of the genome, and proteins, with examples of interesting applications in biology and medicine.
- An **"On Our Website" Feature,** located at the end of each chapter, directs students and teachers to additional, more detailed information on specialized topics not found in the textbook. This information is in the form of new content, references, or links to other websites.
- **Interactive Web Exercises** offer students an interactive way to analyze genetic data on the Web and complete exercises that test their understanding of the data.
- A **New Design** is more user friendly and emphasizes the pedagogical structure and features of the presentation.

A Word About the Portraits of Model Organisms

Five **Genetic Portraits** are included on the book-specific website at www.mhhe.com/hartwell3 as easy-to-download PDF files. The Genetic Portraits are also available as a printed supplement upon request. Each Genetic Portrait profiles a different model organism whose study has contributed to genetic research. The five selected were the ones chosen as the focus of the Human Genome Project. They are:

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

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

Guided Tour

Students and instructors can become acquainted with the key features of this book by browsing through the Guided Tour starting on the next page. These pages constitute a visual exposition of the book's pedagogy and art program.

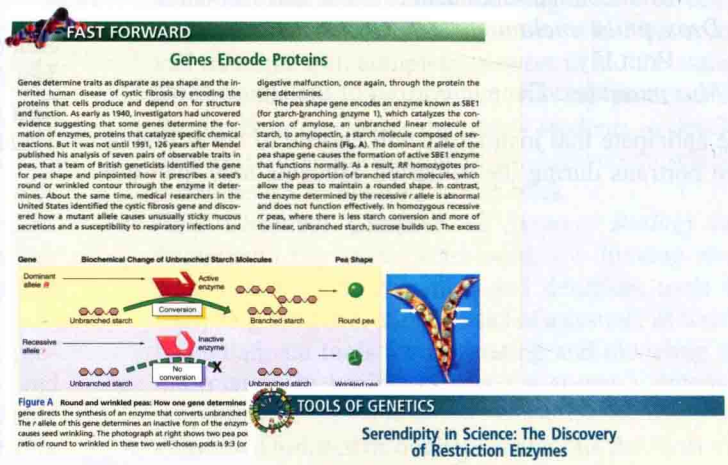
Guided Tour

Integrating Genetic Concepts

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

Fast Forward Essays

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



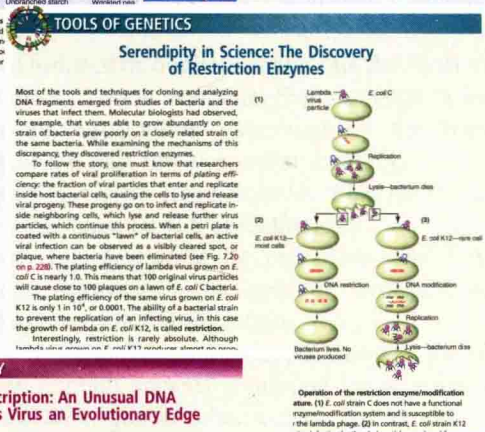
FAST FORWARD

Genes Encode Proteins

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

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

Figure A Round and wrinkled peas: How one gene determines gene directs the synthesis of an enzyme that converts unbranched The *r* allele of this gene determines an inactive form of the enzym causes seed wrinkling. The photograph at right shows two pea po ratio of round to wrinkled in these two well-chosen pods is 9:3 (or



TOOLS OF GENETICS

Serendipity in Science: The Discovery of Restriction Enzymes

Most of the tools and techniques for cloning and analyzing DNA fragments emerged from studies of bacteria and the viruses that infect them. Molecular biologists had observed, for example, that viruses able to grow abundantly on one strain of bacteria grew poorly on a closely related strain of the same bacteria. While examining the mechanisms of this discrepancy, they discovered restriction enzymes.

To follow the story, one must know that researchers compare rates of viral proliferation in terms of *plating efficiency*: the fraction of viral particles that enter and replicate inside host bacterial cells, causing the cells to lyse and release viral progeny. These progeny go on to infect and replicate inside neighboring cells, which lyse and release further virus particles, which continue this process. When a petri plate is coated with a continuous "lawn" of bacterial cells, an active viral infection can be observed as a visibly cleared spot, or plaque, where bacteria have been eliminated (see Fig. 7.20 on p. 228). The plating efficiency of lambda virus grown on *E. coli* C is nearly 1.0. This means that 100 original virus particles will cause close to 100 plaques on a lawn of *E. coli* C bacteria.

The plating efficiency of the same virus grown on *E. coli* K12 is only 1 in 10^4, or 0.0001. The ability of a bacterial strain to prevent the replication of an infecting virus, in this case the growth of lambda on *E. coli* K12, is called **restriction.**

Interestingly, restriction is rarely absolute. Although

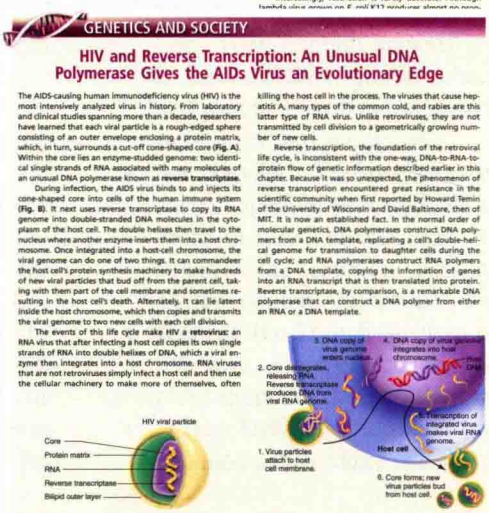
Operation of the restriction enzyme/modification ature. (1) *E. coli* strain C does not have a functional nzyme/modification system and is susceptible to the lambda phage. (2) In contrast, *E. coli* strain K12

Tools of Genetics Essays

Current readings explain various techniques and tools used by geneticists, including examples of applications in biology and medicine.

Genetics and Society Essays

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



GENETICS AND SOCIETY

HIV and Reverse Transcription: An Unusual DNA Polymerase Gives the AIDs Virus an Evolutionary Edge

The AIDS-causing human immunodeficiency virus (HIV) is the most intensively analyzed virus in history. From laboratory and clinical studies spanning more than a decade, researchers have learned that each viral particle is a rough-edged sphere consisting of an outer envelope enclosing a protein matrix, which, in turn, surrounds a cut-off cone-shaped core (**Fig. A**). Within the core lies an enzyme-studded genome: two identical single strands of RNA associated with many molecules of an unusual DNA polymerase known as **reverse transcriptase.**

During infection, the AIDS virus binds to and injects its cone-shaped core into cells of the human immune system (**Fig. B**). It next uses reverse transcriptase to copy its RNA genome into double-stranded DNA molecules in the cytoplasm of the host cell. The double helixes then travel to the nucleus where another enzyme inserts them into a host chromosome. Once integrated into a host-cell chromosome, the viral genome can do one of two things. It can commandeer the host cell's protein synthesis machinery to make hundreds of new viral particles that bud off from the parent cell, taking with them part of the cell membrane and sometimes resulting in the host cell's death. Alternately, it can lie latent inside the host chromosome, which then copies and transmits the viral genome to two new cells with each cell division.

The events of this life cycle make HIV a **retrovirus:** an RNA virus that after infecting a host cell copies its own single strands of RNA into double helixes of DNA, which a viral enzyme then integrates into a host chromosome. RNA viruses that are not retroviruses simply infect a host cell and then use the cellular machinery to make more of themselves, often killing the host cell in the process. The viruses that cause hepatitis A, many types of the common cold, and rabies are this latter type of RNA virus. Unlike retroviruses, they are not transmitted by cell division to a geometrically growing number of new cells.

Reverse transcription, the foundation of the retroviral life cycle, is inconsistent with the one-way, DNA-to-RNA-to-protein flow of genetic information described earlier in this chapter. Because it was so unexpected, the phenomenon of reverse transcription encountered great resistance in the scientific community when first reported by Howard Temin of the University of Wisconsin and David Baltimore, then of MIT. It is now an established fact. In the normal order of molecular genetics, DNA polymerases construct DNA polymers from a DNA template, replicating a cell's double-helical genome for transmission to daughter cells during the cell cycle; and RNA polymerases construct RNA polymers from a DNA template, copying the information of genes into an RNA transcript that is then translated into protein. Reverse transcriptase, by comparison, is a remarkable DNA polymerase that can construct a DNA polymer from either an RNA or a DNA template.

Figure A Structure of the AIDS virus

Figure B Life cycle of the AIDS virus

Comprehensive Examples

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

18.4 Sex Determination in *Drosophila*: A Comprehensive Example of Gene Regulation

Male and female *Drosophila* exhibit many sex-specific differences in morphology, biochemistry, behavior, and function of the germ line (**Fig. 18.20**). By examining the phenotypes of flies with different chromosomal constitutions, researchers confirmed that the ratio of X to autosomal chromosomes (X:A) helps determine sex, fertility, and viability (**Table 18.2**). They then carried out genetic experiments that showed that the X:A ratio influences sex through three independent pathways: One determines whether the flies look and act like males or females; another determines whether germ cells develop; and a third produces dosage compensation by doubling the rate of transcription of X-lin

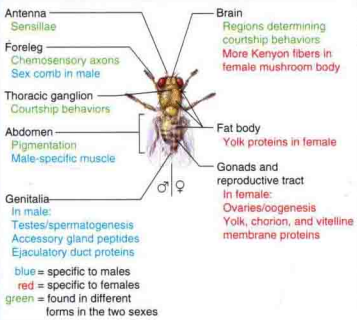


Figure 18.20 **Sex-specific traits in *Drosophila*.** Objects or traits shown in *blue* are specific to males. Objects or traits shown in *red* are specific to females. Objects or traits shown in *green* are found in different forms in the two sexes.

TABLE 18.2 **How Chromosomal Constitution Affects Phenotype in *Drosophila***

Sex Chromosomes	X:A	Sex Phenotype
Autosomal Diploids		
XO	0.5	Male (sterile)
XY	0.5	Male
XX	1.0	Female
XXY	1.0	Female
Autosomal Triploids		
XXX	1.0	Female
XYY	0.33	Male
XXY	0.66	Intersex

Connections

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

Connections

The existence of numerous controls in each of several cell-cycle pathways suggests that evolution has erected many barriers in multicellular animals to the uncontrolled reproduction of "selfish" cells. At the same time, the hundreds of genes contributing to normal cell-cycle regulation provide hundreds of targets for cancer-producing mutations.

Variations on the theme of cell-cycle regulation play a key role in the development of eukaryotic organisms. During the development of multicellular organisms, cells must not only control their cell cycles, they must also adopt different fates and differentiate into different tissues. In *Drosophila*, for example, after fertilization, nuclear division occurs without cell division for the first 13 cycles; during these cycles, the nuclei go through many rapid S and M phases without any intervening G_1 or G_2 (**Fig. 19.25**). In cycles 10–13, the synthesis and degradation of cyclinB regulates mitosis. Sometime during cycles 14–16, a G_2 phase appears, and distinct patches of cells with different-length cycles become evident within the embryo. The differences in cycle time between the different cell types is the result of variable G_2 phases. Late in G_2, *CDC25* activates cyclin-dependent kinases to control the timing of mitosis. Many tissues stop dividing at cycle 16, but a few continue. In the still-dividing cells, a G_1 phase appears. Some of these cells will arrest in G_1 during larval growth, only to start dividing again in response to signals relayed during metamorphosis.

In Chapter 20, we present the basic principles of development and describe how biologists have used genetic analysis in various model organisms to examine development at the cellular and molecular levels.

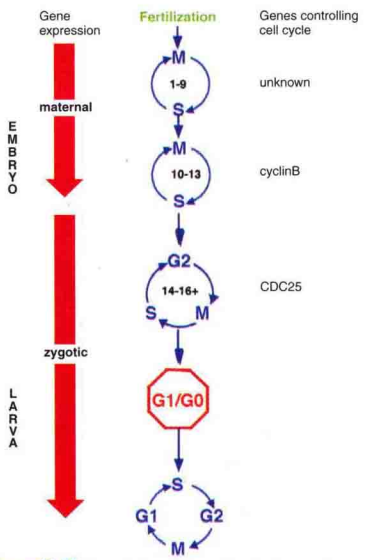


Figure 19.25 **Regulation of the cell-cycle changes during *Drosophila* development.** Each step of development has built-in regulators that act as barriers to uncontrolled reproduction of "selfish" cells. Some of these regulators, such as cyclinB and *CDC25*, are known; others are not.

Visualizing Genetics

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

Feature Figures

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

Feature Figure 4.13

Meiosis: One Diploid Cell Produces Four Haploid Cells

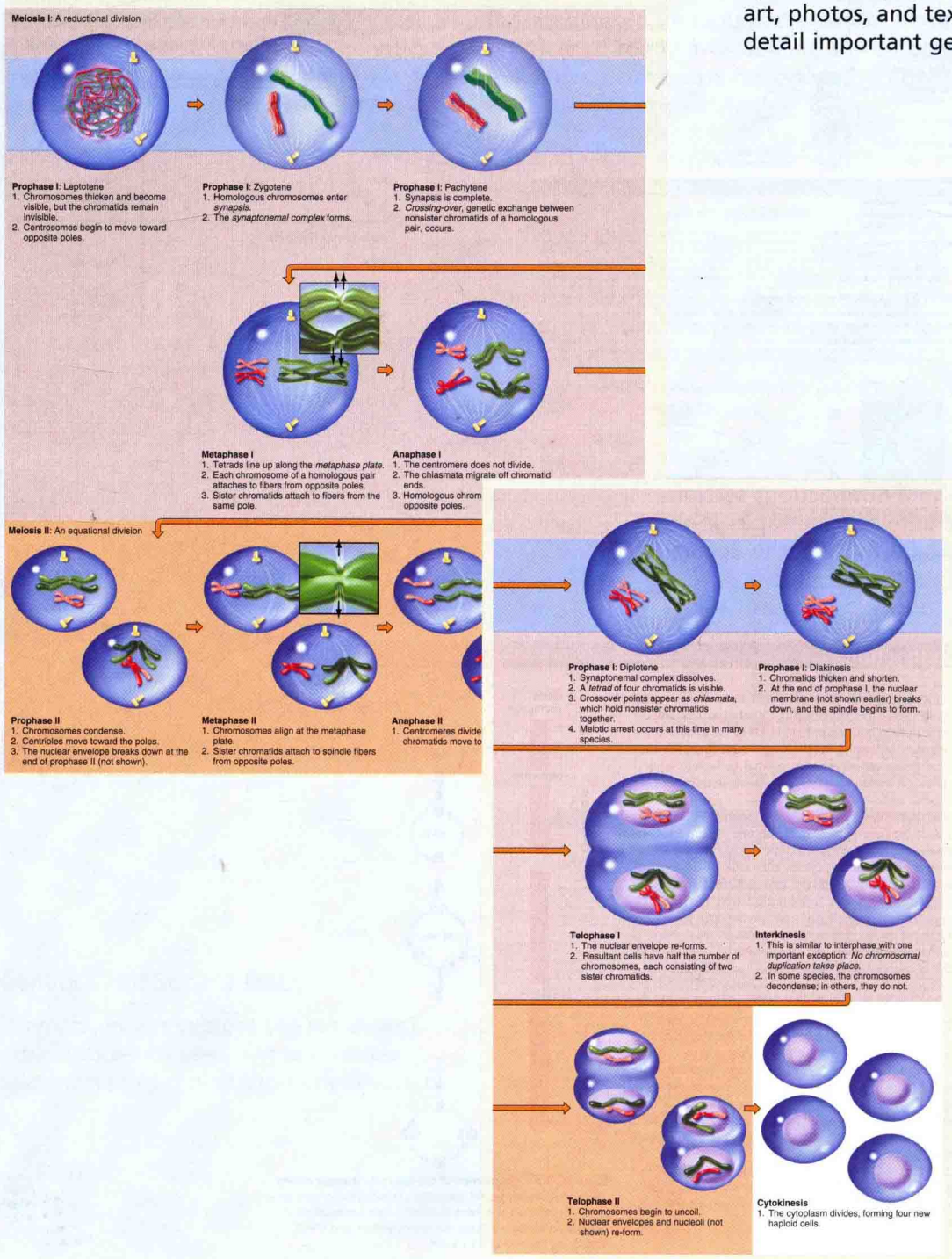


Figure 4.13 To aid visualization of the chromosomes, the figure is simplified in two ways: (1) The nuclear envelope is not shown during prophase of either meiotic division. (2) The chromosomes are shown as fully condensed at zygotene; in reality, the chromosomes continue to condense throughout prophase such that full condensation does not occur until diakinesis.

Process Figures

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

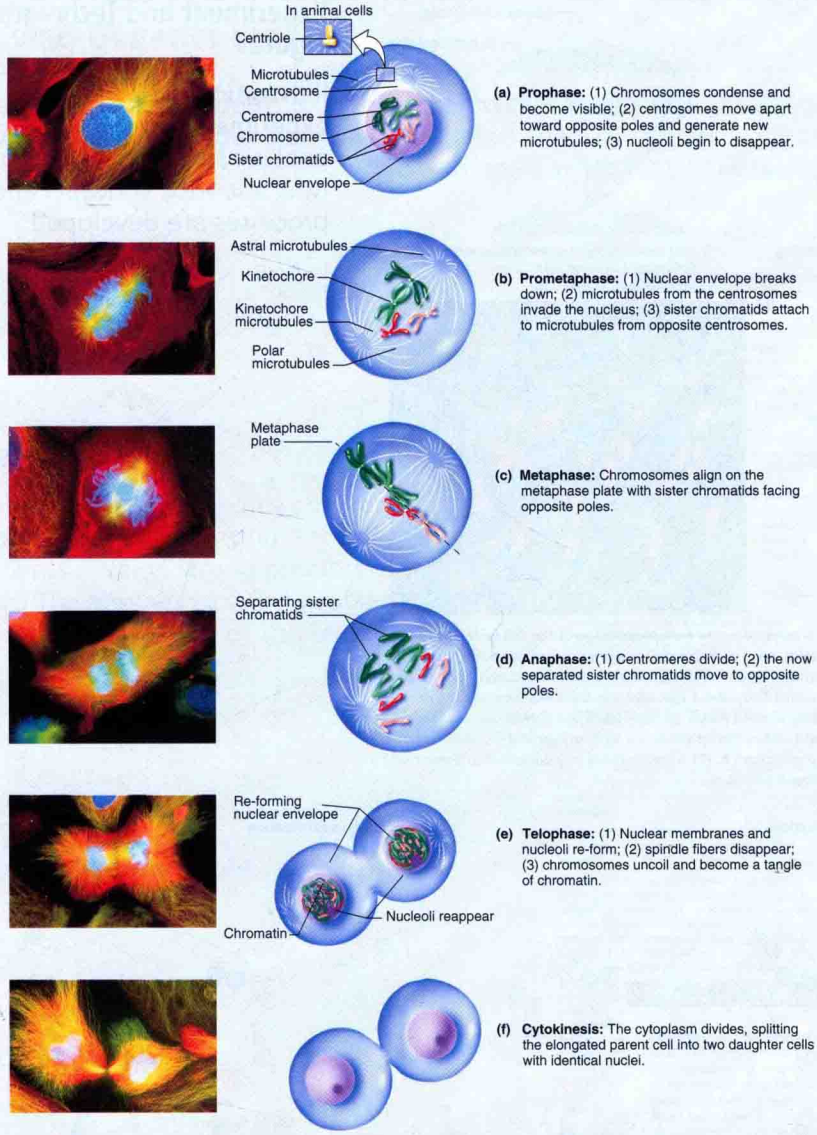
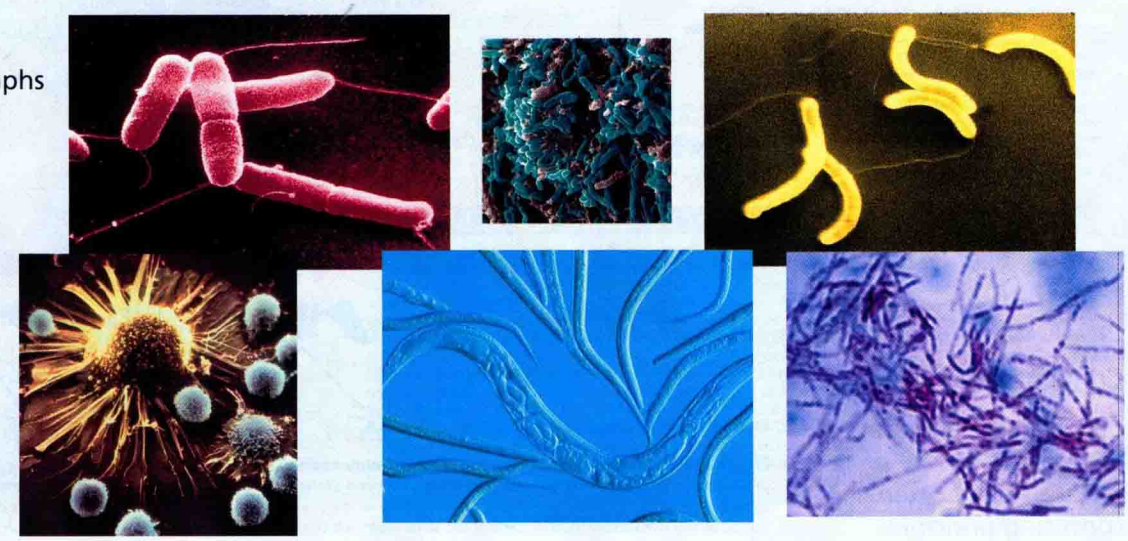


Figure 4.8 **Mitosis maintains the chromosome number of the parent cell nucleus in the two daughter nuclei.** In the photomicrographs of newt lung cells, chromosomes are stained *blue* and microtubules appear either *green* or *yellow*.

Micrographs

Stunning micrographs bring the genetics world to life.



Experiment and Technique Figures

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

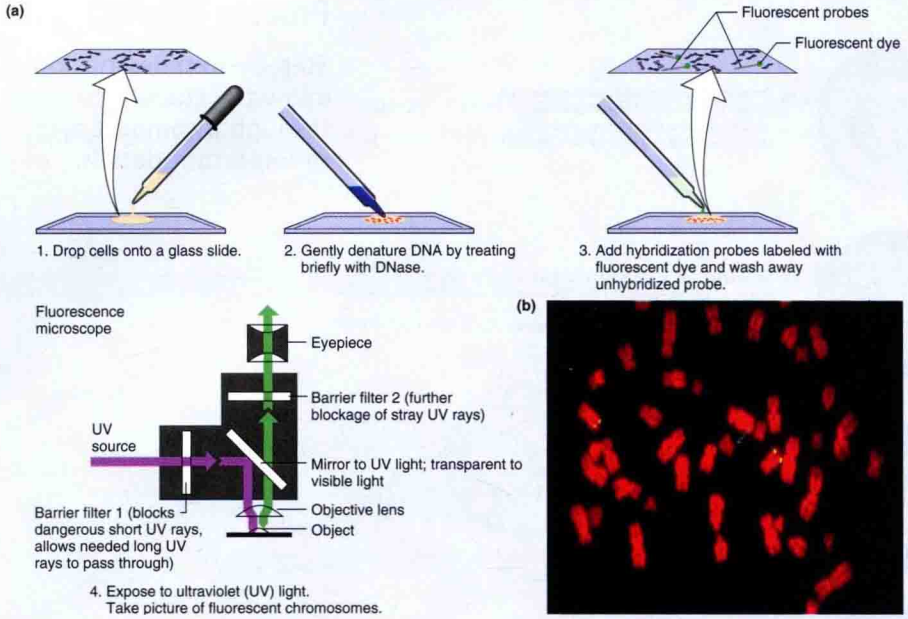
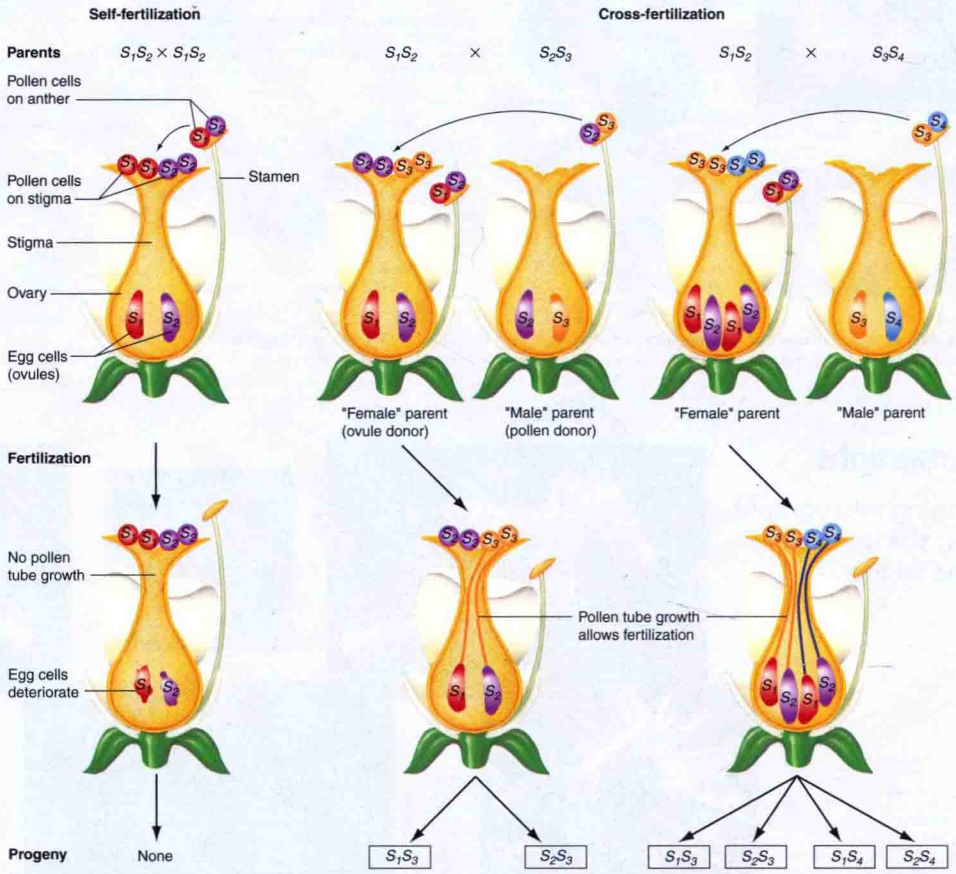


Figure 10.8 **The FISH protocol. (a)** The technique. (1) First, drop cells arrested in the metaphase stage of the cell cycle onto a microscope slide. The force of the droplet hitting the slide causes the cells to burst open with the chromosomes spread apart. (2) Next, fix the chromosomes and gently denature the DNA within them such that the overall chromosomal structure is maintained even though each DNA double helix opens up at numerous points. (3) Label a DNA probe with a fluorescent dye, add it to the slide, incubate the probe with the slide long enough for hybridization to occur, and wash away unhybridized probe. (4) Now place the slide under a special microscope that focuses ultraviolet (UV) light on the chromosomes. The UV light causes the bound probe to fluoresce in the visible range of the spectrum. You can view the fluorescence through the eyepiece and photograph it. **(b)** A fluorescence micrograph. Photograph of a baby hamster kidney cell subjected to FISH analysis. It shows the microtubular structure.



Comparative Figures

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

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

Solving Genetics Problems

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

Review Problems

Problems are organized by chapter section and in order of increasing difficulty to help students develop strong problem-solving skills. The answers to select problems can be found in the back of this text.

Solved Problems

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

Social and Ethical Issues

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

Problems

Vocabulary

1. The following is a list of mutational changes. For each of the specific mutations described, indicate which of the terms in the right-hand column applies, either as a description of the mutation or as a possible cause. More than one term from the right column can apply to each statement in the left column.

   1. an A–T base pair in the wild-type gene is changed to a G–C pair
   2. an A–T base pair is changed to a T–A pair
   3. the sequence AAGCTTATCG is changed to AAGCTATCG
   4. the sequence AAGCTTATCG is changed to AAGCTTTATCG
   5. the sequence AACGTTATCG is changed to AATGTTATCG
   6. the sequence AACGTCACACACACATCG is changed to AACGTCACATCG
   7. the gene map in a given chromosome arm is changed from *beg-rad-fox1-fox2-try-duf* (where *fox1* and *fox2* are highly homologous, recently diverged genes) to *beg-rad-fox1-fox3-fox2-try-duf* (where *fox3* is a new gene with one end similar to *fox1* and the other similar to *fox2*)
   8. the gene map in a chromosome is changed from *beg-rad-fox1-fox2-try-duf* to *beg-rad-fox2-fox1-try-duf*
   9. the gene map in a given chromosome is changed from *beg-rad-fox1-fox2-try-duf* to *beg-rad-fox1-mel-qui-tux-sam*

   a. transition
   b. base substitution
   c. transversion
   d. inversion
   e. translocation
   f. deletion
   g. insertion
   h. deamination
   i. X-ray irradiation
   j. intercalator
   k. unequal crossing-over

Section 7.1

2. The DNA sequence of a gene from three independently isolated mutants is given here. Using this information, what is the sequence of the wild-type gene in this region?

   mutant 1 ACCGTAATCGACTGGTAAACTTTGCGCG
   mutant 2 ACCGTAGTCGACCGGTAAACTTTGCGCG
   mutant 3 ACCGTAGTCGACTGGTTAACTTTGCGCG

3. Over a period of several years, a large hospital kept track of the number of births of babies displaying the trait achondroplasia. Achondroplasia is a very rare autosomal dominant condition resulting in dwarfism with abnormal body proportions. After 120,000 births, it was noted that there had been 27 babies born with achondroplasia. One physician was interested in determining how many of these dwarf babies result from new mutation in his area w families of th the dwarf bat

4. Among mammals, measurements of the rate of generation of autosomal recessive mutations have been made almost exclusively in mice, while many measurements of the rate of generation of dominant mutations have been made both in mice and in humans. Why do you think there has been this difference?

5. In a genetics lab, Kim and Maria infected a sample from an *E. coli* culture with a particular virulent bacteriophage. They noticed that most of the cells were lysed, but a few survived. The survival rate in their sample was about 1×10^{-4}. Kim was sure the bacteriophage induced the resistance in the cells, while Maria thought that resistant mutants probably already existed in the sample of cells they used. Earlier, for a different experiment, they had spread a dilute suspension of *E. coli* onto solid medium in a large petri dish, and, after seeing that about 10^3 colonies were growing up, they had replica-plated that plate onto three other plates. Kim and Maria decided to use these plates to test their theories. They pipette a suspension of the bacteriophage onto each of the three replica plates. What should they see if Kim is right? What should they see if Maria is right?

6. Suppose you wanted to study genes controlling the structure of bacterial cell surfaces. You decide to start by isolating bacterial mutants that are resistant to infection by a bacteriophage that binds to the cell surface. The selection procedure is simple: Spread cells from a culture of sensitive bacteria on a petri plate, expose them to a high concentration of phages, and pick the bacterial colonies that grow. To set up the selection you could (1) spread cells from a single liquid culture of sensitive bacteria on many different plates and pick every resistant colony *or* (2) start many different cultures, each grown from a single colony of sensitive bacteria, spread one plate from each culture, and then pick a single mutant from each plate. Which method would ensure that you are isolating many independent mutations?

7. A wild-type male *Drosophila* was exposed to a large dose of X-rays and was then mated to an unirradiated female, one of whose X chromosomes carried both a dominant mutation for the trait *Bar* eyes and several inversions. Many F_1 females from this mating were recovered who had the *Bar*, multiply inverted X chromo-

Solved Problems

1. Mutations can often be reverted to wild type by treatment with mutagens. The type of mutagen that will reverse a mutation gives us information about the nature of the original mutation. The mutagen EMS almost exclusively causes transitions; proflavin is an intercalating agent that causes insertion or deletion of a base; ultraviolet (UV) light causes single-base substitutions. Cultures of several *E. coli met*$^-$ mutants were treated with three mutagens separately and spread onto a plate lacking methionine to look for revertants. (In the chart, − indicates that no colonies grew, and + indicates that some *met*$^+$ revertant colonies grew.)

	Mutagen treatment		
Mutant number	EMS	Proflavin	UV light
1	+	−	+
2	−	+	−
3	−	−	−
4	−	−	+

   a. Given the results, what can you say about the nature of the original mutation in each of the strains?
   b. Experimental controls are designed to eliminate possible explanations for the results, thereby ensuring that data are interpretable. In the experiment described, we scored the presence or absence of colonies. How do we know if colonies that appear on plates are mutagen-induced revertants? What else could they be? What control would enable us to be confident of our revertant analysis?

Answer

To answer this question, you need to understand the concepts of mutation and reversion.

a. Mutation 1 is reverted by the mutagen that causes transitions, *so mutation 1 must have been a transition*. Consistent with this conclusion is the fact the UV light can also revert the mutation and the intercalating agent proflavin does not cause reversion. *Mutation 2 is reverted by proflavin and therefore must be either an insertion or a deletion of a base*. The other two mutagens do not revert mutation 2. Mutation 3 is not reverted by any of these mutagenic agents. It is therefore not a single-base substitution, a single-base insertion, or a single-base deletion. *Mutation 3 could be a deletion of several bases or an inversion*. Mutation 4 is reverted by UV light, so it is a single-base change, but it is not a transition, since EMS did not revert the mutation. *Mutation 4 must be a transversion*.

Social and Ethical Issues

1. Chemicals that are mutagenic are identified by the Ames test, which measures the level of mutagenesis in bacteria. The susceptibility of humans to mutagenic chemicals may vary depending on the genetic makeup of the individual. The dose that affects one person may be different from that which affects another. However, there are few, if any, reliable tests that determine a person's level of susceptibility. If this is true, is it a good idea to translate the results of the Ames test of mutability in bacteria to a prediction of carcinogenicity in humans? Often, reports of Ames test results on a chemical make newspaper headlines. Is this a useful and honest way to report findings that could affect human health, or do people need to consider other variables to make an informed decision?

2. Mr. and Mrs. Aswari have a child with fragile X syndrome (see the Genetics and Society box on p. 216–217). They want to have a second child but are considering egg donation because genetic screening has indicated that Mrs. Aswari carries a premutation allele with 120 CGG repeats. If you were the Aswari's genetic counselor, what would you tell them about their risk of having a second child with fragile X syndrome? What are the ethical issues related to genetic screening when (1) a result indicates no risk, (2) a result indicates that the phenotype being screened for will be exhibited, and (3) an intermediary result does not clearly fall into either category?

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