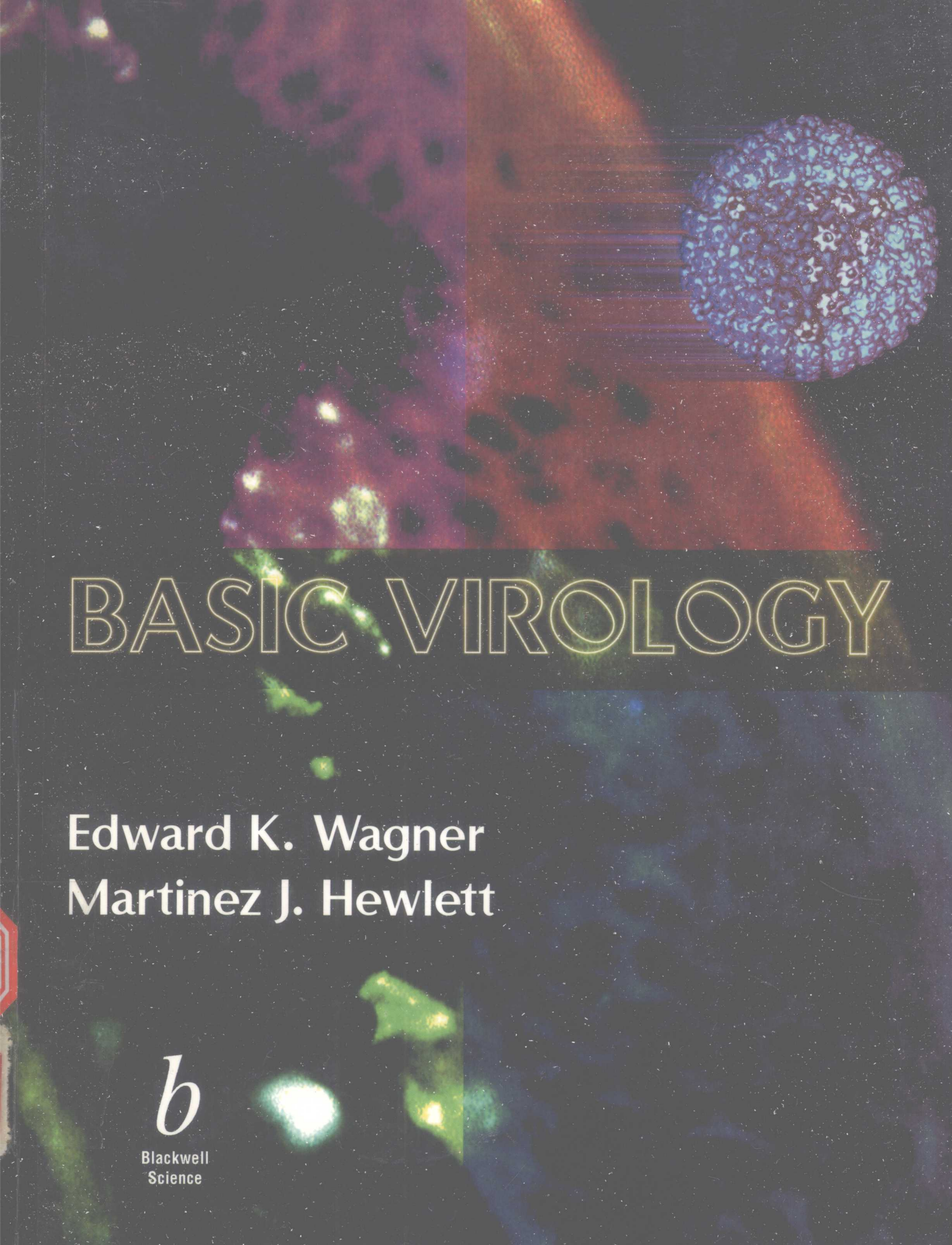

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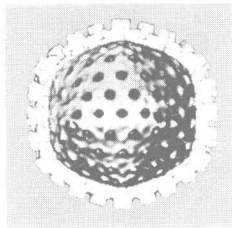

BASIC VIROLOGY

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Blackwell Wissenschafts-Verlag GmbH, Kurfürstendamm 57, 10707 Berlin, Germany
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DISTRIBUTORS:

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Acquisitions: Nancy Hill-Whilton
Development: Jill Connor
Production: Irene Herlihy
Manufacturing: Lisa Flanagan
Cover and interior design: Leslie Haimes
Illustrations: Karin Christensen
Typeset by: Best-set Typesetter Ltd., Hong Kong
Printed and bound by: Edwards Brothers, Inc.

Printed in the United States of America
00 01 02 5 4 3 2

Library of Congress Cataloging-in-Publication Data
Wagner, Edward K.
Basic virology / by Edward K. Wagner and Martinez J. Hewlett.
p. cm.
Includes bibliographical references and index.
ISBN 0-632-04299-0
1. Viruses. 2. Virus diseases. 3. Virology. 4. Medical virology. I. Hewlett, Martinez. II. Title.
QR360.W26 1999
579.2—dc21

99-21382
CIP

Preface

This book is based on more than 40 years in aggregate of undergraduate lectures on virology commencing in 1970 given by the coauthors at the University of California, Irvine (UCI) and the University of Arizona. The field of virology has matured and grown immensely during this time, but one of the major joys of teaching this subject continues to be the solid foundation it provides in topics running the gamut of the biological sciences. Concepts range from population dynamics and population ecology, through evolutionary biology and theory, to the most fundamental and detailed analyses of the biochemistry and molecular biology of gene expression and biological structures. Thus, teaching virology has been a learning tool for us as much, or more, than it has been for our students.

Our courses are consistently heavily subscribed, and we credit that to the subject material, certainly not to any special performance tricks or instructional techniques. Participants have been mainly premedical students, but we have enjoyed the presence of other students bound for postgraduate studies, as well as a good number of those who are just trying to get their degree and get out of the "mill" and into the "grind."

At UCI, in particular, the course has had a tremendous enrollment (approximately 250 students per year) in the past 5 to 8 years, and it has become very clear that the material is very challenging for a sizable minority studying it. This is good. There is a lot of material to master, and mastery requires a solid working knowledge of basic biology. To help students acquire such working knowledge, we have encouraged further reading. We have also included a good deal of reinforcement material to help students learn the basic skills of molecular biology and rudimentary aspects of immunology, pathology, and disease. Further, we have incorporated numerous study and discussion questions at the end of chapters and sections to aid in discussion of salient points.

It is our hope that this book will serve as a useful text and source for many undergraduates interested in acquiring a solid foundation in virology and its relationship to modern biology. It is also hoped that the book may be of use to more advanced workers who want to make a quick foray into virology but who do not want to wade through the details present in more advanced works.

TEXT ORGANIZATION

Virology is a huge subject, and can be studied from many points of view. We believe that coverage from the most general aspects to more specific examples with corresponding details is a logical way to present an overview, and we have organized this text accordingly. Many of our students are eagerly pursuing careers in medicine and related areas, and our organization has the added advantage that their major interests are addressed at the outset. Further development of material is intended to encourage the start of a sophisticated understanding of the biological basis of medical problems, and to introduce sophistication as general mastery matures. We are fully aware that the organization reflects our prejudices and backgrounds as molecular biologists, but hopefully it will not deter those with a more population-based bias from finding some value in the material.

Following this plan, the book is divided into four sections, each discussing aspects of virology in greater molecular detail. General principles such as approaches toward understanding viral disease and its spread, the nature of viral pathogenesis, and the mechanistic basis for these principles are repeatedly refined and applied to more detailed examples as the book unfolds.

Part I covers the interactions between viruses and populations and the impact of viral disease and its study on our ever-expanding understanding of the molecular details behind the biological behavior of populations. A very basic discussion of theories of viral origins is presented, but not stressed. This was an editorial decision based on our opinion that a satisfactory molecular understanding of the relationship between biological entities will require an appreciation and mastery of the masses of comparative sequence data being generated now and into the next several decades.

The major material covered in this introductory section is concerned with presenting a generally consistent and experimentally defensible picture of viral pathogenesis and how this relates to specific viral diseases—especially human disease. The use of animal models for the study of disease, which is a requisite for any careful analysis, is presented in terms of several well-established systems that provide general approaches applicable to any disease. Finally, the section concludes with a description of some important viral diseases organized by organ system affected.

Part II introduces experimental studies of how viruses interact with their hosts. It begins with some basic descriptions of the structural and molecular basis of virus classification schemes. While such schemes and studies of virus structure are important aspects of virology, we have not gone into much detail in our discussion. We believe that such structural studies are best covered in detail after a basic understanding of virus replication and infection is mastered; then further detailed study of any one virus or virus group can be digested in the context of the complete picture. Accordingly, more detailed descriptions of some virus structures are covered in later chapters in the context of the techniques they illustrate.

This elementary excursion into structural virology is followed by an in-depth general discussion of the basic principles of how viruses recognize and enter cells and how they assemble and exit the infected cell. This chapter includes an introduction to the interaction between animal and bacterial viruses and the cellular receptors that they utilize in entry. It concludes with a description of virus maturation and egress. While it can be argued that these two aspects of virus infection are the "soup and nuts" of the process and do not belong together, we would argue that many of the same basic principles and approaches for the study of the one are utilized in understanding the other. Further, by having the beginnings and ends of infection in one integrated unit, the student can readily begin to picture the fact that virus infection cannot take place without the cell, and that the cell is a vital part of the process from beginning to end.

Part II concludes with two chapters describing how the host responds to viral infections. The first of these chapters is a basic outline of the vertebrate immune response. We believe that any understanding of virus replication must be based on the realization that virus replication in its host evokes a large number of complex and highly evolved responses. It just makes no sense to attempt to teach virology without making sure that students understand this fact. While the immune system is (to a large degree) a vertebrate response to viral infection, understanding it is vital to understanding the experimental basis of much of what we

know of disease and the effects of viral infections on cells. The last chapter in this section deals with the use of immunity and other tools in combating viral infection. While "natural" cell-based defenses such as interferon responses and restriction endonucleases are described, the emphasis is on the understanding of virus replication and host responses in countering and preventing virus-induced disease. It seems logical to conclude this section with a description of vaccines and antiviral drug therapy since these, too, are important host responses to virus infection and disease.

Experimental descriptions of some of the tools scientists use to study virus infections, and the basic molecular biological and genetic principles underlying these tools are described in **Part III**. We emphasize the quantitative nature of many of these tools, and the use that such quantitative information can be put to. This organization ensures that a student who is willing to keep current with the material covered in preceding chapters will be able to visualize the use of these tools against a background understanding of some basic concepts of pathology and disease.

The section begins with the use of the electron microscope in the study of virus infection and virus structure, and, perhaps as importantly, in counting viruses. While some of our colleagues would argue that such material is "old-fashioned" and detracts from discussion of modern methodology, we would argue that the fundamental quantitative nature of virology really requires a full understanding of the experimental basis of such quantitation. Accordingly, we have included a fairly complete description of virus assay techniques, and the statistical interpretation of such information. This includes a fairly thorough discussion of cell culture technology and the nature of cultured cells.

The next two chapters introduce a number of experimental methods for the study and analysis of virus infection and viral properties. Again, while we attempt to bring in important modern technology, we base much of our description on the understanding of some of the most basic methods in molecular biology and biochemistry. These include the use of differential centrifugation, incorporation of radioactive tracers into viral products, and the use of immune reagents in detecting and characterizing viral products in the infected cell. We have also included basic descriptions of the methodology of cloning recombinant DNA and sequencing viral genomes. We are well aware that there are now multitudes of novel technical approaches, many using solid-state devices, but all such devices and approaches are based on fundamental experimental principles and are best understood by a description of the original technology developed to exploit them.

Since virology can only be understood in the context of molecular processes occurring inside the cell, we include in Part III a chapter describing (essentially reviewing) the molecular biology of cellular gene expression and protein synthesis. Part III concludes with a brief overview of some of the principles of molecular and classic genetics that have special application to the study of viruses. The basic processes of using genetics to characterize important mutations and to produce recombinant genomes are an appropriate ending point for our general description of the basics of virology.

Part IV, which essentially comprises the book's second half, deals with the replication processes of individual groups of viruses. We emphasize the replication strategies of viruses infecting vertebrate hosts, but include discussions of some important bacterial and plant viruses to provide scope. The presentation is roughly organized according to increasing complexity of viral gene expression mechanisms. Thus, it follows a modified "Baltimore"-type

classification. The expression of viral proteins is implicitly taken as the fundamental step in virus gene expression, and accordingly, those viruses that do not need to transcribe their genomes prior to translation of viral proteins (the "simple" positive-sense RNA viruses) are described first.

The description of viruses that use RNA genomes but that must transcribe this RNA into messenger RNA (mRNA) prior to viral gene expression follows. We logically include the replication of viruses using double-stranded RNA and "subviral" pathogens in this chapter. Somewhat less logically, we include a short discussion of the nature of prions here. This is not because we wish to imply that these pathogens utilize an RNA genome (they almost certainly do not), but rather because the techniques for their study are based in the virologist's "tool kit." Also, the problems engendered by prion pathogenesis are similar in scope and potential for future concern to those posed by numerous "true" viruses.

Organization of DNA viruses generally follows the complexity of encoded genetic information, which is roughly inversely proportional to the amount of unmodified cellular processes utilized in gene expression. According to this scheme, the poxviruses and the large DNA-containing bacteriophages rather naturally fall into a single group, as all require the expression of their own or highly modified transcription machinery in the infected cell.

We complete the description of virus replication strategies with two chapters covering retroviruses and their relatives. We depart from a more usual practice of placing a discussion of retrovirus replication as a "bridge" between discussions of replication strategies of viruses with RNA or DNA genomes, respectively, for a very good reason. We believe that the subtle manner by which retroviruses utilize cellular transcription and other unique aspects in their mode of replication is best understood by beginning students in the context of a solid background of DNA-mediated gene expression illustrated by DNA viruses. Further, while arguments can be made for covering the lentiviruses (such as HIV) in a separate chapter, it seems more logical to include them with the other retroviruses, to contrast and compare their similarities and differences.

The final chapter in this section is included for balance and closure. Clearly, some of the students taking this course will be continuing their studies in much greater depth, but many students may not. It is important to try to remind both groups of the general lessons that can be learned and (perhaps) remembered by their first (and possibly only) excursion into virology.

SPECIFIC FEATURES OF THIS TEXT DESIGNED TO AID INSTRUCTORS AND STUDENTS IN PURSUING TOPICS IN GREATER DEPTH

Depth of coverage

This book is intended as a basic text for a course that can be covered fully in a single semester. Clearly, the coverage is not deep, nor is such depth necessary for such an introduction. While the first solid virology text emphasizing molecular biology, *General Virology* by S. E. Luria and (later) by J. E. Darnell, was only about half the length of this present text, it covered much of what was known in virology to a high level of completion. The present wealth of our detailed mechanistic knowledge of biological processes (one of the glories of modern biology) cannot

be condensed in any meaningful way. More detailed information on individual virus groups or topics covered in this text can be found in their own dedicated books. For similar reasons, we have generally eschewed citing contributions by individual scientists by name. This is certainly not to denigrate such contributions, but is in recognition of the fact that a listing of the names and efforts of all who have participated in the discoveries leading to modern molecular biology and medicine would fill several books the size of this one.

Sources for further study

We have provided the means of increasing the depth of coverage so that instructors or students can pursue their own specific interests in two ways. First, we suggest appropriate further reading at the end of each section. Second, we include a rather extensive survey of sources on virology and the techniques for the study of viruses in an appendix following the body of the text. We hope that these sources will be used because we are convinced that students must be presented with source material and encouraged to explore on their own at the start of this study. Mastery of the literature (if it is ever really possible) comes only by experience and ease of use of primary sources. This comes, in turn, by undergraduate, graduate, and postgraduate students assimilating the appreciation of those sources. Therefore, the detailed foundations of this very brief survey of the efforts of innumerable scientists and physicians carried out over a number of centuries are given the prominence they deserve.

The Internet

The Internet is providing a continually expanding source of up-to-date information concerning a vast number of topics. We have carried out an opinionated but reasonably thorough survey of Web sites that should be of use to both students and instructors in developing topics in-depth. This survey is included in the appendix. To maximize flexibility and timeliness of our coverage of individual viruses in Part IV, we include as many sites on the Web dedicated to specific viruses as we could locate that we found to be useful. One word of caution, however: While some Web sites are carefully reviewed, and frequently updated, others may not be. *Caveat emptor*!

Chapter outlines

We include an outline of the material covered in each section and each chapter at their respective beginnings. This is to provide a quick reference that students can skim and use for more detailed chapter study. These outlines also provide a ready list of the topics covered for the instructor.

Review material

Each chapter is followed with a series of relatively straightforward review questions. These are approximately the level and complexity that we use in our midterm and final exams. They should be of some value in discussion sections and informal meetings among groups of students and instructors. Rather more integrative questions are included at the end of each major section of the book. These are designed to be useful in integrating the various concepts covered in the individual chapters.

Glossary Because a major component of learning basic science is mastery of the vocabulary of science, we include a glossary of terms at the end of the text. Each term is highlighted at its first usage in the body of the text.

Acknowledgments

Even the most basic text cannot be solely the work of its author or authors; this is especially true for this one. We are extremely grateful to a large number of colleagues, students, and friends. They provided critical reading, essential information, experimental data, and figures, as well as other important help. This group includes the following scholars from other research centers: D. Bloom, Arizona State University; J. Brown, University of Virginia; J. Conway, National Institutes of Health; K. Fish and J. Nelson, Oregon Health Sciences University; D. W. Gibson, Johns Hopkins University; H. Granzow, Friedrich-Loeffler-Institute—Insel Riems; J. Hill, Louisiana State University Eye Center—New Orleans; J. Langland, Arizona State University; F. Murphy, University of California, Davis; S. Rice, University of Alberta–Edmonton; S. Silverstein, Columbia University; B. Sugden, University of Wisconsin; Gail Wertz, University of Alabama–Birmingham; and J. G. Stevens, University of California, Los Angeles. Colleagues at University of California, Irvine who provided aid include R. Davis, S. Larson, A. McPherson, T. Osborne, R. Sandri-Goldin, D. Senear, B. Semler, S. Stewart, W. E. Robinson, and L. Villarreal. Both current and former workers in Edward Wagner's laboratory did many experiments that aided in a number of illustrations; these people include J. S. Aguilar, K. Anderson, R. Costa, G. B. Devi-Rao, R. Frink, S. Goodart, J. Guzowski, P. Lieu, N. Pande, M. Petroski, M. Rice, J. Singh, and J. Stringer.

Many people contributed to the physical process of putting this book together. R. Spaete of the Aviron Corp carefully read every page of the manuscript and suggested many important minor and a couple of major changes. This was done purely in the spirit of friendship and collegiality. K. Christensen used her considerable expertise and incredible skill in working with us to generate the art. Not only did she do the drawings, but also she researched many of them to help provide missing details. Two undergraduates were invaluable to us. A. Azarian at University of California, Irvine made many useful suggestions on reading the manuscript from a student's perspective, and D. Natan, an MIT student who spent a summer in Edward Wagner's laboratory, did most of the Internet site searching, which was a great relief and time saver. Finally, J. Wagner carried out the very difficult task of copyediting the manuscript.

A number of people at Blackwell Science represented by Senior Acquisitions Editor N. Hill-Whilton demonstrated a commitment to a quality product. We especially thank J. Connor and I. Herlihy who made great efforts to maintain effective communications and to expedite many of the very tedious aspects of this project. Blackwell Science directly contacted a number of virologists who also read and suggested useful modifications to this manuscript: David C. Bloom, Arizona State University; Howard Ceri, University of Calgary; Steve Dewhurst, University of Rochester Medical Center; Susan Gdovin, University of Maryland; Donna Leombruno, Massachusetts Biologic Laboratories; Philip I. Marcus, University of Connecticut; G. F. Rohrmann, Oregon State University; Mark Stinski, University of Iowa; and Suresh Subramani, University of California, San Diego.

To Our Families and Students

Brief Contents

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