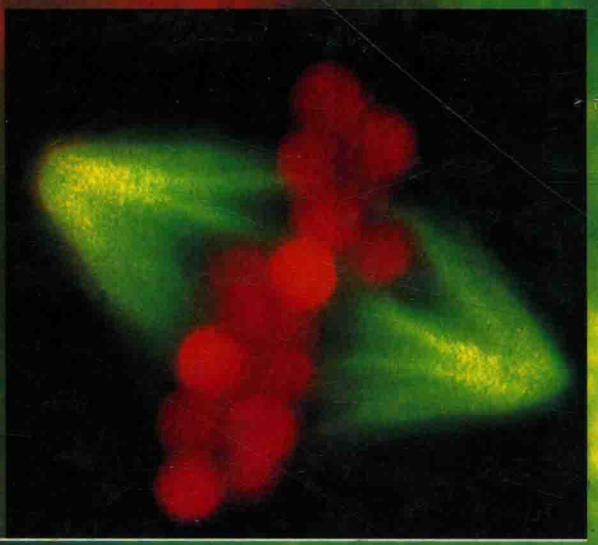
Cell and Molecular Biology

Concepts and Experiments

2nd Edition



Gerald Karp

CELL AND MOLECULAR BIOLOGY

CONCEPTS AND EXPERIMENTS

Second Edition

Gerald Karp

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NOBEL PRIZES AWARDED FOR RESEARCH IN CELL AND MOLECULAR BIOLOGY SINCE 1958

Year	*Recipient**	*Prize*	*Area of Research*	*Pages in Text*
1997	Rolf M. Zinkernagel Peter C. Doherty	M & P**	Recognition of virus-infected cells by the immune system	761
1996	Jens C. Skou	Chemistry	Na^+/K^+-ATPase	159
	Paul Boyer John Walker		Mechanism of ATP synthesis	204
	Stanley B. Prusiner	M & P	Protein structure of prions	22
1995	Edward B. Lewis Christiane Nüsslein-Volhard Eric Wieschaus	M & P	Genetic control of embryonic development	565
1994	Alfred Gilman Martin Rodbell	M & P	Structure and Function of GTP-binding (G) proteins	691
1993	Richard Roberts Phillip Sharp	M & P	Split genes and RNA processing	476
1993	Kary Mullis	Chemistry	Polymerase chain reaction (PCR)	811
	Michael Smith		Site-directed mutagenesis (SDM)	807
1992	Edmond Fischer Edwin Krebs	M & P	Alteration of enzyme activity by phosphorylation/dephosphorylation	112, 656
1991	Erwin Neher Bert Sakmann	M & P	Measurement of ion flux by patch-clamp recording	154
1989	J. Michael Bishop Harold Varmus	M & P	Cellular genes capable of causing malignant transformation	727
	Thomas R. Cech Sidney Altman	Chemistry	Ability of RNA to catalyze reactions	506
1988	Johann Deisenhofer Robert Huber Hartmut Michel	Chemistry	Bacterial photosynthetic reaction center	232
1987	Susumu Tonegawa	M & P	DNA rearrangements responsible for antibody diversity	746
1986	Rita Levi-Montalcini Stanley Cohen	M & P	Factors that affect nerve outgrowth	402
1985	Michael S. Brown Joseph L. Goldstein	M & P	Regulation of cholesterol metabolism and endocytosis	338
1984	George Köhler Cesar Milstein	M & P	Monoclonal antibodies	814
	Niels K. Jerne		Antibody formation	737
1983	Barbara McClintock	M & P	Mobile elements in the genome	440
1982	Aaron Klug	Chemistry	Structure of nucleic acid-protein complexes	71
1980	Paul Berg	Chemistry	Recombinant DNA technology	800
	Walter Gilbert Frederick Sanger		DNA sequencing technology	812
	Baruj Bennacerraf Jean Dausset George D. Snell	M & P	Major histocompatibility complex	750
1978	Werner Arber Daniel Nathans Hamilton Smith	M & P	Restriction endonuclease technology	444
	Peter Mitchell	Chemistry	Chemiosmotic mechanism of oxidative phosphorylation	215

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1976	D. Carleton Gajdusek	M & P	Prion-based diseases	22
1975	David Baltimore Renato Dulbecco Howard M. Temin	M & P	Reverse transcriptase and tumor virus activity	726
1974	Albert Claude Christian de Duve George E. Palade	M & P	Structure and function of internal components of cells	295
1972	Gerald Edelman Rodney R. Porter	M & P	Immunoglobulin structure	743
	Christian B. Anfinsen	Chemistry	Relationship between primary and tertiary structure of proteins	65
1971	Earl W. Sutherland	M & P	Mechanism of hormone action and cyclic AMP	658
1970	Bernard Katz Ulf S. von Euler	M & P	Nerve impulse propagation and transmission	168
	Luis F. Leloir	Chemistry	Role of sugar nucleotides in carbohydrate synthesis	308
1969	Max Delbrück Alfred D. Hershey Salvador E. Luria	M & P	Genetic structure of viruses	18, 451
1968	H. Gobind Khorana Marshall W. Nirenberg	M & P	Genetic code	493
	Robert W. Holley		Transfer RNA structure	495
1966	Peyton Rous	M & P	Tumor viruses	725
1965	Francois Jacob Andre M. Lwoff Jacques L. Monod	M & P	Bacterial operons and messenger RNA	538, 472
1964	Dorothy C. Hodgkin	Chemistry	Structure of complex organic molecules	795
1963	John C. Eccles Alan L. Hodgkin Andrew F. Huxley	M & P	Ionic basis of nerve membrane potentials	165
1962	Francis H. C. Crick James D. Watson Maurice H. F. Wilkins	M & P	Three-dimensional structure of DNA	423
	John C. Kendrew Max F. Perutz	Chemistry	Three-dimensional structure of globular proteins	60
1961	Melvin Calvin	Chemistry	Biochemistry of CO_2 assimilation during photosynthesis	239
1960	F. MacFarlane Burnet Peter B. Medawar	M & P	Clonal selection theory of antibody formation	737
1959	Arthur Kornberg Severo Ochoa	M & P	Synthesis of DNA and RNA	581, 461
1958	George W. Beadle Joshua Lederberg Edward L. Tatum	M & P	Gene expression	458
	Frederick Sanger	Chemistry	Primary structure of proteins	56

* In a few cases, corecipients whose research was in an area outside of cell and molecular biology have been omitted from this list.

** Medicine and Physiology

CELL AND MOLECULAR BIOLOGY

Second Edition

Dedication

To Patsy and Jenny

About the Author

Gerald C. Karp received a bachelor's degree from UCLA and a Ph.D. from the University of Washington. He conducted postdoctoral research at the University of Colorado Medical Center before joining the faculty at the University of Florida. Karp is the author of numerous research articles on the cell and molecular biology of early development. His interests have included the synthesis of RNA in early embryos, the movement of mesenchyme cells during gastrulation, and cell determination in slime molds. For 13 years, he taught courses in molecular, cellular, and developmental biology at the University of Florida. During this period, Gerry coauthored a text in developmental biology with N. John Berrill and authored a text in cell and molecular biology. Finding it impossible to carry on life as both full-time professor and author, Gerry gave up his faculty position to concentrate on writing. Between the years spent at the library and computer, he has continued to work in the laboratories of friends and colleagues.

ABOUT THE COVER

The cover of this text displays a brightly stained mitotic spindle, the molecular machine that separates duplicated chromosomes during cell division. The mitotic spindle depicted in the photograph did not take shape inside a living, dividing cell, as is normally the case. Instead, it assembled in a test tube containing a high concentration of spindle protein. Cell and molecular biologists have discovered that many complex cellular activities, including spindle formation, can occur outside of an intact cell, making these processes more accessible to experimental investigation. In fact, the micrograph displayed on the cover sheds light on an important issue in cell biology: the role of the chromosomes in spindle formation. The red spherical objects in the center of the spindle are not chromosomes, but magnetic beads covered by a DNA-protein complex. It is evident from this experiment that a mitotic spindle of normal appearance can assemble in the absence of normal chromosomes (discussed further on pp. 626–627).

Preface for the Second Edition

Before I began work on the first edition of this text, I drew up a number of basic guidelines regarding the type of book I planned to write.

- I wanted a text suited for a course that ran either a single semester or 1–2 quarters that would be taken in the sophomore or junior year. I set out to draft a text of about 800 pages that would not overwhelm or discourage students at this level.
- I wanted a text that elaborated on fundamental concepts, such as the relationship between molecular structure and function, the dynamic character of cellular organelles, the use of chemical energy in running cellular activities and ensuring accurate macromolecular biosynthesis, unity and diversity at the macromolecular and cellular levels, and the mechanisms that regulate cellular activities.
- I wanted a text that was grounded in the experimental approach. Cell and molecular biology is an experimental science and, like most instructors, I believe students should gain some knowledge of how we know what we know. With this in mind, I decided to approach the experimental nature of the subject in two ways. As I wrote each chapter, I included enough experimental evidence to justify many of the conclusions that were being made. Along the way, I described the salient features of key experimental techniques and referred the reader to a more detailed discussion in the last chapter on methodologies. Chapters 8 and 9, for example, contain introductory sections on techniques that have proven most important in the analysis of cytomembranes and the cytoskeleton, respectively. I included brief discussions of selected experiments in the body of the chapters to reinforce the experimental basis of our knowledge.

  For students and instructors that wanted to explore the experimental approach in greater depth, I included the Experimental Pathways, at the end of each chapter. Each of these narratives describes some of the key experimental findings that have led to our current understanding of a particular subject that is relevant to the chapter at hand. Because the scope of the narrative is limited, the design of the experiments can be considered in some detail. The figures and tables provided in these sections are often those that appeared in the original research article, which provides the reader an opportunity to examine original data and to realize that its analysis is not beyond their means. The Experimental Pathways also illustrate the stepwise nature of scientific discovery, showing how the result of one study raises questions that provide the basis for subsequent studies.
- I wanted a text that was interesting and readable. To make the text more relevant to undergraduate readers, particularly premedical students, I included The Human Perspective. These sections illustrate that virtually all human disorders can be traced to disruption of activities at the cellular and molecular level. Furthermore, they reveal the importance of basic research as the pathway to understanding and eventually treating most disorders. In Chapter 11, for example, The Human Perspective describes how ribozymes may prove to be an important new tool in the treatment of cancer and viral diseases, including AIDS. In this same chapter, the reader will learn how ribozymes were first discovered in studies on the processing of ribosomal RNA in a protozoan. It becomes evident that one can never predict the practical importance of basic research in cell and molecular biology.
- I wanted a high-quality illustration program that helped students visualize complex cellular and molecular processes. To meet this goal, many of the illustrations have been "stepped-out" so that information can be more easily broken down into manageable parts. Events occurring at each step are described in the figure legend and/or in the corresponding text. I also sought to include a large number of micrographs to enable students to see actual representations of most subjects being discussed. Included among the photographs are many fluorescence micrographs that illustrate either the dynamic properties of cells or provide a means to localize a specific protein or nucleic acid sequence. Wherever possible, I have tried to pair line-art drawings with micrographs to help students compare idealized and actual versions of a structure.

I have been gratified by the mail I have received from teachers and students containing both praise and criticism of the first edition. These communications, together with the numerous fine reviews of the current manuscript, have guided the preparation of the second edition. The most important changes in the second edition can be delineated as follows.

- Many cell and molecular biology courses include some coverage of immunology. To accommodate these instructors, a chapter on immune responses has been added.
- Several of the Experimental Pathways were considered by many as too lengthy and complex. In response, I have shortened and simplified these sections of the text. New Experimental Pathways on the evolution of eukaryotic cells and on protein chaperones have replaced those of Chapters 1 and 2 of the first edition. Experimental Pathways have been updated where appropriate.
- Instructors reported that their students responded very positively to The Human Perspective. I have included additional Human Perspectives on mad cow disease, mitochondrial and peroxisomal diseases, muscular dystrophy, trinucleotide expansion diseases, and antisense oligonucleotides.
- The illustration program received high marks and I have continued with the same approach in the second edition. Now that line-art illustrations are drawn by computer and stored electronically, they are much easier to render and modify than in earlier days. Every single illustration in the first edition has been scrutinized and many of those that were reused in the second edition have been modified to some extent. In addition, many of the drawings from the first edition have been deleted to make room for approximately 130 new pieces. Instructors have responded positively to the use of "stepped-out" illustrations, and many of the new illustrations also follow this model. Instructors also like figures that juxtapose line art and micrographs, and this style of illustration has been expanded in the second edition. Altogether, the second edition contains approximately 95 new micrographs and computer-derived images. In addition, labels have been added to many of the micrographs picked up from the first edition.
- Most chapters now contain an overview figure, i.e., a drawing designed to provide students with the "big picture" before they read about the topic in depth. Examples of new overview drawings can be found in Figures 2.11, 7.1, 9.1, 10.1, and 17.2. Examples of overview drawings that have been picked up from the first edition include Figures 1.9, 4.2, 5.5, 6.4, 8.2, 11.3, 12.29, 14.1, and 15.1.
- The writing style of the first edition was generally well received, but a number of reviewers called attention to the inclusion of superfluous words and phrases that produced unnecessarily complex or ambiguous sentences. With the help of a couple of key reviewers, I have made a concerted effort to simplify sentences and reduce verbiage.
- The body of information in cell and molecular biology is continually changing, which provides much of the excitement we all feel about our selected field. Even though only three years have passed since the publication of the first edition, nearly every discussion in the text has been modified to a greater or lesser degree. This has been done without allowing the chapters to increase in length. The content of the text has been updated through the first few months of 1998.

SUPPLEMENTS

Problems Book and Study Guide, by Nancy Pruitt, Colgate University (0-471-29852-2) This Study Guide is designed to help students focus on concepts by providing learning objectives, a list of key terms and phrases, and a brief outline for each chapter. Extensive review questions and analytical problems (with stepped-out solutions) are also included. In addition, students are asked to answer questions about a key figure from each chapter of the text.

Cellview Student CD, developed by Donald Keefer, Loyola College (0-471-32617-8) Interactive CD which provides stepped-out animations of fundamental concepts and links to relevant Study Guide material.

Instructor's Manual, by Joel Piperberg, Millersville University (available on CD-ROM) Includes lecture outlines, key learning objectives, lecture hints, and a comprehensive selection of sample test questions.

CD Resource Manager (0-471-32322-5) Includes Instructor's Manual and key images from the text for use in lecture presentations. This Resource Manager now includes micrographs and illustrations that can be exported to PowerPoint.

Transparencies (0-471-32463-9) Full-color acetates of key illustrations are included. The images have been enlarged and fonts bolded for better projection.

Take Note! (0-471-33031-0) A spiral bound notebook which contains noteworthy figures from the text, allowing students to take notes directly on the page during class or lecture.

Web Site (www.wiley.com/college/karp) Links the chapters of the text to the resources of the world wide web.

Laboratory Investigations in Cell and Molecular Biology, by Allyn Bregmen, SUNY New Paltz (0-471-51155) Contains 21 investigations of major topics in cell and molecular biology.

To the Student

At the time I began college, biology would have been at the bottom of a list of potential majors. I enrolled in a physical anthropology course to fulfill the life science requirement by the easiest possible route. During that course, I learned for the first time about chromosomes, mitosis, and genetic recombination, and I became fascinated by the intricate activities that could take place in such a small volume of cellular space. The next semester, I took Introductory Biology and began to seriously consider becoming a cell biologist. I am burdening you with this personal trivia so you will understand why I wrote this book and to warn you of possible repercussions.

Even though many years have passed, I still find cell biology the most fascinating subject to explore, and I still love spending the day reading about the latest findings by colleagues in the field. Thus, for me, writing a text in cell biology provides a reason and an opportunity to keep abreast with what is going on throughout the field. My primary goal in writing this text is to help generate an appreciation in students for the activities in which the giant molecules and minuscule structures that inhabit the cellular world of life are engaged. Another goal is to provide the reader with an insight into the types of questions that cell and molecular biologists ask and the experimental approaches they use to seek answers. As you read the text, think like a researcher; consider the evidence that is presented, think of alternate explanations, plan experiments that could lead to new hypotheses.

You might begin this approach by looking at one of the many electron micrographs that fill the pages of this text. To take this photograph, you would be sitting in a small, pitch-black room in front of a large metallic instrument whose column rises several meters above your head. You are looking through a pair of binoculars at a vivid, bright green screen. The parts of the cell you are examining appear dark and colorless against the bright green background. They are dark because they've been stained with heavy metal atoms that deflect a fraction of the electrons within a beam that is being focused on the viewing screen by large electromagnetic lenses in the wall of the column. The electrons that strike the screen are accelerated through the evacuated space of the column by a force of tens of thousands of volts. One of your hands may be gripping a knob that controls the magnifying power of the lenses. A simple turn of this knob can switch the image in front of your eyes from that of a whole field of cells to a tiny part of a cell, such as a few ribosomes or a small portion of a single membrane. By turning other knobs, you can watch different parts of the specimen glide across the screen, giving you the sensation that you're driving around inside a cell. Once you have found a structure of interest, you can turn a handle that lifts the screen out of view, allowing the electron beam to strike a piece of film and produce a photographic image of the specimen.

Since the study of cell function generally requires the use of considerable instrumentation, the investigator is physically removed from the subject being studied. To a large degree, cells are like tiny black boxes. We have developed many ways to probe the boxes, but we are always groping in an area that cannot be fully illuminated. A discovery is made or a new technique is developed and a new thin beam of light penetrates the box. With further work, our understanding of the structure or process is broadened, but we are always left with additional questions. We generate more complete and sophisticated constructions, but we can never be sure how closely our views approach reality. In this regard, the study of cell and molecular biology can be compared to the study of an elephant as conducted by six blind men in an old Indian fable. The six travel to a nearby palace to learn about the nature of elephants. When they arrive, each approaches the elephant and begins to touch it. The first blind man touches the side of the elephant and concludes that an elephant is smooth like a wall. The second touches the trunk and decides that an elephant is round like a snake. The other members of the group touch the tusk, leg, ear, and tail of the elephant, and each forms his impression of the animal based on his own limited experiences. Cell biologists are limited in a similar manner to what they can learn by using a particular technique or experimental approach. Although each new piece of information adds to the preexisting body of knowledge to provide a better concept of the activity being studied, the total picture remains uncertain.

Before closing these introductory comments, let me take the liberty of offering the reader some advice: Don't accept everything you read as being true. There are several reasons for urging such skepticism. Undoubtedly, there are errors in this text that reflect the author's ignorance or misinterpretation of some aspect of the scientific literature. But, more importantly, we should consider the nature of biological research.

Biology is an empirical science; nothing is ever *proved.* We compile data concerning a particular cell organelle, metabolic reaction, intracellular movement, etc., and draw some type of conclusion. Even if there is a consensus of agreement concerning the "facts" regarding a particular phenomenon, there are often several possible interpretations of the data. Hypotheses are put forth and generally stimulate further research, thereby leading to a reevaluation of the original proposal. A theory is constructed in terms of the concepts and prevailing perspectives of the time. As new techniques and information become available, new insights are made. Most hypotheses that remain valid undergo a sort of evolution and, when presented in the text, should not be considered wholly correct or incorrect. Remain skeptical.

Acknowledgments

Many people contributed to the development of this book. David Harris, the biology editor at John Wiley & Sons, has provided unwavering support for this project. His unbounded optimism has kept my spirits high and his sound judgement has helped me focus on the important issues. Thanks, David, for your help and advice. I am also indebted to Barbara Russiello, production editor for the book. Always calm and organized, Barbara skillfully coordinated the activities of a host of different people and cheerfully incorporated the many requests from a pestering author. I could always count on Barbara to do it right. Hilary Newman and Edward Starr played very important roles in the preparation of this book. Hilary was responsible for the photo program and Edward for the line art program. After working with both of them on the first edition, I can rest assured that each and every part of every figure will be in its correct place, with the correct labels, and the correct legend. Thanks also to Harry Nolan for the elegant design of the text and its cover; to Catherine Beckham, who has worked so conscientiously as marketing manager; and to Jennifer Yee, who has developed the supplements. A special thanks to Catherine Donovan, editorial assistant, who is always there when something needs to get done immediately.

All of the new art for the second edition, and all of the modifications to first-edition illustrations, were executed by a highly creative and talented artist, Michelle North-Klug. Time was short and the job was long, yet Michelle met every deadline. Thanks for working so hard and taking the work so much to heart. I would also like to express my gratitude to Professors David Bruck, Thomas Chiles, and Robert Leamnson, who spent so much time and effort to improve the quality of the manuscript. Your help was very much appreciated. Thanks also to Professor David Asai for his many valuable comments and, together with Professsor Ken Robinson, for providing a number of interesting analytic questions in Chapters 2–5. I would also like to thank Cathy Lundmark, a biologist who copy edited the manuscript and greatly improved its quality. Thanks also to Gloria Hamilton, who prepared a superb index; to Laura Ierardi, who laid out the pages; and to Dr. Elizabeth Coolidge-Stolz, who wrote the glossary.

I am especially grateful to the many biologists who have contributed micrographs for use in this book; more than any other element it is these images that bring the study of cell biology to life on a printed page. Finally, I would like to apologize, in advance, for any errors that may occur in the text, and express my heartfelt embarassment. Any comments or criticisms from readers would be greatly appreciated. They can be directed to: Biology Editor, John Wiley & Sons, 605 Third Avenue, New York, NY 10158 or e-mail gkarp@wiley.com.

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