

Essential **Genetics**

Second Edition

Daniel L. Hartl
Elizabeth W. Jones



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Harvard University

Elizabeth W. Jones
Carnegie Mellon University



JONES AND BARTLETT PUBLISHERS

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For Christopher
DLH
In Memory of Herschel
EWJ

ABOUT THE AUTHORS

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ABOUT THE COVER

There are many examples of genetic diversity all around us. Even animals of the same species can appear quite different from each other. The two tigers on our cover, Prince Charles and Whiskers, are both Bengal tigers from the same litter. Prince Charles has a strikingly unusual white coat, while his sister Whiskers has the typical orange coat.
[Cover photograph © Ron Kimball Photography.]

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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

A. C. Allison, 1954

Radcliffe Infirmary, Oxford, England
Protection Afforded by Sickle-Cell Trait against Subtertian Malarial Infection

Joe Hin Tijo¹ and Albert Levan², 1956

¹Estacion Experimental de Aula Dei, Zaragoza, Spain

²Institute 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

Mary F. Lyon, 1961

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

Francis Collins¹ and David Galas², 1993

¹National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

²Office of Health and Environmental Research, Department of Energy, Washington, DC
A New Five-Year Plan for the U.S. Human Genome Project

Frederick S. Leach and 34 other investigators, 1993

Johns Hopkins University, Baltimore, MD, and 10 other research institutions
Mutations of a mutS Homolog in Hereditary Nonpolyposis Colorectal Cancer

José M. Fernández-Cañón¹, Begoña

Granadino¹, Daniel Beltrán-Valero de Bernabé¹, Monica Renedo², Elena Fernández-Ruiz², Miguel A. Peñalva¹, and Santiago Rodríguez de Córdoba¹, 1996

¹Consejo Superior de Investigaciones Científicas, Madrid, Spain

²Universidad Autónoma de Madrid, Madrid, Spain
The Molecular Basis of Alkaptonuria

Carl T. Montague and 14 other authors, 1997

University of Cambridge, Cambridge, UK, and 5 other research institutions
Congenital Leptin Deficiency Is Associated with Severe Early-Onset Obesity in Humans

David H. Skuse¹, Rowena S. James², Dorothy V. M. Bishop³, Brian Coppin⁴, Paola Dalton², Gina Aamodt-Leeper¹, Monique Barcarese-Hamilton¹, Catharine Creswell¹, Rhona McGurk¹, and Patricia A. Jacobs², 1997

¹Institute of Child Health, London, England

²Salisbury District Hospital, Salisbury, Wiltshire, UK

³Medical Research Council Applied Psychology Unit, Cambridge, UK

⁴Princess 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

Preface

Today's college students come to a course in genetics full of enthusiasm stimulated by social and ethical controversies related to genetics reported in the popular press. The challenges for the instructor are to sustain this enthusiasm, to kindle a desire to understand the principles of genetics, and to help students integrate genetic 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 in genetics. 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 genetics resources and information that are available through the World Wide Web

Many special features are included to make the book “user friendly.” These are discussed individually below. Based on our own experiences in teaching genetics, they have been implemented and found to be effective in the classroom.

CHAPTER ORGANIZATION

The text is written in a clear, direct, lively, and concise manner. 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. There is also an **Outline** showing 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. Each chapter also includes **The Human Connection**. This is a special feature highlighting 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 **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 some of the problems and a complete **Glossary**.

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, classical, and evolutionary genetics are integrated throughout. 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 Chernobyl nuclear accident. A novel feature in Chapter 6 is 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, with special emphasis on *E. coli* and temperate and virulent bacteriophages. There is an extensive discussion of mechanisms of genetic recombination in microbes, including transformation, conjugation, transduction, and the horizontal transfer of genes present in plasmids, such as F' plasmids.

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 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. Also discussed are methods used in the analysis of complex genomes, such as the human genome, in which a gene that has been localized by genetic mapping to a region of tens of millions of base pairs must be isolated in cloned form and identified.

Chapter 11 is an integrative chapter dealing with genetic mechanisms of regulation. The first half of the chapter focuses on gene regulation in prokaryotes, the second half on that in eukaryotes.

Chapter 12 examines the genetic control of development. In addition to a discussion of developmental mechanisms in animals, there is a section on the genetic analysis of floral development in *Arabidopsis thaliana*. The material on pattern formation in *Drosophila* development is illustrated with spectacular color photographs by James Langeland, Stephen Paddock, and Sean Carroll, showing the discrete, overlapping patterns of gene expression as the embryo becomes segmented. The section on the development of flowers in plants is beautifully illustrated with photographs by Elliot Meyerowitz and John Bowman.

Chapters 13 and 14 deal with population and evolutionary genetics. The discussion of population genetics includes DNA typing in criminal investigations and paternity testing. The material on quantitative genetics includes a discussion of methods by which particular genes influencing quantitative traits (QTLs, or quanti-

tative-trait loci) may be identified and mapped by linkage analysis. There is also a discussion of QTL identification through the study of "candidate" genes, as exemplified by the identification of the "natural Prozac" polymorphism in the human serotonin transporter gene.

Human genetics is integrated in every chapter of the book. *Essential Genetics* could qualify as a textbook in human genetics, were it not so much broader. The integration is necessary in a modern treatment of genetics, because human genetics plays such a central role in the field. Integrating human genetics is also a sensible way to teach genetics, since students typically have a great interest in the subject. Chapter 1 sets the stage with an examination of inborn errors of metabolism, with emphasis on phenylketonuria and alkaptonuria. These are superb cases with which to motivate a desire to understand gene structure, expression, and mutation. Chapter 2 includes human pedigree analysis for autosomal genes. Chapter 3 does human X-linked inheritance with special emphasis on the "Royal hemophilia." Chapter 4 emphasizes the study of molecular markers in human pedigrees. Human chromosomes and their disorders are a major part of Chapter 5. And on it goes throughout the entire book. Chapter 10 makes special reference to the human genome project and the research resources, such as Expressed Sequence Tags (ESTs) that have already emerged from it. Chapter 13 includes human DNA typing, the effects of inbreeding in humans, and the controversial mitochondrial "Eve." The discussion of QTLs and candidate genes in Chapter 14 brings into focus two of the most important current approaches for identifying the genetic basis of human disease. Throughout the book The Human Connections also serve to integrate human genetics with other aspects of genetics. In addition, human genetics is highlighted in the GeNETics on the Web exercises at the end of each chapter.

THE HUMAN CONNECTION

A unique and special feature of this book is found in boxes called The Human Connection, one in each chapter. They are 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. Half of The Human Connection papers are from the

1990's, which serves to emphasize the fast-moving pace of this field.

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 Internet Exercises, called GeNETics on the Web, which make use of Internet resources related to human genetics. One reason for developing these exercises is that 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 up to date. The addresses of the relevant genetic sites are not printed in the book. Instead, the 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. Each Internet Exercise includes a short assignment such as to draw a map, create a list, or write a short paper. Many instructors may wish to develop their own assignments.

LEVELS AND TYPES OF PROBLEMS

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

- **Essential Concepts** 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.

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 highlight some of the most common mistakes made by beginning students and give pointers on how the student can avoid falling into these conceptual traps.

ANSWERS TO PROBLEMS AND GLOSSARY

The answers to the even-numbered Concepts in Action are included in the answer section at the end of the book. There is also a Glossary of Key Words. 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 Test Bank and Solutions Manual. We find that many of our students, like students everywhere, often sneak a look at the answer before attempting to solve a problem. This is a pity. Working backward from the answer should be a last resort. This is because problems are valuable opportunities to learn. Problems that the student cannot solve are usually more important than the ones that can be solved, because the sticklers usually identify trouble spots, areas of confusion, or gaps in understand-

ing. So, forever in hope but against all experience, we urge our students to try answering each question before looking at the answer.

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 inviting as well as informative. They also allow the illustrations to stand relatively independently of the text, enabling the student to review material without rereading the whole chapter.

The art program is used not only for its visual appeal but also to increase the pedagogical value of the book:

- Characteristic colors and shapes have been used consistently throughout the book to indicate different types of molecules—DNA, mRNA, tRNA, and so forth. For example, DNA is illustrated in any one of a number of ways, depending on the level of resolution necessary for the illustration, and each time a particular level of resolution is depicted, the DNA is shown in the same way. It avoids a great deal of potential confusion that DNA, RNA, and proteins are represented in the same manner in Chapter 13 as they are in Chapter 1.
- There are numerous full-color photographs of molecular models in three dimensions; these give a strong visual reinforcement of the concept of macromolecules as physical entities with defined three-dimensional shapes and charge distributions that serve as the basis of interaction with other macromolecules.
- The page design is clean, crisp, and uncluttered. As a result, the book is pleasant to look at and easy to read.

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 be a genomes-first format, which could be implemented by continuing with Chapter 10. 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

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

- **Printed Test Bank and Solutions Manual**—The Test Bank, prepared by Sarah C. Martinelli of Southern Connecticut State University with contributions from Michael Draper, Patrick McDermot, and Elena R. Lozovskaya, contains 700 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 Solutions Manual, authored by Elena R. Lozovskaya of Harvard University, contains worked solutions for all the end of chapter problems 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.

- **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:

PowerPoint Slide Set—The PowerPoint slide set, authored by Sarah C. Martinelli of Southern Connecticut State University, provides outline summaries of each chapter and hyperlinks to selected key figures from the text. 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.

The WebCD—The CD contains key simulated web sites that allow you to bring the Internet into the classroom without the need for a live connection.

The Computerized Test Bank and Solutions Manual—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 to all end-of-chapter problems are supplied as a Microsoft Word document.

- **Visual Genetics Plus: Tutorials and Laboratory Simulations. Faculty Version**—This Mac/IBM CD-ROM, created by Alan W. Day and Robert L. Dean of the University of Western Ontario and Harry Roy of Rensselaer Polytechnic Institute, is already in use at over 200 institutions worldwide. Visual Genetics 3.0 continues to provide a unique, dynamic presentation tool for viewing key genetic and molecular processes in the classroom. With this new, greatly expanded version of the Virtual Genetics Lab 2.0, instructors can now assign 18 comprehensive lab simulations. You can also bring the Lab into the classroom, as the program allows you to perform tasks on-screen—such as dragging of mutant colonies, using a pipette to make a dilution series, inoculating mutants to Petri dishes to test for response to growth factors—then to analyze and interpret the data. Through the testing feature and presentation capabilities you can offer a complete lab environment. Site Licenses and Instructor Copies are available.

- **An Electronic Companion to Genetics**
© 1998, 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.
- **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**
© 1998, 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. 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.

- **Visual Genetics Plus: Tutorials and Laboratory Simulations. Student Version**—This Mac/IBM CD-ROM is already in use at over 300 institutions worldwide. Visual Genetics 3.0 continues to provide a unique, dynamic multimedia review of key genetic and molecular processes. With this new, greatly expanded version of the Virtual Genetics Lab 2.0, students can now work on 18 comprehensive lab simulations. The Lab allows students to perform tasks on-screen—dragging of mutant colonies, using a pipette to make a dilution series, inoculating mutants to Petri dishes to test for response to growth factors—then to analyze and interpret the data. The Student Version is available for purchase and can be packaged with our text.

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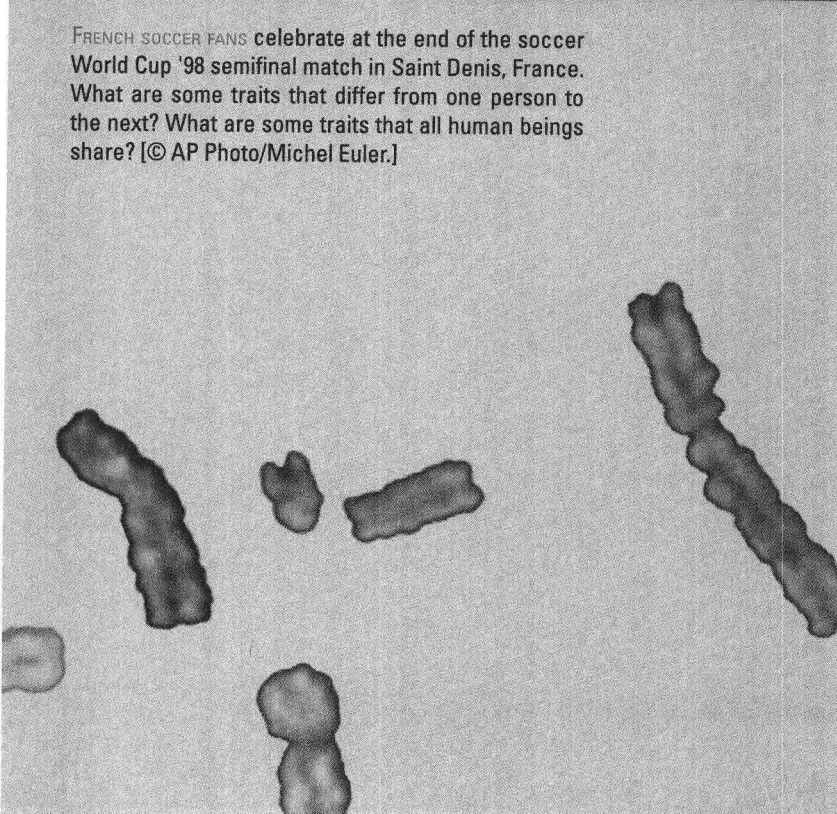


Key Concepts

- 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.



FRENCH SOCCER FANS celebrate at the end of the soccer World Cup '98 semifinal match in Saint Denis, France. What are some traits that differ from one person to the next? What are some traits that all human beings share? [© AP Photo/Michel Euler.]



Contents in Brief

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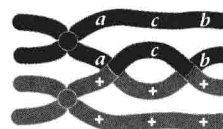
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