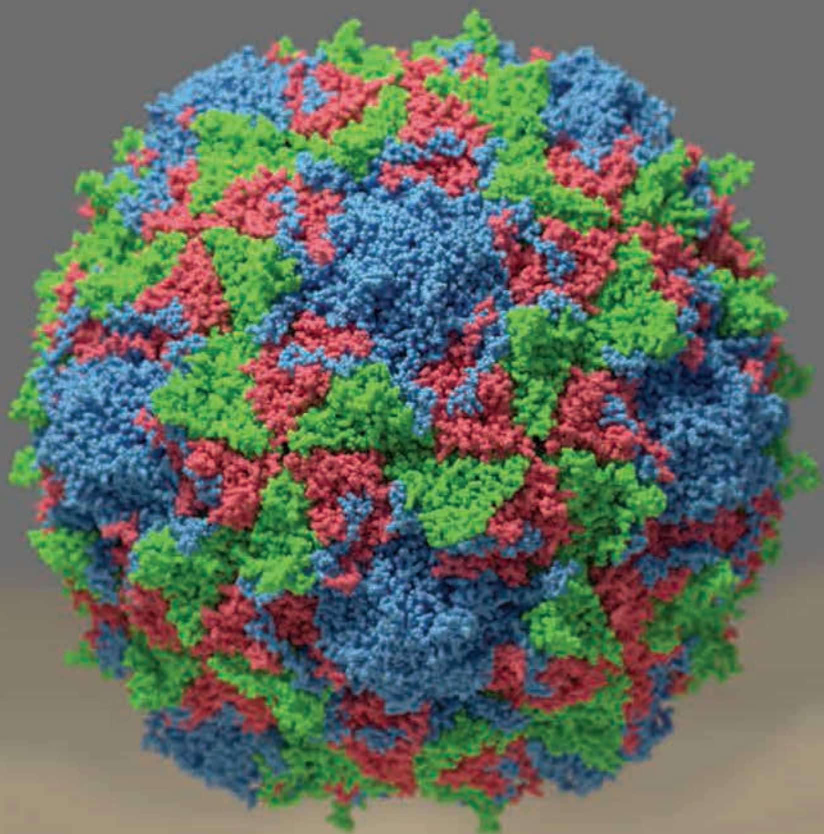
VOLUME I *Molecular Biology*

PRINCIPLES OF
Virology

4TH EDITION



JANE FLINT, VINCENT R. RACANIELLO,
GLENN F. RALL, AND ANNA MARIE SKALKA
WITH LYNN W. ENQUIST

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PRINCIPLES OF
Virology
4th Edition

VOLUME I *Molecular Biology*

PRINCIPLES OF Virology

4TH EDITION

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We dedicate this book to the students, current and future scientists, physicians, and all those with an interest in the field of virology, for whom it was written.
We kept them ever in mind.

We also dedicate it to our families:
Jonn, Gethyn, and Amy Leedham
Doris, Aidan, Devin, and Nadia
Eileen, Kelsey, and Abigail
Rudy, Jeanne, and Chris
And
Kathy and Brian

Oh, be wiser thou!
Instructed that true knowledge leads to love.
William Wordsworth
Lines left upon a Seat in a Yew-tree
1888

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Preface

The enduring goal of scientific endeavor, as of all human enterprise, I imagine, is to achieve an intelligible view of the universe. One of the great discoveries of modern science is that its goal cannot be achieved piecemeal, certainly not by the accumulation of facts. To understand a phenomenon is to understand a category of phenomena or it is nothing. Understanding is reached through creative acts.

A. D. HERSHEY
Carnegie Institution Yearbook 65

All four editions of this textbook have been written according to the authors' philosophy that the best approach to teaching introductory virology is by emphasizing shared principles. Studying the phases of the viral reproductive cycle, illustrated with a set of representative viruses, provides an overview of the steps required to maintain these infectious agents in nature. Such knowledge cannot be acquired by learning a collection of facts about individual viruses. Consequently, the major goal of this book is to define and illustrate the basic principles of animal virus biology.

In this information-rich age, the quantity of data describing any given virus can be overwhelming, if not indigestible, for student and expert alike. The urge to write more and more about less and less is the curse of reductionist science and the bane of those who write textbooks meant to be used by students. In the fourth edition, we continue to distill information with the intent of extracting essential principles, while providing descriptions of how the information was acquired. Boxes are used to emphasize major principles and to provide supplementary material of relevance, from explanations of terminology to descriptions of trail-blazing experiments. Our goal is to illuminate process and strategy as opposed to listing facts and figures. In an effort to make the book readable, rather than comprehensive, we are selective in our choice of viruses and examples. The encyclopedic *Fields Virology* (2013) is recommended as a resource for detailed reviews of specific virus families.

What's New

This edition is marked by a change in the author team. Our new member, Glenn Rall, has brought expertise in viral immunology and pathogenesis, pedagogical clarity, and down-to-earth humor to our work. Although no longer a coauthor, our colleague Lynn Enquist has continued to provide insight, advice, and comments on the chapters.

Each of the two volumes of the fourth edition has a unique appendix and a general glossary. Links to Internet resources such as websites, podcasts, blog posts, and movies are provided; the digital edition provides one-click access to these materials.

A major new feature of the fourth edition is the incorporation of in-depth video interviews with scientists who have made a major contribution to the subject of each chapter. Students will be interested in these conversations, which also explore the factors that motivated the scientists' interest in the field and the personal stories associated with their contributions.

Volume I covers the molecular biology of viral reproduction, and Volume II focuses on viral pathogenesis, control of virus infections, and virus evolution. The organization into two volumes follows a natural break in pedagogy and provides considerable flexibility and utility for students and teachers alike. The volumes can be used for two courses, or as two parts of a one-semester course. The two volumes differ in content but are integrated in style and presentation. In addition to updating the chapters and Appendices for both volumes, we have organized the material more efficiently and new chapters have been added.

As in our previous editions, we have tested ideas for inclusion in the text in our own classes. We have also received constructive comments and suggestions from other virology instructors and their students. Feedback from students was particularly useful in finding typographical errors, clarifying confusing or complicated illustrations, and pointing out inconsistencies in content.

For purposes of readability, references are generally omitted from the text, but each chapter ends with an updated list of relevant books, review articles, and selected research papers for readers who wish to pursue specific topics. In general, if an experiment is featured in a chapter, one or more references are listed to provide more detailed information.

Principles Taught in Two Distinct, but Integrated Volumes

These two volumes outline and illustrate the strategies by which all viruses reproduce, how infections spread within a host, and how they are maintained in populations. The principles of viral reproduction established in Volume I are essential for understanding the topics of viral disease, its control, and the evolution of viruses that are covered in Volume II.

Volume I The Science of Virology and the Molecular Biology of Viruses

This volume examines the molecular processes that take place in an infected host cell. It begins with a general introduction and historical perspectives, and includes descriptions of the unique properties of viruses (Chapter 1). The unifying principles that are the foundations of virology, including the concept of a common strategy for viral propagation, are then described. An introduction to cell biology, the principles of the infectious cycle, descriptions of the basic techniques for cultivating and assaying viruses, and the concept of the single-step growth cycle are presented in Chapter 2.

The fundamentals of viral genomes and genetics, and an overview of the surprisingly limited repertoire of viral strategies for genome replication and mRNA synthesis, are topics of Chapter 3. The architecture of extracellular virus particles in the context of providing both protection and delivery of the viral genome in a single vehicle are considered in Chapter 4. Chapters 5 through 13 address the broad spectrum of molecular processes that characterize the common steps of the reproductive cycle of viruses in a single cell, from decoding genetic information to genome replication and production of progeny virions. We describe how these common steps are accomplished in cells infected by diverse but representative viruses, while emphasizing common principles. Volume I concludes with a new chapter, "The Infected Cell," which presents an integrated description of cellular responses to illustrate the marked, and generally, irreversible, impact of virus infection on the host cell.

The appendix in Volume I provides concise illustrations of viral life cycles for members of the main virus families discussed in the text; five new families have been added in the fourth edition. It is intended to be a reference resource when reading individual chapters and a convenient visual means by which specific topics may be related to the overall infectious cycles of the selected viruses.

Volume II Pathogenesis, Control, and Evolution

This volume addresses the interplay between viruses and their host organisms. The first five chapters have been reorganized and rewritten to reflect our growing appreciation of the host immune response and how viruses cause disease. In Chapter 1 we introduce the discipline of epidemiology, provide historical examples of epidemics in history, and consider basic aspects that govern how the susceptibility of a population is controlled and measured. With an understanding of how viruses affect human populations, subsequent chapters focus on the impact of viral infections on hosts, tissues and individual cells. Physiological barriers to virus infections, and how viruses spread in a host, invade organs, and spread to other hosts are the topics of Chapter 2. The early host response to infection, comprising cell autonomous (intrinsic) and innate immune responses, are the topics of Chapter 3, while the next chapter considers adaptive immune defenses, that are tailored to the pathogen, and immune memory. Chapter 5 focuses on the classic patterns of virus infection within cells and hosts, the myriad ways that viruses cause illness, and the value of animal models in uncovering new principles of viral pathogenesis. In Chapter 6, we discuss virus infections that transform cells in culture and promote oncogenesis (the formation of tumors) in animals. Chapter 7 is devoted entirely to the AIDS virus, not only because it is the causative agent of the most serious current worldwide epidemic, but also because of its unique and informative interactions with the human immune defenses.

Next, we consider the principles involved in treatment and control of infection. Chapter 8 focuses on vaccines, and Chapter 9 discusses the approaches and challenges of antiviral drug discovery. The topics of viral evolution and emergence have now been divided into two chapters. The origin of viruses, the drivers of viral evolution, and host-virus conflicts are the subjects of Chapter 10. The principles of emerging virus infections, and humankind's experiences with epidemic and pandemic viral infections, are considered in Chapter 11. Volume II ends with a new chapter on unusual infectious agents, viroids, satellites, and prions.

The Appendix of Volume II provides snapshots of the pathogenesis of common human viruses. This information is presented in four illustrated panels that summarize the viruses and diseases, epidemiology, disease mechanisms, and human infections.

Reference

Knipe DM, Howley PM (ed). 2013. *Fields Virology*, 6th ed. Lippincott Williams & Wilkins, Philadelphia, PA.

For some behind-the-scenes information about how the authors created the fourth edition of *Principles of Virology*, see: http://bit.ly/Virology_MakingOf

Acknowledgments

These two volumes of *Principles* could not have been composed and revised without help and contributions from many individuals. We are most grateful for the continuing encouragement from our colleagues in virology and the students who use the text. Our sincere thanks also go to colleagues (listed in the Acknowledgments for the third edition) who have taken considerable time and effort to review the text in its evolving manifestations. Their expert knowledge and advice on issues ranging from teaching virology to organization of individual chapters and style were invaluable, and are inextricably woven into the final form of the book.

We also are grateful to those who gave so generously of their time to serve as expert reviewers of individual chapters or specific topics in these two volumes: Siddharth Balachandran (Fox Chase Cancer Center), Patrick Moore (University of Pittsburgh), Duane Grandgenett (St. Louis University), Frederick Hughson (Princeton University), Bernard Moss (Laboratory of Viral Diseases, National Institutes of Health), Christoph Seeger (Fox Chase Cancer Center), and Thomas Shenk (Princeton University). Their rapid responses to our requests for details and checks on accuracy, as well as their assistance in simplifying complex concepts, were invaluable. All remaining errors or inconsistencies are entirely ours.

Since the inception of this work, our belief has been that the illustrations must complement and enrich the text. Execution of this plan would not have been possible without the support of Christine Charlip (Director, ASM Press), and the technical expertise and craft of our illustrator. The illustrations are an integral part of the text, and credit for their execution goes to the knowledge, insight, and artistic talent of Patrick Lane of ScEYEnce Studios. We also are indebted to Jason Roberts (Victorian Infectious Diseases Reference Laboratory, Doherty Institute, Melbourne, Australia) for the computational expertise and time he devoted to producing the beautiful renditions of poliovirus particles on our new covers. As noted in the figure legends, many could not have been completed without the help and generosity of numerous colleagues who provided original images. Special thanks go to those who crafted figures or videos tailored specifically to our needs, or provided multiple pieces: Chantal Abergel (CNRS, Aix-Marseille Université, France), Mark Andrake (Fox Chase Cancer Center), Timothy Baker (University of California), Bruce Banfield (The University of Colorado), Christopher Basler and Peter Palese (Mount Sinai School of Medicine), Ralf Bartenschlager (University of Heidelberg, Germany), Eileen Bridge (Miami University, Ohio), Richard Compans (Emory University), Kartik Chandran (Albert Einstein College of Medicine), Paul Duprex (Boston University School of Medicine), Ramón González (Universidad Autónoma del Estado de Morelos), Urs Greber (University of Zurich), Reuben Harris (University of Minnesota), Hidesaburo Hanafusa (deceased), Ari Helenius (University of Zurich), David Knipe (Harvard Medical School), J. Krijnse-Locker (University of Heidelberg, Germany), Petr G. Leiman (École Polytechnique Fédérale de Lausanne), Stuart Le Grice (National Cancer Institute, Frederick MD), Hongrong Liu (Hunan Normal University), David McDonald (Ohio State University), Thomas Mettenleiter (Federal Institute for Animal Diseases, Insel Reims, Germany), Bernard Moss (Laboratory of Viral Diseases, National Institutes of Health), Norm Olson (University of California), B. V. Venkataram Prasad (Baylor College of Medicine), Andrew Rambaut (University of Edinburgh), Jason Roberts (Victorian Infectious Diseases Reference Laboratory, Doherty Institute, Melbourne, Australia), Felix Rey (Institut Pasteur, Paris, France), Michael Rossmann (Purdue University), Anne Simon (University of Maryland), Erik Snijder (Leiden University Medical Center), Alasdair Steven (National Institutes of Health), Paul Spearman (Emory University), Wesley Sundquist (University of Utah), Livia Varstag (Castleton State College, Vermont), Jiri Vondrasek (Institute of organic Chemistry and Biochemistry, Czech Republic), Matthew Weitzman (University of Pennsylvania), Sandra Weller (University of Connecticut Health Sciences Center, Connecticut), Tim Yen (Fox Chase Cancer Center), and Z. Hong Zhou (University of California, Los Angeles).

The collaborative work undertaken to prepare the fourth edition was facilitated greatly by several authors' retreats. ASM Press generously provided financial support for these retreats as well as for our many other meetings.

We thank all those who guided and assisted in the preparation and production of the book: Christine Charlip (Director, ASM Press) for steering us through the complexities inherent in a team effort, Megan Angelini and John Bell (Production Managers, ASM Press) for keeping us on track during production, and Susan Schmidler for her elegant and creative designs for the layout and cover. We are also grateful for the expert secretarial and administrative support from Ellen Brindle-Clark (Princeton University) that facilitated preparation of this text. Special thanks go to Ellen for obtaining many of the permissions required for the figures.

There is little doubt in undertaking such a massive effort that inaccuracies still remain, despite our best efforts to resolve or prevent them. We hope that the readership of this edition will draw our attention to them, so that these errors can be eliminated from future editions of this text.

This often-consuming enterprise was made possible by the emotional, intellectual, and logistical support of our families, to whom the two volumes are dedicated.

About the Authors

Jane Flint is a Professor of Molecular Biology at Princeton University. Dr. Flint's research focuses on investigation of the molecular mechanisms by which viral gene products modulate host cell pathways and antiviral defenses to allow efficient reproduction in normal human cells of adenoviruses, viruses that are widely used in such therapeutic applications as gene transfer and cancer treatment. Her service to the scientific community includes membership of various editorial boards and several NIH study sections and other review panels. Dr. Flint is currently a member of the Biosafety Working Group of the NIH Recombinant DNA Advisory Committee.

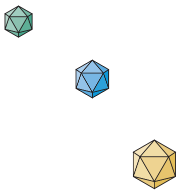
Vincent Racaniello is Higgins Professor of Microbiology & Immunology at Columbia University Medical Center. Dr. Racaniello has been studying viruses for over 35 years, including poliovirus, rhinovirus, enteroviruses, and hepatitis C virus. He teaches virology to graduate, medical, dental, and nursing students and uses social media to communicate the subject outside of the classroom. His Columbia University undergraduate virology lectures have been viewed by thousands at iTunes University, Coursera, and on YouTube. Vincent blogs about viruses at virology.ws and is host of the popular science program This Week in Virology.

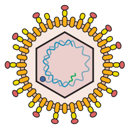
Glenn Rall is a Professor and the Co-Program Leader of the Blood Cell Development and Function Program at the Fox Chase Cancer Center in Philadelphia. At Fox Chase, Dr. Rall is also the Associate Chief Academic Officer and Director of the Postdoctoral Program. He is an Adjunct Professor in the Microbiology and Immunology departments at the University of Pennsylvania, Thomas Jefferson, Drexel, and Temple Universities. Dr. Rall's laboratory studies viral infections of the brain and the immune responses to those infections, with the goal of defining how viruses contribute to disease in humans. His service to the scientific community includes membership on the Autism Speaks Scientific Advisory Board, Opinions Editor of *PLoS Pathogens*, chairing the Education and Career Development Committee of the American Society for Virology, and membership on multiple NIH grant review panels.

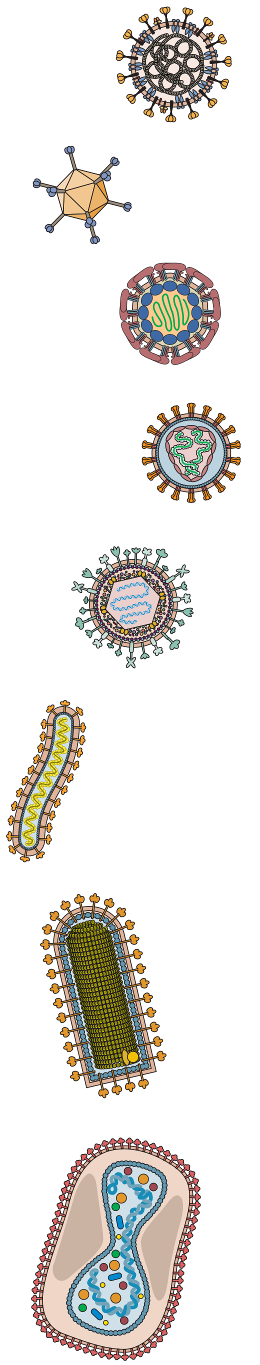
Anna Marie Skalka is a Professor and the W.W. Smith Chair in Cancer Research at Fox Chase Cancer Center in Philadelphia and an Adjunct Professor at the University of Pennsylvania. Dr. Skalka's major research interests are the molecular aspects of the replication of retroviruses. Dr. Skalka is internationally recognized for her contributions to the understanding of the biochemical mechanisms by which such viruses (including the AIDS virus) replicate and insert their genetic material into the host genome. Both an administrator and researcher, she has been deeply involved in state, national, and international advisory groups concerned with the broader, societal implications of scientific research, including the NJ Commission on Cancer Research and the U.S. Defense Science Board. Dr. Skalka has served on the editorial boards of peer-reviewed scientific journals and has been a member of scientific advisory boards including the National Cancer Institute Board of Scientific Counselors, the General Motors Cancer Research Foundation Awards Assembly, the Board of Governors of the American Academy of Microbiology, and the National Advisory Committee for the Pew Biomedical Scholars Program.

PART I

The Science of Virology



1  Foundations



LINKS FOR CHAPTER 1

- *Video: Interview with Dr. Donald Henderson*
  http://bit.ly/Virology_Henderson
- *This Week in Virology (TWIV): A weekly podcast about viruses featuring informal yet informative discussions and interviews with guests about the latest topics in the field.*
  http://www.twiv.tv
- *Marine viruses and insect defense*
  http://bit.ly/Virology_Twiv301
- *Giants among viruses*
  http://bit.ly/Virology_Twiv261
- *Latest update of virus classification from the ICTV.*
  http://www.ictvonline.org/virusTaxonomy.asp?bhcp=1
- *The abundant and diverse viruses of the seas.*
  http://bit.ly/Virology_3-20-09
- *How many viruses on Earth?*
  http://bit.ly/Virology_9-6-13

Thus, we cannot reject the assumption that the effect of the filtered lymph is not due to toxicity, but rather to the ability of the agent to replicate.

F. Loeffler *1898*

Luria's Credo

"There is an intrinsic simplicity of nature and the ultimate contribution of science resides in the discovery of unifying and simplifying generalizations, rather than in the description of isolated situations—in the visualization of simple, overall patterns rather than in the analysis of patchworks." More than half a century has passed since Salvador Luria wrote this credo in the introduction to the classic textbook *General Virology*.

Despite an explosion of information in biology since Luria wrote these words, his vision of unity in diversity is as relevant now as it was then. That such unifying principles exist may not be obvious considering the bewildering array of viruses, genes, and proteins recognized in modern virology. Indeed, new viruses are being described regularly, and viral diseases such as acquired immunodeficiency syndrome (AIDS), hepatitis, and influenza continue to challenge our efforts to control them. Yet Luria's credo still stands: even as our knowledge continues to increase, it is clear that all viruses follow the same simple strategy to ensure their survival. This insight has been hard-won over many years of observation, research, and debate; the history of virology is rich and instructive.

Why We Study Viruses

Viruses Are Everywhere

Viruses are all around us, comprising an enormous proportion of our environment, in both number and total mass (Box 1.1). All living things encounter billions of virus particles every day. For example, they enter our lungs in the 6 liters of air each of us inhales every minute; they enter our digestive systems with the food we eat; and they are transferred to our eyes, mouths, and other points of entry from the surfaces we touch and the people with whom we interact. Our bodies are reservoirs for viruses that reside in our respiratory, gastrointestinal, and urogenital tracts. In addition to viruses that can infect us, our intestinal tracts are loaded with myriad plant and insect viruses, as well as hundreds of bacterial species that harbor their own constellations of viruses.

Viruses Can Cause Human Disease

With such constant exposure, it is nothing short of amazing that the vast majority of viruses that infect us have little or no impact on our health or well-being. As described in Volume II, we owe such relative safety to our elaborate immune defense systems, which have evolved to fight microbial infection. When these defenses are compromised, even the most common infection can be lethal. Despite such defenses, some of the most devastating human diseases have been or still are caused by viruses; these diseases include smallpox, yellow fever, poliomyelitis, influenza, measles, and AIDS. Viral infections can lead to life-threatening diseases that impact virtually all organs, including the lungs, liver, central nervous system, and intestines. Viruses are responsible for approximately 20% of the human cancer burden, and viral infections of the respiratory and gastrointestinal tracts kill millions of children in the developing world each year. As summarized in Volume II, Appendix, there is no question about the biomedical importance of these agents.

Viruses Infect All Living Things

While most of this textbook focuses on viral infections of humans, it is important to bear in mind that viruses also infect pets, food animals, plants, insects, and wildlife throughout

PRINCIPLES ***Foundations***

- The field of virology encompasses viral discovery, the study of virus structure and reproduction, and the importance of viruses in biology and disease.
- While this text focuses primarily on viruses that infect vertebrates, especially humans, it is important to keep in mind that viruses infect **all** living things including insects, plants, bacteria, and even other viruses.
- Viruses are not solely pathogenic nuisances; they can be beneficial. Viruses contribute to ecological homeostasis, keep our immune responses activated and alert, and can be used as molecular flashlights to illuminate cellular processes.
- Viruses have been part of all of human history: they were present long before *Homo sapiens* evolved, and the majority of human infections were likely acquired from other animals (zoonoses). As viruses continue to be discovered, our understanding of how human health and well-being are affected by these agents remains incomplete.
- Viruses are obligate intracellular parasites and depend on their host cell for all aspects of the viral life cycle.
- While Koch's postulates were essential for defining many agents of disease, not all pathogenic viruses fulfilled these criteria.
- Viruses can be cataloged based on their appearance, the hosts they infect, or the nature of their nucleic acid genome.
- The Baltimore classification allows relationships among various viral genomes and the pathway to mRNA to be determined.
- A common strategy underlies the propagation of all viruses. This textbook describes that strategy and the similarities and differences in the manner in which it is accomplished by different viruses.

BOX 1.1

BACKGROUND

Some astounding numbers

- Viruses are the most abundant entities in the biosphere. The biomass on our planet of bacterial viruses *alone* exceeds that of all of Earth's elephants by more than 1,000-fold. There are more than 10^{30} bacteriophage particles in the world's oceans, enough to extend out into space for 200 million light-years if arranged head to tail (http://www.virology.ws/2009/03/20/the-abundant-and-diverse-viruses-of-the-seas/).
- Whales are commonly infected with a member of the virus family *Caliciviridae* that causes rashes, blisters, intestinal problems, and diarrhea and can also infect humans. Infected whales excrete more than 10^{13} calicivirus particles daily.
- The average human body contains approximately 10^{13} cells, but these are outnumbered 10-fold by bacteria and as much as 100-fold by virus particles.
- With about 10^{16} human immunodeficiency virus (HIV) genomes on the planet today, it is highly probable that somewhere there exist HIV genomes that are resistant to every one of the antiviral drugs that we have now or are likely to have in the future.

Earth and its oceans. Courtesy: NASA/Goddard Space Flight Center.

the world. They infect microbes such as algae, fungi, and bacteria, and some even interfere with the reproduction of other viruses. Viral infection of agricultural plants and animals can have enormous economic and societal impact. Outbreaks of infection by foot-and-mouth disease and avian influenza viruses have led to the destruction (**culling**) of millions of cattle, sheep, and poultry to prevent further spread. Losses in the United Kingdom during the 2001 outbreak of foot-and-mouth disease ran into billions of dollars and caused havoc for both farmers and the government (Box 1.2). More recent outbreaks of the avian influenza virus H5N1 in Asia have resulted in similar disruption and economic loss. Viruses that infect crops such as potatoes and fruit trees are common and can lead to serious food shortages as well as financial devastation.

Viruses Can Be Beneficial

Despite the appalling statistics from human and agricultural epidemics, it is important to realize that viruses can also be beneficial. Such benefit can be seen most clearly in marine ecology, where virus particles are the most abundant biological entities (Box 1.1). Indeed, they comprise 94% of all nucleic acid-containing particles in the oceans and are 15 times more abundant than the *Bacteria* and *Archaea*. Viral infections in the ocean kill 20 to 40% of marine microbes daily, converting these living organisms into particulate matter, and in so doing release essential nutrients that supply phytoplankton at the bottom of the ocean's food chain, as well as carbon dioxide and other gases that affect the climate of the earth. Pathogens can also influence one another: infection by one virus can have an ameliorating effect on the pathogenesis of a second virus or even bacteria. For example, human immunodeficiency virus-infected AIDS patients show a substantial decrease in their disease progression if they are persistently infected with hepatitis G virus, and mice latently infected with some murine herpesviruses are resistant to infection with the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis*. The idea that viruses are solely agents of disease is giving way to the notion that they can exert positive, even necessary, effects.

Viruses Can Cross Species Boundaries

Although viruses generally have a limited host range, they can and do spread across species barriers. As the world's human population continues to expand and impinge on the wilderness, cross-species (**zoonotic**) infections of humans are occurring with increasing frequency. In addition to the AIDS pandemic, the highly fatal Ebola hemorrhagic fever and the severe acute respiratory syndrome (SARS) are recent examples of viral diseases to emerge from zoonotic infections. The current pandemic of influenza virus H5N1 in avian species has much of the world riveted by the frightening possibility that a new, highly pathogenic strain might emerge following transmission from birds to human hosts. Indeed, given the eons over which viruses have had the opportunity to interact with various species, today's "natural" host may simply be a way station in viral evolution.

Viruses "R" Us

Every cell in our body contains viral DNA. Human endogenous retroviruses, and elements thereof, make up about 5 to 8% of our DNA. Most are inactive, fossil remnants from infections of germ cells that have occurred over millions of years during our evolution. Some of them are suspected to be associated with specific diseases, but the protein products of other endogenous retroviruses are essential for placental development.

Recent genomic studies have revealed that our viral "heritage" is not limited to retroviruses. Human and other