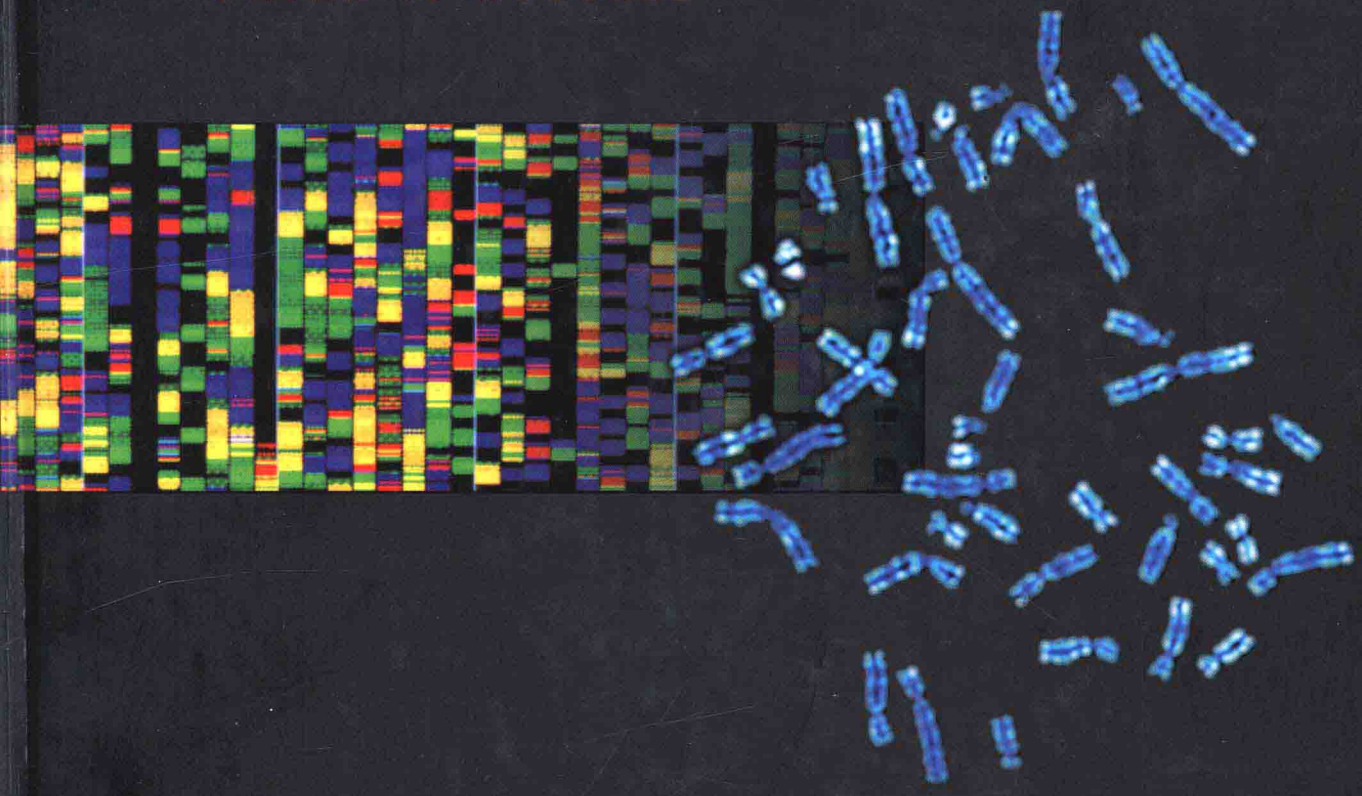
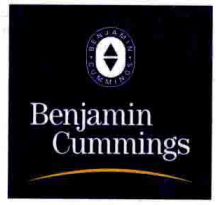
PETER J. RUSSELL



iGENETICS

PETER J. RUSSELL

Reed College



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The front cover shows a computer screen display of a human DNA sequence generated by an automated sequencing procedure as part of the Human Genome Project to decipher the sequence and function of the three billion base pairs of DNA in our genome. Each color represents one of the four bases in DNA. This image was photographed at the Joint Genome Project, part of the Human Genome Project, in Walnut Creek, California. © David Parker, Science Source/Photo Researchers. The blue stained chromosome image is a photomicrograph of a set of normal human metaphase chromosomes. © ISM, Phototake.

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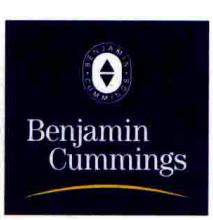

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Timeline of Important Events in Genetics

1856-1863 **Gregor Mendel** Conducted his famous pea experiments concerning gene segregation

1859 **Charles Darwin** Published *On the Origin of Species*; modern theory of evolution is identified with Darwin

1866 **Gregor Mendel** Published a research paper on his work establishing the basic principles of heredity

1868 **Fredrich Miescher** Isolated nuclein from nuclei; nuclein is now known to be DNA

1875 **O. Hertwig** Showed nucleus required for fertilization and cell division, and hence contained information for those processes

1882-1885 **E. Strasburger, Walther Flemming** Showed that nuclei contained chromosomes

1900 **Hugo de Vries, Carl Correns, Erich von Tschermak-Seysenegg** Independently produced results confirming Mendel's principles of heredity

1902 **Archibald Garrod** Identified the first human genetic disease

1902 **Walter Sutton, Theodor Boveri** Proposed the chromosome theory of heredity

1903 **William E. Castle** First to recognize the relationship between allele and genotypic frequencies *(see 1908, Hardy and Weinberg)*

1905 **William Bateson** Called the science of heredity "genetics"

William Bateson, R. C. Punnett Demonstrated linkage between genes

1908 **Godfrey H. Hardy, Wilhelm Weinberg** Formulated the Hardy-Weinberg principle relating mathematically the frequencies of genotypes to the frequencies of alleles in randomly mating populations

Herman Nilsson-Ehle Obtained experimental proof for multigene inheritance as the basis for continuous traits.

1909 **W. Johannsen** Introduced the word "gene"

1910 **Edward M. East** Elucidated the role of sexual reproduction in evolution

Thomas Hunt Morgan Found the first sex-linked gene, *white*, an eye color gene in *Drosophila melanogaster*

1911 **Thomas Hunt Morgan** Proposed that genetic linkage was the result of the genes involved being on the same chromosome

1913 **Alfred Sturtevant** Devised the principle for constructing a genetic linkage map

1916 **Thomas Hunt Morgan** Proposed a theory relating mutation and selection

1922 **Ronald A. Fisher** Published a substantial paper presenting a quantitative examination of the evolutionary consequences of Mendelian inheritance.

1924-1932 **John B. S. Haldane** Published a series of papers on his mathematical theory of natural and artificial selection.

1927 **Herman J. Müller** Showed that X-rays can induce mutations

1928 **Frederick Griffith** Discovered genetic transformation of a bacterium and called the agent responsible the "transforming principle"

1930 **Ronald A. Fisher** His comprehensive theory of evolution, synthesizing Mendelian inheritance and Darwinian selection was published as "The Genetical Theory of Natural Selection"

1930s **Sewall Wright** Developed his own genetical theory for natural selection, and laid the important theoretical foundation for genetic drift, the random change in gene frequency.

1931 **Harriet Creighton, Barbara McClintock** Showed that genetic recombination in maize results from a physical exchange of homologous chromosomes

Curt Stern Showed that genetic recombination in *Drosophila* results from a physical exchange of homologous chromosomes

1941 **George Beadle, Edward Tatum** Proposed the one gene-one enzyme hypothesis

1944 **Oswald Avery, Colin MacLeod, Maclyn McCarty** Showed that Griffith's transforming principle *(see 1928)* was DNA

1946 **Joshua Lederberg, Edward Tatum** Discovered conjugation in bacteria

1950 **Barbara McClintock** Reported results of maize experiments indicating movable genes, now called transposable elements

1952 **Alfred Hershey, Martha Chase** Showed that the genetic material of bacteriophage T2 is DNA

1953 **James Watson, Francis Crick** Proposed double helical model for DNA

1957 **Heinz Fraenkel-Conrat, B. Singer** Showed that the genetic material of tobacco mosaic virus was RNA

1958 **Matthew Meselson, Franklin Stahl** Proved the semiconservative model for DNA replication

Arthur Kornberg Isolated DNA polymerase I from *E. coli*

1959 **Severo Ochoa** Discovered the first RNA polymerase

1961 **Sidney Brenner, François Jacob, Matthew Meselson** Discovered messenger RNA (mRNA)

François Jacob, Jacques Monod Put forward the operon model for the regulation of gene expression in bacteria

1965 **Robert Holley** Obtained the first nucleotide sequence of a tRNA

1966 **Marshall Nirenberg, H. Gobind Khorana** Worked out the complete genetic code

1972 **Paul Berg** Constructed the first recombinant DNA molecule *in vitro*

1973 **Herb Boyer, Stanley Cohen** First to use a plasmid to clone DNA

1975 **Edward M. Southern** Developed a method for transferring DNA fragments separated in a gel to a filter, preserving the relative positioning of the fragments. This is one of the most valuable techniques for identifying cloned genes.

1977 **Walter Gilbert, Frederick Sanger** Devised methods for sequencing DNA

Phillip Sharp, and others Discovered introns in eukaryotic genes

Frederick Sanger Obtained the complete nucleotide sequence of a virus, bacteriophage ΦX174

1983 **Thomas Cech, Sidney Altman** Discovered self-splicing of an intron RNA

1986 **Kary Mullis and others** Developed the polymerase chain reaction (PCR), a technique for amplification of selected DNA segments without cloning

1989 **L.-C Tsui and John Riordan, and Francis Collins's group** Identification and cloning of the human gene responsible for cystic fibrosis

1990 **James Watson and many other scientists** Launched the Human Genome Project to map and sequence the complete genomes of a number of genetically important organisms, including humans

1993 **Huntington's Disease Collaborative Research Group** Discovered molecular basis for Huntington's disease, a human genetic trait

1994 **M. Skolnick and other scientists** Cloned the first breast cancer gene (*BRCA1*)

1996 **Many scientists in several international research groups** Published the first complete DNA sequence of a eukaryotic organism, the yeast *Saccharomyces cerevisiae*

J. Craig Venter and many other scientists in several U.S. research groups Published the complete DNA sequence of a member of the archaeon, *Methanococcus jannaschii*. The sequence data confirm that the Archaea are a third major branch of life distinct from prokaryotes and eukaryotes.

National Institutes of Health Reported that almost 150 clinical trials have been approved for the transfer of genes into humans as part of long-term goals to treat genetic diseases by gene therapy

1997 **The Roslin Institute** A lamb named Dolly is the first mammal to be cloned from an adult using the techniques of transgenic cloning

Escherichia coli genome sequence completed

1998 **Celera Genomics Company** formed to sequence much of human genome in 3 years using Human Genome Project-generated resources

Caenorhabditis elegans genome sequence completed

1999 **Human Genome Project** Announced the complete sequencing of the DNA making up human chromosome 22

2000 **International collaborators** Published genome of fruit fly, *Drosophila melanogaster,* the largest genome sequenced to date

International research consortium Published chromosome 21 genome, the smallest human chromosome

2001 **Human Genome Project** Announced the completion of a "working draft" DNA sequence of the entire human genome

Preface

Overview of the Text

The structure of DNA was first described in 1953, and since that time genetics has become one of the most exciting and ground-breaking sciences. A continual flood of discoveries not only expands our understanding about heredity but also affects our daily lives in areas ranging from disease therapy to courtroom evidence. Experimentally, the development of gene cloning techniques in the 1970s revolutionized the way we look at genes and their expression, and the development of PCR in the 1980s enabled a second revolution, enhancing our abilities to examine genes at the molecular level. In the past 10 or so years, the rapid advances in molecular techniques have made it possible to consider sequencing entire genomes to identify all genes and to study the organization of genes in the chromosomes. At this writing in 2001, the genomes of many viruses, many bacteria, and some eukaryotes have been completely sequenced. Most importantly, a working draft of the human genome sequence has been accomplished, and efforts are under way to refine the sequence and interpret its contents. Complete genome sequences enable us to focus on genomes rather than individual genes and therefore to ask more complex questions about gene expression. As we move into the postgenomic era, then, our knowledge about genes and gene functions will increase enormously. Thus, it is a very important time to learn about the basic concepts of genetics, and this textbook has been written to teach both the classic and modern molecular aspects of this subject.

iGenetics reflects the dynamic nature of the field of genetics. *iGenetics* emphasizes an experimental, inquiry-based approach, with solid treatment of many research experiments that have contributed to our knowledge of genetics. In this way, students are exposed to the processes of science, learning about the formulation and study of scientific questions in a way that will be of value in their study of genetics and in all areas of science.

A consistent effort has been made to present the important experiments without including excessive facts and detail that could obscure the central concepts of genetics. *iGenetics* is ideally suited for students who have had some background in biology and chemistry and who are interested in learning the concepts of genetics from a research-oriented perspective. Great care has been taken to keep the text accessible to students by making it easy to read, with a consistent level of coverage and a logical progression of ideas.

iGenetics contains pedagogical features such as "Principal Points," "Keynotes," "Summaries," and "Analytical Approaches for Solving Genetics Problems," designed to be useful learning tools for students of genetics. Problem solving is a major feature of the book, and the end-of-chapter "Questions and Problems" have been consistently praised by class testers. *iGenetics* maintains a format that allows instructors to use the chapters out of sequence to accommodate various teaching approaches.

iGenetics includes the following features:

- The text has a modern molecular organization to reflect the increasingly molecular emphasis in the experimental study of genes. The text is divided into six major parts: Part 1, "Genes and Their Functions," covers DNA structure, replication, and gene expression; Part 2, "Gene Manipulation and Genomic Analysis," covers DNA cloning and manipulation, applications of recombinant DNA technology, and the analysis of genomes; Part 3, "Principles of Gene Segregation Analysis," covers Mendelian genetics and its extensions, gene mapping, and non-Mendelian inheritance; Part 4, "Regulation of Gene Expression," covers the control of gene transcription and the genetics of cancer; Part 5, "Genetic Change," covers DNA mutation and repair, transposable elements, and chromosomal mutations; and Part 6, "Genetics of Populations," covers population genetics, quantitative genetics, and molecular evolution. As mentioned earlier, the chapters can readily be used in any sequence to fit the needs of individual instructors.
- Twenty-four interactive activities called *iActivities* have been designed to promote interactive problem solving. Found on the *iGenetics* CD-ROM, these activities are based on case studies presented at the beginnings of the chapters. An example from Chapter 9 is the analysis of DNA microarray results for a fictional patient with breast cancer to determine gene expression differences and then determine which drugs would be useful for treating her cancer. I have checked all *iActivities* at every stage of their development to

help ensure accuracy and quality. A brief description of the *iActivity* appears in the text at the appropriate time in chapter, urging students to try it out.

- Fifty narrated animations on the *iGenetics* CD-ROM help students visualize challenging concepts or complex processes, such as meiosis, DNA replication, translation, restriction mapping, and gene mapping. As with the *iActivities*, I have been involved with the entire development of the animations, outlining them, editing the storyboards, helping describe the steps for the artists, and working closely with the animators until the animations were complete. We have made a special effort to base the animations on the text figures so that students do not have to think about the processes in a different graphic format. These animations are of very high quality, showing a level of detail not typical of animations that are supplements to texts. A media flag with the title of the animation appears next to the discussion of that topic in the chapter.
- The material on recombinant DNA technology and the manipulation of DNA is covered over three chapters. Recombinant DNA Cloning Technology (Chapter 7) discusses how to clone DNA, how to make and screen recombinant DNA libraries, how to analyze genes and gene transcripts, how to sequence DNA, and how to amplify DNA using PCR. "Applications of Recombinant DNA Technology" (Chapter 8) describes how the molecular tools presented in Chapter 7 can be applied to study biological processes, test for genetic disease mutations, isolate human genes, fingerprint DNA, develop gene therapy approaches, develop commercial products, and engineer plants genetically. "Genome Analysis" (Chapter 9) assembles in one chapter an overview of the state of the art of the analysis of genomes, including how genomes are sequenced completely, a summary of the properties of key genomes that have been sequenced, how genome sequences are analyzed, and how transcriptional and translational profiles can be analyzed for many genes simultaneously.
- All the molecular aspects of genetics are included so that the book reflects our current understanding of genes at the molecular level.
- Human examples are used extensively throughout the text, and discussions include our current molecular understandings of various human genetic diseases. Human genes mentioned in the text are keyed to the OMIM (Online Mendelian Inheritance in Man) online database of human genes and genetic disorders at http://www3.ncbi.nlm.nih.gov/Omim/, where the most up-to-date information is available about the genes.
- The Suggested Reading section contains references to papers that were key to the development of concepts and references to current research in the areas being discussed.

Organization and Coverage

The four major areas of genetics—transmission genetics, molecular genetics, population genetics, and quantitative genetics—are covered in 24 chapters. Chapter 1 is an introductory chapter designed to summarize the main branches of genetics, explain the basic concepts of genetics (the molecular nature of genes, the transmission of genetic information, the expression of genes, and the sources of genetic variation), describe what geneticists do and what their areas of research encompass, introduce genetic databases and maps, and discuss the transmission of chromosomes from cell division to cell division and from generation to generation by the processes of mitosis and meiosis, respectively. This knowledge will help you understand your subsequent study of molecular genetics and transmission genetics.

The remaining 23 chapters are divided among six parts. The "molecular core" of *iGenetics* is found in ***Part 1, "Genes and Their Functions,"*** and ***Part 2, "Gene Manipulation and Genomic Analysis,"*** detailing the current level of our knowledge about the molecular aspects of genetics and about DNA cloning and genome analysis. The five chapters in Part 1 focus on the nature of the genetic material and the expression of genes. In Chapter 2, we cover the structure of DNA, presenting the classic experiments that revealed DNA and RNA to be genetic material and that established the double helix model as the structure of DNA, and the details of DNA structure and organization in prokaryotic and eukaryotic chromosomes. We cover DNA replication in prokaryotes and eukaryotes and recombination between DNA molecules in Chapter 3. In Chapter 4, we examine some aspects of gene function, such as the genetic control of the structure and function of proteins and enzymes and the role of genes in directing and controlling biochemical pathways. A number of examples of human genetic diseases that result from enzyme deficiencies are described to reinforce the concepts. The discussion of gene function in Chapter 4 enables students to understand the important concept that genes specify proteins and enzymes, setting them up for the next two chapters, in which gene expression is discussed. In Chapter 5, we discuss the first step in the expression of a gene: transcription. We describe the general process of transcription and then present the currently understood details of the transcription of messenger RNA, transfer RNA, and ribosomal RNA genes and the processing of the initial transcripts to the mature RNAs for both prokaryotes and eukaryotes. In Chapter 6, we describe the structure of proteins, the evidence for the nature of the genetic code, and a detailed expression of our current knowledge of translation in both prokaryotes and eukaryotes.

There are three chapters in ***Part 2, "Gene Manipulation and Genomic Analysis."*** In Chapter 7, we discuss

recombinant DNA technology and other molecular techniques that are essential tools of most areas of modern genetics. There are descriptions of the use of recombinant DNA technology to clone and characterize genes and to manipulate DNA. Then, in Chapter 8 we discuss the applications of recombinant DNA technology in the analysis of biological processes, the diagnosis of human diseases, the isolation of human genes, forensics (DNA typing), gene therapy, the development of commercial products, and the genetic engineering of plants. In Chapter 9 we discuss genome analysis, focusing on the Human Genome Project for mapping and sequencing the complete genomes of humans and other selected organisms. The chapter describes the methods for sequencing complete genomes, discusses the features of a number of genomes that have been sequenced, and goes into the types of research scientists are engaging in to detail the global expression of genes in cells at the RNA and protein levels.

In ***Part 3, "Principles of Gene Segregation Analysis,"*** six chapters deal with the transmission genetics. Chapters 10 and 11 present the basic principles of genetics in relation to Mendel's laws. Chapter 10 is focused on Mendel's contributions to our understanding of the principles of heredity, and Chapter 11 covers mitosis and meiosis in the context of animal and plant life cycles, the experimental evidence for the relationship between genes and chromosomes, and methods of sex determination. Mendelian genetics in humans is introduced in Chapter 10 with a focus on pedigree analysis and autosomal traits. The topic is continued in Chapter 13 with respect to sex-linked genes. The exceptions to and extensions of Mendelian analysis (such as the existence of multiple alleles, the modification of dominance relationships, gene interactions and modified Mendelian ratios, essential genes and lethal alleles, and the relationship between genotype and phenotype) are described in Chapter 12. In Chapter 13, gene mapping in eukaryotes is presented. In this chapter, we describe how the order of and distance between the genes on eukaryotic chromosomes are determined in genetic experiments designed to quantify the crossovers that occur during meiosis. We also discuss the more specialized analysis of genes by tetrad analysis, primarily in fungal systems, and the phenomenon of recombination in mitosis. In Chapter 14, we discuss the ways of mapping genes in bacteria and in bacteriophages, which take advantage of the processes of conjugation, transformation, and transduction. Fine structure analysis of bacteriophage genes concludes this chapter. In Chapter 15, we address the organization and genetics of extranuclear genomes of mitochondria and chloroplasts. We cover the current molecular information about the organization of genes within the extranuclear genomes and the classic genetic experiments that are used to study non-Mendelian inheritance. We also discuss two contrasts to non-Mendelian inheritance: maternal effect and genomic imprinting.

Part 4, "Regulation of Gene Expression," follows with three chapters on this topic. Chapter 16 focuses on the regulation of gene expression in prokaryotes. In this chapter, we discuss the operon as a unit of gene regulation, the current molecular details in the regulation of gene expression in bacterial operons, and regulation of genes in bacteriophages. Chapter 17 focuses on the regulation of gene expression and development in eukaryotes, explaining how eukaryotic gene expression is regulated, stressing molecular changes that accompany gene regulation, short-term gene regulation in simple and complex eukaryotes, gene regulation in development and differentiation, and immunogenetics. Next, in Chapter 18 we discuss the relationship of the cell cycle to cancer and the various types of genes that, when mutated, play a role in the development of cancer. We also discuss the fact that cancer usually requires a number of independent mutational events to develop. Finally, we consider the induction of cancer by chemicals and radiation (carcinogens).

Part 5, "Genetic Change," contains three chapters that describe some of the ways in which genetic material can change or be changed. Chapter 19 covers the processes of gene mutation, the procedures that screen for potential mutagens and carcinogens (the Ames test), some of the mechanisms that repair damage to DNA, and some of the procedures used to screen for particular types of mutants. Chapter 20 presents the structures and movements of transposable genetic elements in prokaryotes and eukaryotes. Chromosomal mutations—changes in normal chromosome structure or chromosome number—are discussed in Chapter 21. Chromosomal mutations in eukaryotes and human disease syndromes that result from chromosomal mutations, including triplet repeat mutations, are emphasized.

Part 6, "Genetics of Populations," ends the book. In Chapters 22 and 23, we describe the genetics of populations and quantitative genetics, respectively. In Chapter 22, "Population Genetics," we present the basic principles in population genetics, extending our studies of heredity from the individual organism to a population of organisms. This chapter includes an integrated discussion of the developing area of conservation genetics. In Chapter 23, "Quantitative Genetics," we consider the heredity of traits in groups of individuals that are determined by many genes simultaneously. In this chapter we also discuss heritability: the relative extent to which a characteristic is determined by genes or by the environment. Both Chapters 22 and 23 include discussions of the application of molecular tools to these areas of genetics. Chapter 24, "Molecular Evolution," discusses evolution at the molecular level of DNA and protein sequences. The study of molecular evolution uses the theoretical foundation of population genetics to address two essentially different sets of questions: how DNA and protein molecules evolve and how genes and organisms are evolutionarily related.

Pedagogical Features

Because the field of genetics is complex, making the study of it potentially difficult, we have incorporated a number of special pedagogical features to assist students and to enhance their understanding and appreciation of genetic principles:

- Each chapter opens with an outline of its contents and a section called "Principal Points." "Principal Points" are short summaries that alert students to the key concepts they will encounter in the material to come.
- Throughout each chapter, strategically placed "Keynote" summaries emphasize important ideas and critical points allow students to check their progress.
- Important terms and concepts—highlighted in bold—are defined where they are introduced in the text. For easy reference, they are also compiled in a glossary at the back of the book.
- Some chapters include boxes covering special topics related to chapter coverage. Some of these boxed topics are *Equilibrium Density Gradient Centrifugation* (Chapter 3), *Sucrose Gradient Centrifugation* (Chapter 5), *Labeling DNA* (Chapter 7), *Genetic Terminology* (Chapter 10), *Elementary Principles of Probability* (Chapter 10); *DNA Recombination* (Chapter 13); *Cloning of a Sheep* (Chapter 17); and *Hardy, Weinberg, and the History of Their Contribution to Population Genetics* (Chapter 22).
- Each chapter closes with a "Summary," further reinforcing the major points that have been discussed.
- With the exception of the introductory Chapter 1, all chapters conclude with a section titled "Analytical Approaches for Solving Genetics Problems." Genetics principles have always been best taught with a problem-solving approach. However, beginning students often do not acquire the necessary experience with basic concepts that would enable them to attack assigned problems methodically. In the "Analytical Approaches" sections, typical genetic problems are talked through in step-by-step detail to help students understand how to tackle a genetics problem by applying fundamental principles.
- The problem sets that close the chapters include approximately 600 questions and problems designed to give students further practice in solving genetics problems. The problems for each chapter represent a range of topics and difficulty. The answers to questions marked by an asterisk (*) can be found at the back of the book, and answers to all questions are available in a separate supplement, the *Study Guide and Solutions Manual*.
- Comprehensive and up-to-date suggested readings for each chapter are listed at the back of the book.
- Special care has been taken to provide an extensive, accurate, and well cross-referenced index.

Supplements

For Students

Study Guide and Solutions Manual (0-8053-4545-0)
Prepared by Bruce Chase of the University of Nebraska, the *Study Guide and Solutions Manual* has detailed solutions for all the problems in the text and contains the following features for each chapter: chapter outline of text material, key terms, suggestions for analytical approaches, problem-solving strategies; and 1,000 additional questions for practice and review. It also includes a review of important terms and concepts; a "Thinking Analytically" section, which provides guidance and tips on solving problems and avoiding common pitfalls; additional questions for practice and review; and questions that relate to chapter-specific animations and *iActivities*. (The CD-ROM that is included free with the *iGenetics* text comes in two versions, one with all the solutions from the manual and one without solutions.)

The Genetics Place (www.geneticsplace.com)
This online learning environment offers interactive learning activities, practice quizzes, links to related Web sites, a syllabus manager, and a glossary. A subscription to the Genetics Place is included free with every new copy of the text.

For Instructors

Instructor's Guide (0-8053-4539-6)
This guide presents sample lecture outlines, teaching tips for the text, and media tips for using and assigning the media component in class.

PowerPoint CD-ROM (0-8053-4541-8)
This cross-platform CD-ROM features all illustrations from the text, which can be edited and customized for lecture presentation. You can edit labels, import illustrations and photos from other sources, and export figures into other programs, including PowerPoint, or for use on the Web.

Transparency Acetates (0-8053-4543-4)
Approximately 175 full-color figures from the text are included.

Printed Test Bank (0-8053-4544-2)
Prepared by Holly Ahern of Adirondack Community College, the test bank includes approximately 1,100 multiple-choice and true-or-false questions. The entire set of questions is also available in Macintosh and Windows test-generating software (0-8053-4546-9).

Acknowledgments

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A number of talented individuals worked with me to develop the *iGenetics* CD-ROM and have contributed to its success: Margy Kuntz (*iActivities*), who did an excellent job researching this subject matter and then authoring highly creative and rich *iActivities* that are designed to enhance critical thinking in genetics; Dr. Todd Kelson (Ricks College; animation storyboards); Dr. Hai Kinal (Springfield College, animation storyboards); Dr. Robert Rothman (Rochester Institute of Technology; animation storyboards); Steve McEntee (*iActivity* art development, art style for the animations and text art); Kristin Mount (animations); Richard Sheppard (animations); Eric Stickney (animations); Holly Ahern (Adirondack Community College; CD-ROM quiz questions); and the staff of Six Red Marbles and Binary Labs.

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Peter J. Russell

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