SECOND EDITION

Modern Genetics

Francisco J. Ayala
John A. Kiger, Jr.

SECOND EDITION

Modern Genetics

Francisco J. Ayala
John A. Kiger, Jr.
University of California, Davis

The Benjamin/Cummings Publishing Company, Inc.
Menlo Park, California • Reading, Massachusetts
London • Amsterdam • Don Mills, Ontario • Sydney

Sponsor editor Jane Gillen
Production coordinator Pat Franklin Waldo
Copy editor Lieselotte Hofmann
Book and cover designer Marjorie Spiegelman with Gary Head
Chief artist Georg Klatt; additional art by Fran Milner
Layout artist Gary Head

Library of Congress Cataloging in Publication Data

Ayala, Francisco José, 1934–
Modern Genetics

(The Benjamin/Cummings series in the life sciences)
Bibliography: p.
Includes index.
1. Genetics. I. Kiger, John A. II. Title.
III. Series.
QH430.A92 1984 575.1 83-15763
ISBN 0-8053-0316-2

BCDEFGHIJK-HA-8987654

The Benjamin/Cummings Publishing Company, Inc.
2727 Sand Hill Road
Menlo Park, California 94025

Preface

Genetics is a rapidly advancing science. With these words we opened the preface to the first edition of *Modern Genetics*. The continuing truth of these words, along with the valuable comments of many instructors of genetics who have used the first edition, has necessitated this major revision only four years after the appearance of the first edition.

Modern Genetics is a basic genetics text intended for a one-semester course. Prior college courses in general biology and chemistry are assumed, although some essential concepts (for example, mitosis and meiosis) that the student should have learned in such courses are reviewed here. We have intentionally included more material than can be covered in most one-semester courses. However, the book is written so as to enable instructors to choose topics according to their preferences.

The molecular basis of heredity remains a dominant theme of modern genetics and of this revised text. Recombinant DNA technology has made great advances in the last four years and opened wide the door to a molecular understanding of the genetics of humans and other higher organisms that was only anticipated previously. But in-depth coverage of population genetics and evolutionary genetics remains a distinctive feature of *Modern Genetics*.

As with the first edition, we have exploited our complementary areas of expertise in writing *Modern Genetics*. F.J.A. wrote the first draft of most or all of Chapters 1–3, 10, 18, 19 and 21–26 and Appendix 1; J.A.K. wrote the draft of Chapters 4–9 and 11–17. Chapter 20 was a joint effort. The flip of a coin determined the order of authorship.

Organization

The basic organization of this edition is unchanged from that of the first in spite of the rearrangement of some topics and addition of entirely new chapters on recombinant DNA technology, eukaryotic gene regulation, and somatic cell genetics. *Modern Genetics* is composed of three parts: Part I, Organization and Transmission of the Genetic Materials; Part II, Expression of the Genetic Materials; and Part III, Evolution of the Genetic Materials. We remain convinced that this format is both logical and of practical value in the classroom. It should aid the student in understanding why the various topics are considered and how they contribute to a full comprehension of the processes of heredity. Yet the text is designed to give the instructor maximum flexibility in devising a syllabus. The order in which chapters are taught can be substantially altered without creating serious gaps in knowledge. We believe, however, that each chapter forms a logical unit and may best be taught as such.

The major changes in organization and approach from the first edition begin in Part I. The section on chromosome mapping in eukaryotes (Chapter 5) has been rewritten and expanded based upon comments from instructors and our own students. Complementation analysis and fine-structure mapping in both prokaryotes and eukaryotes form a new Chapter 6. The previous Chapter 9 (DNA Replication, Repair, and Recombination) has become Chapters 13 and 14, which have been moved to Part II, because of the emphasis on the genetic functions that are involved in the processes of DNA replication and recombination. A new Chapter 9 (DNA Manipulation) concludes Part I since the tools of recombinant DNA technology and DNA sequence analysis are properly a part of a section on "Organization and Transmission of the Genetic Materials." The previous Chapters 6 and 7 have been updated and become Chapters 7 and 8. Much of the content of the previous Chapter 8 can now be found in Chapters 6 and 14.

In Part II, an entirely new Chapter 16, Regulation of Gene Expression in Eukaryotes, appears. It is based largely on the fruits of recombinant DNA research. The material in the previous chapter by this name has also been updated and is found in the new Chapter 17, Genetic Analysis of Development. A new Chapter 18, Genetics with Somatic Cells, where we have included the recent spectacular advances in mapping the human genome, has been added. Chapters 11 and 12 have been updated to incorporate our deepened understanding of an evolving genetic code and information flow in cells; the incorporation of Chapters 13 and 14 has been mentioned previously.

In Part III, we have enlarged in Chapter 21 the section on duplications because of the increased understanding of this topic provided by the availability of DNA sequences, and we have added a section on the evolution of the human chromosomes. In Chapter 22 the discussion of gene variation incorporates the results from the studies of cryptic protein variation and of nucleotide heterogeneity. The topic of linkage disequilibrium reviewed in Chapter 25 receives new light from examination of long DNA sequences.

Chapter 26 has new sections on the reconstruction of phylogeny from DNA sequences, on the evolution of the genome by gene elongation, adjoining, and duplication, and on the intriguing question of horizontal gene transfer between species.

Special Features

- This edition, like the previous one, is generously illustrated to enhance the clarity of the text.
- Special topics of various kinds are set apart as "boxes," most of which can be skipped without loss of comprehension of the text. These boxes provide an additional element of choice in selecting material for study.
- Important terms and concepts are now listed at the end of each chapter as an aid for review. A glossary is provided at the end of the book for easy reference.
- The problems at the ends of the chapters are an integral part of the book; some contain new information that we consider subsidiary or too detailed to be included in the text proper. At the request of many instructors and students, we have included simple problems within each chapter in addition to more difficult ones, and have added the answers to the odd-numbered problems in Appendix 2 at the back of the book. (The answers to the even-numbered problems are available to instructors in a separate supplement.)
- Students who have not taken a course in statistics will find in Appendix 1 the concepts and methods needed to understand the text and solve the problems.
- The bibliography at the end of each chapter lists many basic references that document the material covered in the text; the credit lines for figures and tables cite additional sources of information.

Acknowledgments

Our most fundamental debt is to all the scientists whose brilliant efforts have made genetics such an exciting science. To many of them we are particularly thankful for their generosity in providing photographs, permission to reproduce illustrations, and other needed items. The manuscript of the first edition was extensively reviewed by both specialists and generalists to ensure a sound and balanced coverage of the subject. The new material of this second edition has also been extensively reviewed. Although we alone bear the responsibility for any shortcomings, they are all the fewer because of these helpful reviews.

We thank Crystal DiModica and Candy Miller, who typed the manuscript, and Lorraine Barr who helped with proofreading. Valuable assistance in preparing this edition was also provided by Dr. Helen K. Salz, Boni Gregory, and Elizabeth Harper. Lieselotte Hofmann has been a skilled editor of the manuscript; we acknowledge the lasting contribution of Fred Raab as production editor of the first edition. The book has greatly benefited from the skill of Georg Klatt who did most of the drawings. We gratefully acknowledge the continued dedication of the Benjamin/Cummings staff, in particular Jim Behnke, Jane Gillen, and Pat Waldo. Working with a publisher is always a challenging experience; in this case, it was also a pleasure.

Davis, California
January, 1984

Francisco J. Ayala
John A. Kiger, Jr.

Reviewers of the First and Second Editions

Joan W. Bennett, Tulane University
Sarane T. Bowen, San Francisco State University
Alice J. Burton, St. Olaf College
M. Campion, University of Keele, United Kingdom
D. J. Cove, University of Leeds, United Kingdom
Rowland H. Davis, University of California, Irvine
Linda K. Dixon, University of Colorado, Denver
Robert Dottin, Johns Hopkins University
James Farmer, Brigham Young University
Irving Finger, Haverford College
A. T. Ganesan, Stanford University
Lawrence T. Grossman, University of Michigan
Gary N. Gussin, University of Iowa
Barbara A. Hamkalo, University of California, Irvine
Philip Hartman, Johns Hopkins University
Eugene R. Katz, S.U.N.Y., Stony Brook
Gary Ketner, Johns Hopkins University
Yun-Tzu Kiang, University of New Hampshire
George Lefevre, California State University, Northridge
Joyce B. Maxwell, California State University, Northridge
John R. Merriam, University of California, Los Angeles
Virginia Merriam, Loyola Marymount University
Roger Milkman, University of Iowa
Jeffrey B. Mitton, University of Colorado
William H. Petri, Boston College
Raymond L. Rodriguez, University of California, Davis
J. A. Roper, University of Sheffield, United Kingdom
Frank A. Ruddle, Yale University
Henry E. Schaffer, North Carolina State University
Steven R. Seavey, Lewis and Clark College
Eli C. Siegel, Tufts University
Franklin W. Stahl, University of Oregon
John Stubbs, San Francisco State University
J. R. Warr, University of York, United Kingdom

Table of Contents

III Evolution of the Genetic Materials 660

1

Introduction

The eminent geneticist Theodosius Dobzhansky stated, "Nothing in biology makes sense except in the light of evolution." It is even more certain that nothing in biology is understandable except in the light of genetics. Genetics is the core biological science; it provides the framework within which the diversity of life and its processes can be comprehended as an intellectual whole.

The foundations of genetics were discovered by Gregor Mendel in 1866, but remained generally unknown until 1900. During the first half of the twentieth century it was gradually established that genes play major roles in the function and evolution of higher organisms. The fundamental significance of these roles, however, became apparent only with the recognition that nucleic acids are the hereditary materials of all organisms. The discovery of the chemical nature of DNA laid open the principles of heredity and led to an understanding of how the genes—in the form of DNA molecules—are transmitted from generation to generation and expressed within each generation. The hereditary information is contained within the nucleotide sequence of the DNA; it is expressed through that sequence as it specifies the amino acid sequences of proteins. The unity of all living things is beautifully demonstrated by the fact that the code relating nucleotide sequences in the nucleus to amino acid sequences is the same in all organisms: in bacteria, in plants, in animals, in human beings.

Within the last ten years geneticists have discovered tools that allow them to recreate, in the laboratory, steps in the evolution of organisms. Indeed, these tools provide the means to perform experiments that nature alone is incapable of performing. With the techniques of recombinant DNA research, geneticists have learned how to transplant genes from one organism to another, thus reshuffling the genetic materials in ways never before experienced in the evolution of life on earth. Such knowledge and our ability to apply it to new purposes have profound implications for all of biology. To "life as we know it" can now be added, to a small but significant degree, "life as we make it."

The purpose of this book is to present the science of genetics in such a way that you will appreciate its place in biology as well as the means by which we have arrived at our current state of knowledge. The genetic material, DNA, has three major features: organization, expression, and evolution. This book is organized in three parts that correspond to these three features. Part I presents the nature and organization of the hereditary materials, as well as the laws by which the information contained in these materials is transmitted from generation to generation. Part II explains how the genetic information inherited by an organism directs the organism's development and activities. Part III discusses the origin of genetic variation and the genetic basis of biological evolution.

This introductory chapter reviews some knowledge that you are assumed to have acquired in introductory biology courses. First, the various kinds of organisms are briefly considered. Then mitosis and meiosis—the two processes by which eukaryotic cells divide—are reviewed.

Viruses

The smallest things that can be considered to be living are the viruses, which are familiar as the agents responsible for diseases such as the common cold, poliomyelitis, and meningitis. Viruses were discovered in the late nineteenth century, when it was shown that some diseases (such as the mosaic disease of tobacco plants) could be transmitted by self-reproducing bodies so small that they passed through the pores of filters that retain bacteria. Viruses are obligatory parasites (i.e., they cannot multiply alone) of animals, plants, and microorganisms, in which they subvert the machinery of the host cell into synthesizing new virus materials. In spite of this and other peculiarities (e.g., they can be crystallized and are unable to carry out their own metabolism), viruses are generally considered to be organisms because they are capable of self-reproduction.

Viruses vary in composition, shape, and size (see Figure 1.1). In 1935 Wendell M. Stanley (1904–1971) discovered that viruses are made up of nucleic acid and protein, the principal constituents of the chromosomes of higher organisms. Some (mainly plant viruses) contain ribonucleic acid (RNA); others (including many bacterial and animal viruses) contain deoxyribonucleic acid (DNA). They may be spherical, be rod-shaped, or consist of a "head" and a "tail." The virus of hoof-and-mouth disease is a sphere with a diameter of about 10 nm (1 nm = 10^{-6} mm). The tobacco mosaic virus is a rod some 15 nm in diameter and 300 nm long.

The viruses most widely used in genetic studies are bacterial vi-