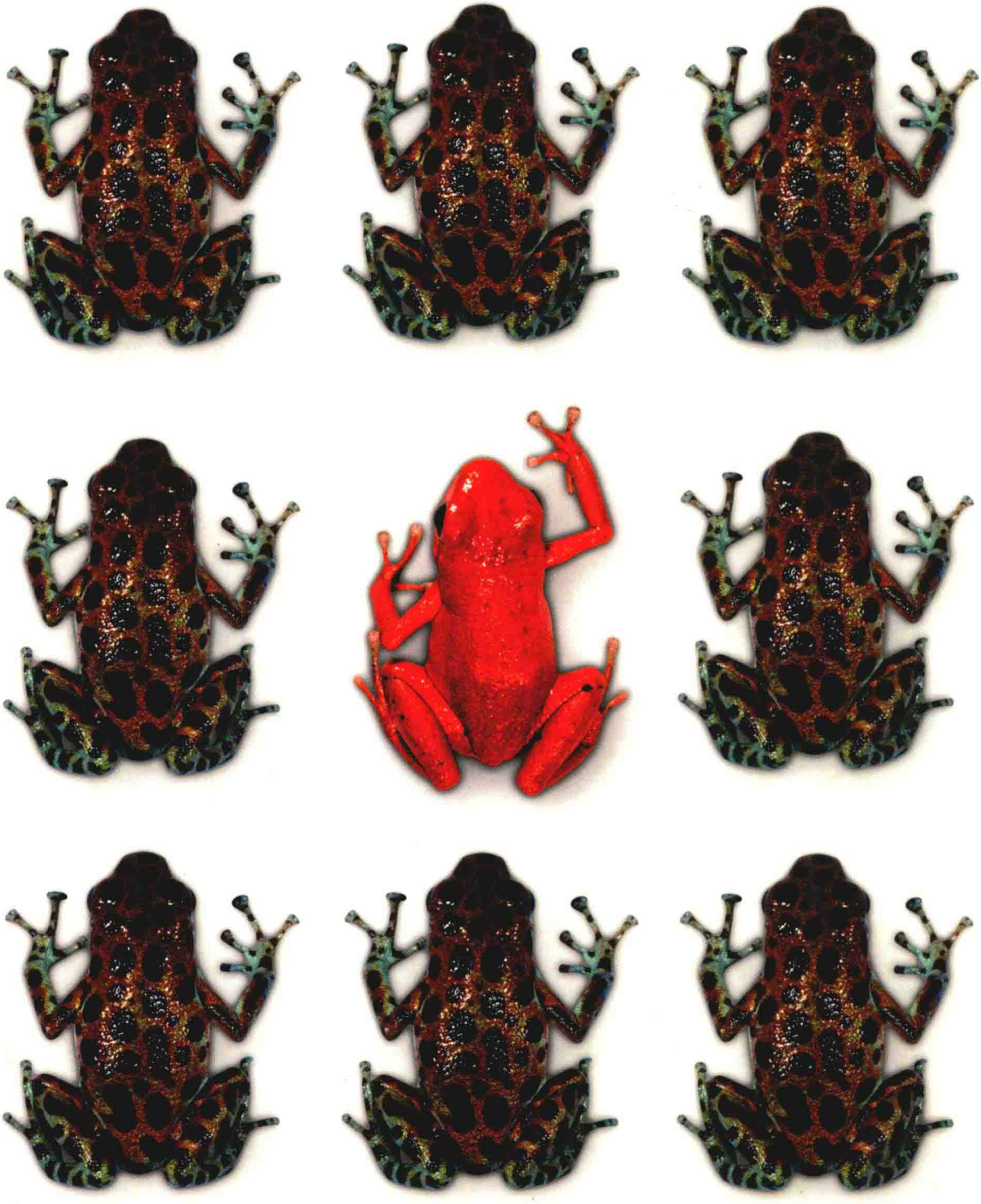
ESSENTIAL GENETICS

A GENOMICS PERSPECTIVE

THIRD EDITION

DANIEL L. HARTL • ELIZABETH W. JONES



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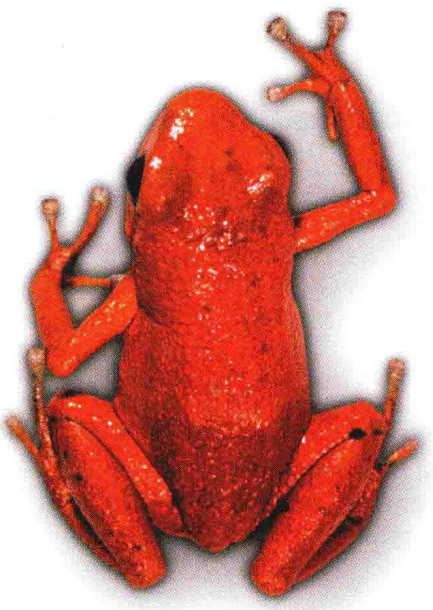

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For Christopher
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In Memory of Herschel
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Daniel L. Hartl is Higgins Professor of Biology and previous Chairman of Organismic and Evolutionary Biology at Harvard University. He received his B.S. degree and Ph.D. from the University of Wisconsin. His research interests include molecular genetics, molecular evolution, and population genetics. Elizabeth W. Jones is a Professor and Department Head of Biological Sciences at Carnegie Mellon University. She received her B.S. degree and Ph.D. from the University of Washington in Seattle. Her research interests include gene regulation and the genetic control of cellular form. Currently she is studying the function and assembly of organelles in the yeast *Saccharomyces*.

ABOUT THE COVER

These frogs are all members of the species *Dendrobates pumilio*, also known as the Strawberry Poison frog. A single gene controls the difference in coloration. Image courtesy Photodisc, ©

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Papers excerpted in Connections in chronological order

Karl Landsteiner 1901
Anatomical Institute,
Vienna, Austria
On Agglutination Phenomena in Normal Blood

Archibald E. Garrod 1908
St. Bartholomew's Hospital,
London, England
Inborn Errors of Metabolism

George W. Beadle and Edward L. Tatum 1941
Stanford University, Stanford, California
Genetic Control of Biochemical Reactions in Neurospora

Anthony C. Allison 1954
Radcliffe Infirmary,
Oxford, England
Protection Afforded by Sickle-Cell Trait Against Subtertian Malarial Infection

Joe Hin Tijo[1] and Albert Levan[2] 1956
[1]Estacion Experimental de Aula Dei, Zaragoza, Spain
[2]Institute of Genetics, Lund, Sweden
The Chromosome Number in Man

Vernon M. Ingram 1957
Cavendish Laboratory, University of Cambridge,
England
Gene Mutations in Human Hemoglobin: The Chemical Difference Between Normal and Sickle-Cell Hemoglobin

Jerome Lejeune, Marthe Gautier, and Raymond Turpin 1959
National Center for Scientific Research, Paris, France
Study of the Somatic Chromosomes of Nine Down Syndrome Children
(original in French)

Mary F. Lyon 1961
Medical Research Council,
Harwell, England
Gene Action in the X Chromosome of the Mouse (Mus musculus L.)

Alfred G. Knudson 1971
M. D. Anderson Hospital
The University of Texas
Houston, Texas
Mutation and Cancer: Statistical Study of Retinoblastoma

Frederick S. Leach and 34 other investigators 1993
Johns Hopkins University,
Baltimore, MD, and ten other
research institutions
Mutations of a mutS Homolog in Hereditary Nonpolyposis Colorectal Cancer

David H. Skuse[1], Rowena S. James[2], Dorothy V. M. Bishop[3], Brian Coppin[4], Paola Dalton[2], Gina Aamodt-Leeper[1], Monique Barcarese-Hamilton[1], Catharine Creswell[1], Rhona McGurk[1], and Patricia A. Jacobs[2] 1997
[1]Institute of Child Health,
London, England
[2]Salisbury District Hospital,
Salisbury, Wiltshire, UK
[3]Medical Research Council
Applied Psychology Unit,
Cambridge, UK
[4]Princess Anne Hospital,
Southampton, UK
Evidence from Turner's Syndrome of an Imprinted X-linked Locus Affecting Cognitive Function

Didier Mazel, Broderick Dychinco, Vera A. Webb, and Julian Davies 1998
University of British Columbia,
Vancouver, Canada
A Distinctive Class of Integron in the Vibrio cholerae *Genome*

Hugh E. Montgomery and 18 other investigators 1998
University College, London,
and 6 other research institutions
Human Gene for Physical Performance

William C. Hahn,[1,2] Christopher M. Counter,[3] Ante S. Lundberg,[1,2] Roderick L. Beijersbergen,[1] Mary W. Brooks,[1] and Robert A. Weinberg[1] 1999
[1]Massachusetts Institute of Technology,
Cambridge, Massachusetts
[2]Harvard Medical School, Boston,
Massachusetts
[3]Duke University Medical Center,
Durham, North Carolina
Creation of Human Tumor Cells with Defined Genetic Elements

Eric S. Lander and 248 other investigators 2001
The Whitehead Institute for Biomedical Research,
Massachusetts Institute of Technology,
Boston, Massachusetts, and
23 other research institutions
Initial Sequencing and Analysis of the Human Genome

preface

Today's college students come to a course in genetics full of enthusiasm stimulated by stories in the media about large-scale genomic sequencing (including the human genome), new studies on inherited diseases (such as breast cancer), and the many social and ethical controversies related to genetics (such as cloning and stem-cell research). The challenges for the instructor are to sustain this enthusiasm, to kindle a desire to understand the principles of genetics and genomics, and to help students integrate their knowledge into a wider social and ethical context. We have written *Essential Genetics* to help instructors meet these challenges. It is designed for the shorter, less comprehensive introductory course. The brevity of the text fits the pace of what can be covered in a typical one-semester or one-quarter course. The topics have been carefully chosen to help students achieve the following learning objectives:

- Understand the basic processes of gene transmission, mutation, expression, and regulation
- Learn to formulate genetic hypotheses, work out their consequences, and test the results against observed data
- Develop basic skills in problem solving, including single-concept exercises, those requiring the application of several concepts in logical order, and numerical problems requiring some arithmetic for solution
- Gain some sense of the social and historical context in which genetics has developed as well as an appreciation of current trends
- Become aware of some of the genetic resources and information that are available through the World Wide Web

Integrated Molecular and Classical Genetics

In this third edition, we have made a special effort to integrate the teaching of "molecular genetics" and "classical genetics." Most modern geneticists realize that the distinction between these subfields has become increasingly artificial in the post-genomics era. Molecular genetics and classical genetics are merely different aspects of the same things—the transmission, mutation, and function of the genetic material. These processes are manifested at the molecular level, which can be studied by such techniques as DNA electrophoresis, as well as at the organismic level through their association with visible traits. Most modern geneticists integrate molecular and classical genetics in their research, and so it is important to integrate the approaches in genetics instruction. We have accomplished this by examining Mendel's classical experiments from a modern molecular perspective, showing how the molecular and organismic approaches are complementary. The appeal to students is tremendous. No longer do we watch our undergraduates' eyes glaze over when we first mention Mendel, as if they were thinking, "We know this round and wrinkled stuff; wake us up when you come to something relevant to the modern world." Rather, they discover that Mendel's experiments have something new and modern to offer.

Chapter Organization

To help the student keep track of the main concepts without being distracted by details, each chapter begins with a list of **Key Concepts** written in simple declarative sentences, highlighting the most important concepts presented in the chapter. An **Outline** shows the principal subjects to be discussed. The body of each chapter provides more detailed information and experimental evidence. An opening paragraph gives an overview of the chapter, illustrates the subject with some specific examples, and shows how the material is connected to genetics as a whole. The section and subsection **Headings** are in the form of complete sentences that encapsulate the main message. The text makes liberal use of **Numbered Lists** and **Bullets** to aid students in organizing their learning, as well as **Summary Statements** set apart from the main text in order to emphasize important principles. A special new feature in this edition, designed to reinforce understanding, is called **A Moment to Think.** This is a problem integrated into the text in which the student is asked to interrupt studying to think about the concept just described, and to use it in solving an actual problem. Each chapter also includes **The Human Connection.** This special feature highlights a research paper in human genetics that reports a key experiment or raises important social, ethical, or legal issues. Each Human Connection has a brief introduction of its own,

explaining the importance of the experiment and the context in which it was carried out. At the end of each chapter is a complete **Chapter Summary, Key Terms, GeNETics on the Web** exercises that guide students in the use of Internet resources in genetics, and several different types and levels of **Problems.** At the back of the book are **Answers** to even-numbered problems and a complete **Glossary** as well as a list of frequently used **Word Roots** that will help students to understand key genetic terms and make them part of their vocabulary.

Contents

The organization of the chapters is that favored by the majority of instructors who teach genetics. It is the organization we use in our own courses. An important feature is the presence of an introductory chapter providing a broad overview of the gene: what it is, what it does, how it changes, how it evolves. Today, most students learn about DNA in grade school or high school. In our teaching, we have found it rather artificial to pretend that DNA does not exist until the middle of the term. The introductory chapter therefore serves to connect the more advanced concepts that students are about to learn with what they already know. It also serves to provide each student with a solid framework for integrating the material that comes later.

Throughout each chapter, there is a balance between challenge and motivation, between observation and theory, and between principle and concrete example. Molecular and classical genetics are integrated throughout, and the principles of human genetics are interwoven into the entire fabric of the book, including discussions of metabolic diseases, the fragile-X syndrome, imprinting, the genetic basis of cancer, expansion of unstable repeats in diseases such as Huntington disease, the relationship of DNA repair enzymes to hereditary colon cancer, the controversial mitochondrial "Eve," genetic diseases associated with defective mitochondria, DNA typing in individual identification, the Human Genome Project, and many other special topics. Although applications to human genetics are often stressed, the book is also liberally supplied with applications to other animals as well as plants.

A number of points related to organization and coverage should be noted:

Chapter 1 is an overview of genetics designed to bring students with disparate backgrounds to a common level of understanding. This chapter enables classical, molecular, and evolutionary genetics to be integrated throughout the rest of the book. Included in Chapter 1 are the basic concepts of genetics: genes as DNA that function through transcription and translation, that change by mutation, and that affect organisms through inborn errors of metabolism. Chapter 1 also includes a discussion of the classical experiments demonstrating that DNA is the genetic material.

Chapters 2 through 5 are the core of Mendelian genetics, including segregation and independent assortment, the chromosome theory of heredity, mitosis and meiosis, linkage and chromosome mapping, tetrad analysis in fungi, and chromosome mechanics. An important principle of genetics, too often ignored or given inadequate treatment, is that of the complementation test and how complementation differs from segregation or other genetic principles. The complementation test is the experimental definition of a gene. Chapter 2 includes a clear and concise description of complementation, with examples, showing how complementation is used in genetic analysis to group mutations into categories (complementation groups), each corresponding to a different gene. Chapter 4 introduces the use of molecular markers in genetics, because these are the principal types of genetic markers in use today.

Chapters 6 and 7 deal with DNA, including the details of DNA structure and replication in Chapter 6 and mechanisms of mutation and DNA repair in Chapter 7, including chemical mutagens and new information on the genetic effects of the Chornobyl nuclear accident. Chapter 6 includes a description of how basic research that revealed the molecular mechanisms of DNA replication ultimately led to such important practical applications as DNA hybridization analysis, DNA sequencing, and the polymerase chain reaction. These examples illustrate the value of basic research in leading, often quite unpredictably, to practical applications.

Chapter 8 deals with the principles of genetics in prokaryotes, beginning with the genetics of mobile DNA, plasmids, and integrons, and their relationships to the evolution of multiple antibiotic resistance. There is a thorough discussion of mechanisms of genetic recombination in microbes, including transformation, conjugation, and transduction, as well as discussion of temperate and virulent bacteriophages.

Chapters 9 through 12 focus on molecular genetics in the strict sense. Chapter 9 examines the details of gene expression, including transcription, RNA

processing, and translation. Chapter 10 is an integrative chapter that deals with genetic mechanisms of regulation, with examples of mechanisms of gene regulation in prokaryotes as well as eukaryotes. For the first time, we include broader aspects of gene regulation that are topics of much current research, such as chromatin remodeling complexes and imprinting. Chapter 11 deals with recombinant DNA and genome analysis. Included are the use of restriction enzymes and vectors in recombinant DNA, cloning strategies, transgenic animals and plants, and applications of genetic engineering. Chapter 12 examines the genetic control of development with emphasis on models in *C. elegans*, *D. melanogaster*, and *A. thaliana*.

Chapter 13 is an entirely new chapter that stresses cancer from the standpoint of the genetic control of cell division, with emphasis on the checkpoints that, in normal cells, result either in inhibition of cell division or in programmed cell death (apoptosis). Cancer results from a series of successive mutations, usually in somatic cells, that overcome the normal checkpoints that control cellular proliferation.

Chapters 14 and 15 deal with population and evolutionary genetics. The discussion includes the population genetics of the CCR5 receptor mutation that confers resistance to infection by HIV virus, as well as DNA typing in criminal investigations, paternity testing, the effects of inbreeding, and the evolutionary mechanisms that drive changes in allele frequency. The approach to quantitative genetics includes a discussion of how particular genes influencing quantitative traits (QTLs, or quantitative-trait loci) may be identified and mapped by linkage analysis. There is also a section on the genetic determinants of human behavior with examples of the approach using "candidate" genes that led to the identification of the "natural Prozac" polymorphism in the human serotonin transporter gene.

Special Features

A Moment to Think

A unique feature of this book is found in boxes called **A Moment to Think.** These are problems that interrupt the text and ask a student to pause and think about a concept and apply it to an actual situation. Often these problems use the results of classical experiments to help the student transform a concept from abstract to concrete, and carry it from thought to action. The answer is also provided, but on a different page.

The Human Connection

The Human Connection, one in each chapter, is our way of connecting genetics to the world of human genetics outside the classroom. All of the Connections include short excerpts from the original literature of genetics, usually papers, each introduced with a short explanatory passage. Many of the Connections are excerpts from classic materials, such as Garrod's book on inborn errors of metabolism, but by no means all of the "classic" papers are old papers, as you will see by examining the publication dates.

The pieces are called The Human Connection because each connects the material in the text to something that broadens or enriches its implications in regard to human beings. Some of the Connections raise issues of ethics in the application of genetic knowledge, social issues that need to be addressed, or issues related to the proper care of laboratory animals. They illustrate other things as well. Because each Connection names the place where the research was carried out, the student will learn that great science is done in many universities and research institutions throughout the world. In papers that use outmoded or unfamiliar terminology, or archaic gene symbols, we have substituted the modern equivalent because the use of a consistent terminology in the text and in the Connections makes the material more accessible to the student.

GeNETics on the Web

The World Wide Web is a rich storehouse of information on all aspects of genetics. Many sites give nontechnical descriptions of human diseases, written at the level of a lay person, for people who have family members affected by a hereditary disease. Other sites give descriptions of ongoing research projects and explain why the research is important. At the most sophisticated level are databases of mutants, DNA and protein sequences, and other genetic information, which are designed for access by the professional geneticist.

To make the genetic information explosion on the Internet available to the beginning student, we have developed **GeNETics on the Web,** exercises that make use of Internet resources related to human genetics. Genetic knowledge of human genetics is currently so vast that there can be no such thing as a comprehensive textbook; detailed information must come from the Internet. The available information changes

rapidly, too. Modern genetics is a dynamic science, and most of the key Internet resources are kept current. The relevant genetics sites are accessed through the use of key words that are highlighted in each exercise. The key words are maintained as hot links at the publisher's Web site (http://www.jbpub.com/genetics) and are kept constantly up to date tracking the address of each site if it should change.

Solutions Step by Step

Each chapter contains a section entitled **Solutions Step by Step** that demonstrates problems worked in full, explaining step by step a path of logical reasoning that can be followed to analyze the problem. The Solutions Step by Step serve as another level of review of the important concepts used in working problems. The solutions also emphasize some of the most common mistakes made by beginning students and give pointers on how the student can avoid falling into these conceptual traps.

Levels and Types of Problems

Each chapter provides numerous problems for solution, graded in difficulty, so students can test their understanding. The problems are of two different types:

- **Concepts and Issues** ask for genetic principles to be restated in the student's own words; some are matters of definition or call for the application of elementary principles.
- **Concepts in Action** are problems that require the student to reason using genetic concepts. The problems make use of a variety of formats, including true or false, multiple choice, matching, and traditional types of word problems. Many of the Concepts in Action require some numerical calculation. The level of mathematics is that of arithmetic and elementary probability as it pertains to genetics. None of the problems uses mathematics beyond elementary algebra.

Answers to Problems

The answers to the even-numbered Concepts in Action are included in the **Answer** section at the end of the book. The answers are complete; they explain the logical foundation of the solution and lay out the methods. The answers to the rest of the Concepts in Action problems are available for the instructor in the Solutions Manual on the Instructor's Toolkit.

Word Roots and Glossary

We have included a compilation of **Word Roots** that students find helpful in interpreting and remembering the meaning of technical terms. This precedes the **Glossary** of Key Words.

Further Reading

Each chapter also includes recommendations for **Further Reading** for the student who either wants more information or who needs an alternative explanation for the material presented in the book. Some additional "classic" papers and historical perspectives are included.

Illustrations

The art program is spectacular, thanks to the creative efforts of J/B Woolsey Associates, with special thanks to John Woolsey and Patrick Lane. Every chapter is richly illustrated with beautiful graphics in which color is used functionally to enhance the value of each illustration as a learning aid. The illustrations are also heavily annotated with "process labels" explaining step-by-step what is happening at each level of the illustration. These labels make the art user-friendly, inviting, and maximally informative.

Adaptability and Flexibility

There is no necessary reason to start at the beginning and proceed straight to the end. Each chapter is a self-contained unit that stands on its own. This feature gives the book the flexibility to be used in a variety of course formats. Throughout the book, we have integrated classical and molecular principles, so you can begin a course with almost any of the chapters. Most teachers will prefer starting with the overview in Chapter 1, possibly as suggested reading, because it brings every student to the same basic level of understanding. Teachers preferring the Mendel-early format should continue with Chapter 2; those preferring to teach the details of DNA early should continue with Chapter 6. Some teachers are partial to a chromosomes-early format, which would suggest continuing with Chapter 3, followed by Chapters 2 and 4. A novel approach would put genetic engineering first, which could be implemented by continuing with Chapter 11. Some teachers like to discuss mechanisms of mutation later in the course, and Chapter 7 can easily be assigned later. The writing and illustration program was designed to accommodate a

variety of formats, and we encourage teachers to take advantage of this flexibility in order to meet their own special needs.

Instructor and Student Supplements

Instructor and Student Supplements

An unprecedented offering of traditional and interactive multimedia supplements is available to assist instructors and aid students in mastering genetics. Additional information and review copies of any of the following items are available through your Jones and Bartlett Sales Representative.

For the Instructor

- **Instructor's ToolKit CD-ROM**—This MAC/IBM CD-ROM provides the instructor with a powerful set of five programs that can easily be integrated into your daily routine to help save time, while making classroom presentations more educational for students. The programs include:

  The Computerized Test Bank—The Test Bank, prepared by Sarah C. Martinelli of Southern Connecticut State University with contributions from Michael Draper, Patrick McDermot, and revisions by Elena R. Lozovsky, contains 750 test items, with 50 questions per chapter. There is a mix of factual, descriptive, analytical, and quantitative question types. A typical chapter file contains 20 multiple-choice objective questions, 15 fill-ins, and 15 quantitative. The Computerized Test Bank, using the ESATEST interface, allows the instructor to easily generate quizzes and tests from the complete set of over 700 questions.

  The Solutions Manual, authored by Elena R. Lozovsky of Harvard University, contains worked solutions for all the Concepts in Action problems found at the end of each chapter in the main text. Only solutions to even-numbered problems are provided in the back of the main text. This allows the instructor to control access to solutions for odd-numbered problems. The solutions to all end-of-chapter problems are supplied as a Microsoft Word document.

  PowerPoint Slide Set—The PowerPoint slide set, authored by Sarah C. Martinelli of Southern Connecticut State University, provides outline summaries of each chapter. The slide set can be customized to meet your classroom needs.

  The Lecture Success Image Bank—The image bank is an easy-to-use multimedia tool containing over 300 figures from the text specially enhanced for classroom presentation. You select the images you need by chapter, topic, or figure number to create your own lecture aid.

- **An Electronic Companion to Genetics™ Version 2.0 © 2001, Cogito Learning Media, Inc.**—This Mac/IBM CD-ROM, by Philip Anderson and Barry Ganetzky of the University of Wisconsin, Madison, reviews important genetics concepts using state of the art interactive multimedia. It consists of hundreds of animations, diagrams, and videos that dynamically explain difficult concepts to students. Brand new to this version are review screens and self-tests on genomics and improved navigation (ISBN: 0-7637-1636-7).

- **Video Resource Library**—A full complement of quality videos are available to qualified adopters. Genetics related topics include: Origin and Evolution of Life, Human Gene Therapy, Biotechnology, the Human Genome Project, Oncogenes, and Science and Ethics.

For the Student

- **The Gist of Genetics: Guide to Learning and Review**—Written by Rowland H. Davis and Stephen G. Weller of the University of California, Irvine, this study aid uses illustrations, tables and text outlines to review all of the fundamental elements of genetics. It includes extensive practice problems and review questions with solutions for self-check. The Gist helps students formulate appropriate questions and generate hypothesis that can be tested with classical principles and modern genetic techniques.

- **GeNETics on the Web**—Corresponding to the end-of-chapter GeNETics on the Web exercises, this World Wide Web site offers genetics-related links, articles and monthly updates to other genetics sites on the Web. Material for this site is carefully selected and updated by the authors, and Jones and Bartlett Publishers ensures that links for the site are regularly maintained. Visit the GeNETics on the Web site at http://www.jbpub.com/genetics.

- **An Electronic Companion to Genetics™ Version 2.0 © 2001, Cogito Learning Media, Inc.**—This Mac/IBM CD-ROM, by Philip Anderson and Barry Ganetzky of the University of Wisconsin, Madison, reviews important genetics concepts covered in class using state of the art interactive multimedia. It consists of hundreds of animations, diagrams, and videos that dynamically explain difficult concepts to students. In addition, it contains over 400 interactive multiple choice, "drop and drag," true/false, and fill-in problems. Brand new to this version are review screens and self-tests on genomics and improved navigation. These

resources will prove invaluable to students in a self-study environment and to instructors as a lecture enhancement tool. This CD-ROM is available for packaging exclusively with Jones and Bartlett Publishers texts.

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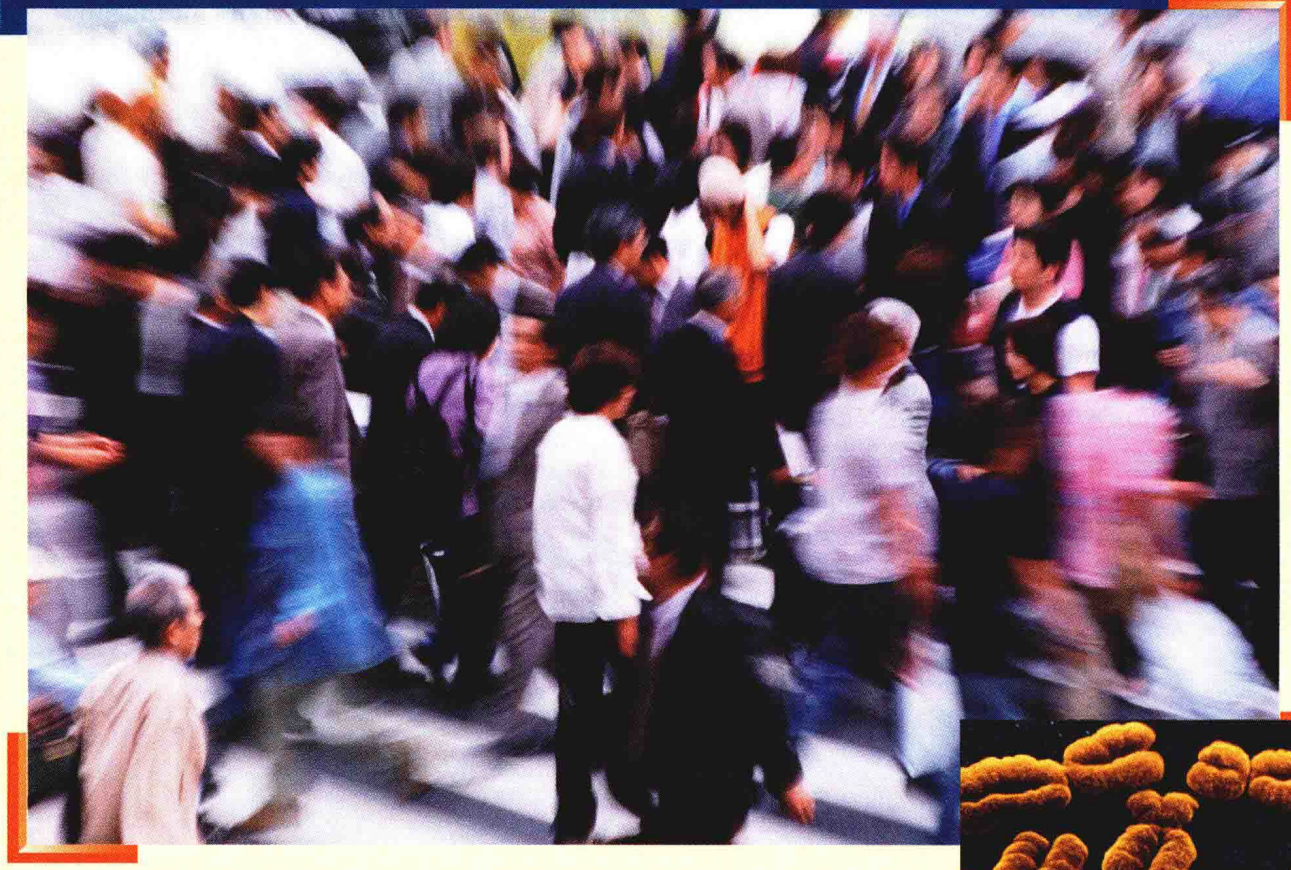

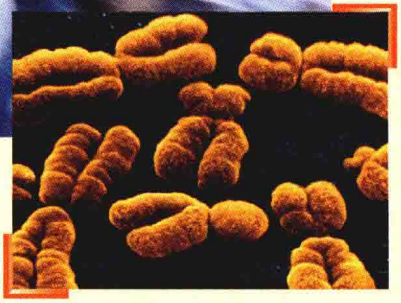

ALTHOUGH ANY TWO unrelated human beings are 99.9 percent identical in their DNA molecules, each person is genetically unique. Genetic differences are reflected in different facial features, body conformation, hair and eye color, and sometimes susceptibility to disease. The DNA inside cells is contained in chromosomes (right). [Above, © Ken Usami/PhotoDisc; right, © Biofoto Associates/Science Source/Photo Researchers, Inc.]

key concepts

- Inherited traits are affected by genes.
- Genes are composed of the chemical deoxyribonucleic acid (DNA).
- DNA replicates to form (usually identical) copies of itself.
- DNA contains a code specifying what types of enzymes and other proteins are made in cells.
- DNA occasionally mutates, and the mutant forms specify altered proteins.
- A mutant enzyme is an "inborn error of metabolism" that blocks one step in a biochemical pathway for the metabolism of small molecules.
- Traits are affected by environment as well as by genes.
- Organisms change genetically through generations in the process of biological evolution.
- Because of their common descent, organisms share many features of their genetics and biochemistry.

contents in brief

contents