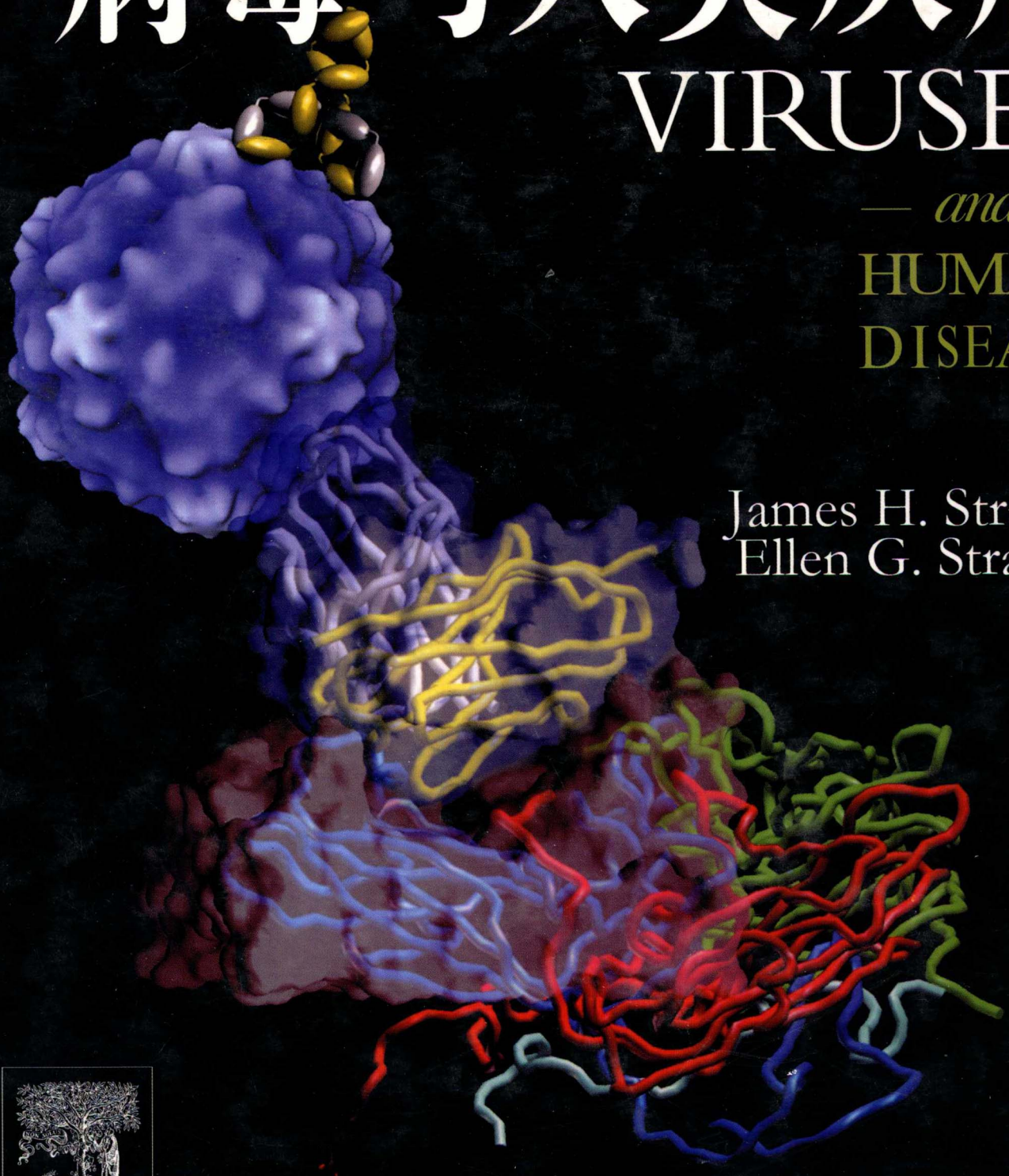
病毒与人类疾病

VIRUSES

— and —

HUMAN DISEASE

James H. Strauss
Ellen G. Strauss



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序　言

本书源于我们在加州理工学院(Caltech)讲授了 30 年的课程。这段时期,学生的兴趣发生了变化。在 20 世纪 70 年代,学生认为病毒是学习关于生命体系分子生物学的有趣对象,这门课程的重点是分子生物学。然而,在过去 10 年间,学生的兴趣转移了,他们把病毒看作传染病介质,而不是研究分子生物学的工具。广大民众越来越认识到传染病的持续的重要性,现代学生的兴趣就反映了这一点。课程的改变反映了学生们的兴趣,更多的授课以专题讲座形式来进行就成为必需,最终导致这本书的诞生。在这里,我们将病毒作为人类疾病介质来阐述。但是,要了解病毒的生物学、流行病学和病理学,它们进行自我复制的分子生物学知识仍然十分重要。因此,我们试图把病毒的分子生物学的知识和它们引起疾病的有关知识结合起来。因为我们也相信了解过去是步入未来的关键,所以,我们也在可能的程度上阐述病毒疾病的历史。

当今的病毒知识是庞大的,我们两人不可能期望收集所有与病毒相关领域的最新知识。我们非常感谢我们的许多同事,他们阅读一些章节,评议了表达的确切性,并提出改进的建议。以字母排列为序,特别向下列同仁致以衷心的谢意:Tom Benjamin, Pamela Bjorkman, Tara Chapman, Bruce Chesebro, Marie Csete, Diana Griffin, Jack Johnson, Bill Joklik, Dennis O'Callaghan, James Ou, Ellen Rothenberg, Gail Wertz, Eckard Wimmer 和 William Wunner。我们也感谢本课程的学生们,几年来他们在此教材形式的各个阶段给予了反馈意见。

James H. Strauss
Ellen G. Strauss

Preface

This book grew out of a course at Caltech that we have taught for the past 30 years. During this time, the interests of the students have changed. In the 1970s, students considered viruses to be interesting objects for learning about the molecular biology of living systems, and the course focused on molecular biology. Within the past decade, however, student interest has shifted to viruses as infectious disease agents rather than as tools with which to study molecular biology. There has been a rising awareness in the general population of the continuing importance of infectious diseases, and the interests of the current students reflect that. The course changed to reflect the interests of the students, which necessitated that more of the teaching be in the form of lecture notes, eventually leading to this book. Here we cover viruses as agents of human disease. But to understand their biology, epidemiology, and pathology, knowledge of their molecular biology of replication is essential. Thus, we attempt to integrate what is known about the molecular biology of viruses with what is known about the diseases they cause. Because we also believe that a key to the future is an understanding of the past, we also cover the history of viral diseases to the extent feasible.

Current knowledge of viruses is vast, and two people cannot hope to keep current in all fields relating to viruses. We are extremely grateful to many of our colleagues who have read individual chapters, commented on the accuracy of presentation, and offered suggestions for improving the presentation. In alphabetical order, the following people are gratefully acknowledged: Tom Benjamin, Pamela Bjorkman, Tara Chapman, Bruce Chesebro, Marie Csete, Diane Griffin, Jack Johnson, Bill Joklik, Dennis O'Callaghan, James Ou, Ellen Rothenberg, Gail Wertz, Eckard Wimmer, and William Wunner. We are also grateful to the students in our course during the past few years for feedback on the text in its various incarnations.

James H. Strauss
Ellen G. Strauss

第1章　病毒和病毒感染总论

本章由导言、病毒分类、病毒复制循环总论、病毒感染宿主细胞的效应、流行病学等部分组成。

在**导言**中，首先指出病毒学是一门相对年轻的科学。大约100年前人们才知道病毒可以通过过滤与细菌分开而感染疾病，约60年前描述出病毒的组成，其后用电镜可看到病毒是颗粒。由于近20年的现代生物技术的进展，人们能更深入地了解病毒本身，及其与宿主的相互作用。病毒可感染许多生物体，包括细菌、藻类、真菌、植物、昆虫和脊椎动物等。病毒可引起疾病，尤其是人类疾病。图1.2列出WHO归纳的1995年和1998年世界上6大感染疾病导致的每年死亡人数（400万～100万），这6大疾病是：急性呼吸疾病、腹泻疾病、获得性免疫缺损综合征（艾滋病）、结核病、疟疾和麻疹，它们许多是由病毒感染引起的。病毒同时也是研究分子生物学和细胞生物学的有用的工具，如作为载体表达外源基因、用于基因治疗等。表1.1列出1946年～1997年与病毒学有关的诺贝尔奖，共有17项。最早是1946年烟草花叶病毒（TMV）的分类、纯化和结晶获奖，1997年则是授予朊病毒（prion）的发现者。

病毒是一类亚细胞的感染介质，感染细胞后复制。成熟的胞外病毒颗粒叫做病毒粒（virion），病毒粒由基因组（DNA或RNA）和环绕的由蛋白质组成的衣壳或核衣壳装配而成。一些病毒还含有脂质包膜。

病毒主要分为三大类，它们有独立的进化起源。第一类病毒的基因组是单链或双链DNA。它们感染宿主后，由细胞或病毒的RNA聚合酶转录，产生mRNA，并翻译得到病毒蛋白质。DNA基因组则被病毒或细胞来源的DNA聚合酶复制。大部分真核DNA病毒的基因组复制和子病毒的装配是在细胞核中进行的。第二类病毒的基因组是RNA。单链RNA又可分为：正链RNA（plus-strand RNA）、负链RNA（minus-strand RNA）、双义RNA（ambisense RNA），还有的RNA病毒含双链RNA基因组。第三类病毒编码逆转录酶（RT），称作含RT病毒（RT-containing virus）。其生活周期中有RNA逆转录产生DNA步骤。这类病毒有的是RNA病毒，如逆转录病毒，其复制过程是RNA→DNA→RNA；有的是DNA病毒，如嗜肝DNA病毒，其复制过程是DNA→RNA→DNA。

国际病毒分类委员会（ICTV）将全世界超过30，000株（strain）的病毒归纳为大概4000个种（species），其中3954种分类为203属（genera）和56家族（family）。表1.2详细列出引起人类疾病的主要病毒家族，包括它们的核酸组分、基因组大小、区段和主要宿主。

关于病毒的复制循环。动物病毒感染宿主从接触细胞表面的受体开始，然后基因组（无论是裸露的核酸或与蛋白质复合）进入细胞质。细胞受体分为许多类别，有一级的高亲和性受体，还有辅助受体、共受体等。本章较详细地介绍不同种类病毒的不同受体及其相互作用。病毒识别特异受体后，下一步是入侵。入侵过程视不同病毒是不一样的，也比较复杂。病毒粒中的蛋白质起到很大作用。入侵的后果是病毒基因组的复制和表达，不同基因组的复制过程不同。本章分别用彩图见书后彩版示出DNA病毒、正链RNA病毒、负链RNA病毒和逆转录病毒的一般复制过程。书中简单叙述了基因组的转录和翻译（包括加工）的一般模式，讨论了mRNA的翻译元件、核糖体移码、多聚蛋白质的加工等。一般情况下，宿主细胞中的一些蛋白质组分也参与病毒基因组的复制和转录。最后由新的基因组和新的蛋

白质装配为新的子代病毒粒。

宿主细胞上的病毒感染效应。病毒感染循环可以区分几种类型：裂解的、潜伏的、持续的和慢性的感染。病毒感染细胞后通常是细胞死亡，并释放出子代病毒。但逆转录病毒持续性感染和嗜肝 DNA 病毒潜伏性感染细胞是例外，此时细胞特性改变而幸存。

病毒的流行病学是指病毒在个体与个体间的扩散。动物病毒扩散方式有：粪口途径、空气传播、血源性传播、性交途径和先天性的。本章介绍了不同病毒可以用不同的方式扩散。

章末给出下列主题的进一步阅读材料：人类史感染疾病的效应、病毒分类、病毒受体和进入、病毒蛋白酶等。

目　录

CHAPTER

1

Overview of Viruses and Virus Infection

INTRODUCTION

The Science of Virology

The science of virology is relatively young. We can recognize specific viruses as the causative agents of epidemics that occurred hundreds or thousands of years ago from written descriptions of disease or from study of mummies with characteristic abnormalities. Furthermore, immunization against smallpox has been practiced for more than a millennium. However, it was only approximately 100 years ago that viruses were shown to be filterable and therefore distinct from bacteria that cause infectious disease. It was only about 60 years ago that the composition of viruses was described, and even more recently before they could be visualized as particles in the electron microscope. Within the last 20 years, however, the revolution of modern biotechnology has led to an explosive increase in our knowledge of viruses and their interactions with their hosts. Virology, the study of viruses, includes many aspects: the molecular biology of virus replication, the structure of viruses, the interactions of viruses and hosts, the evolution and history of viruses, virus epidemiology, and the diseases caused by viruses. The field is vast and any treatment of viruses must perforce be selective.

Viruses are known to infect most organisms, including bacteria, blue-green algae, fungi, plants, insects, and vertebrates, but we attempt here to provide an overview of virology that emphasizes their potential as human disease agents. Because of the scope of virology, and because human viruses that cause disease, especially epidemic disease, are not uniformly distributed across virus families, the treatment is not intended to be comprehensive. Nevertheless, we feel that it is important that the human viruses be presented in the perspective of viruses as a whole so that some overall understanding of this fascinating group of agents can emerge. We also consider many nonhuman viruses that are important for our understanding of the evolution and biology of viruses.

Viruses Cause Disease But Are Also Useful as Tools

Viruses are of intense interest because many cause serious illness in humans or domestic animals, and others damage crop plants. During the last century, progress in the control of infectious diseases through improved sanitation, safer water supplies, the development of antibiotics and vaccines, and better medical care have dramatically reduced the threat to human health from these agents, especially in developed countries. This is illustrated in Fig. 1.1, in which the death rate from infectious disease in the United States during the last century is shown. At the beginning of the 20th century, 0.8% of the population died each year from infectious diseases. Today the rate is less than one-tenth as great. The use of vaccines has led to effective control of the most dangerous of the viruses. Smallpox virus has been eradicated worldwide by means of an ambitious and concerted effort, sponsored by the World Health Organization, to vaccinate all people at risk for the disease. Poliovirus has been eliminated from the Americas, and measles virus eliminated from North America, by intensive vaccination programs. There is hope that these two viruses can also be eradicated worldwide in the near future. Vaccines exist for the control of many other viral diseases, such as mumps, rabies, rubella, yellow fever, and Japanese encephalitis.

The dramatic decline in the death rate from infectious disease has led to a certain amount of complacency. There is a small but vocal movement in the United States to eliminate immunization against viruses, for example. However,

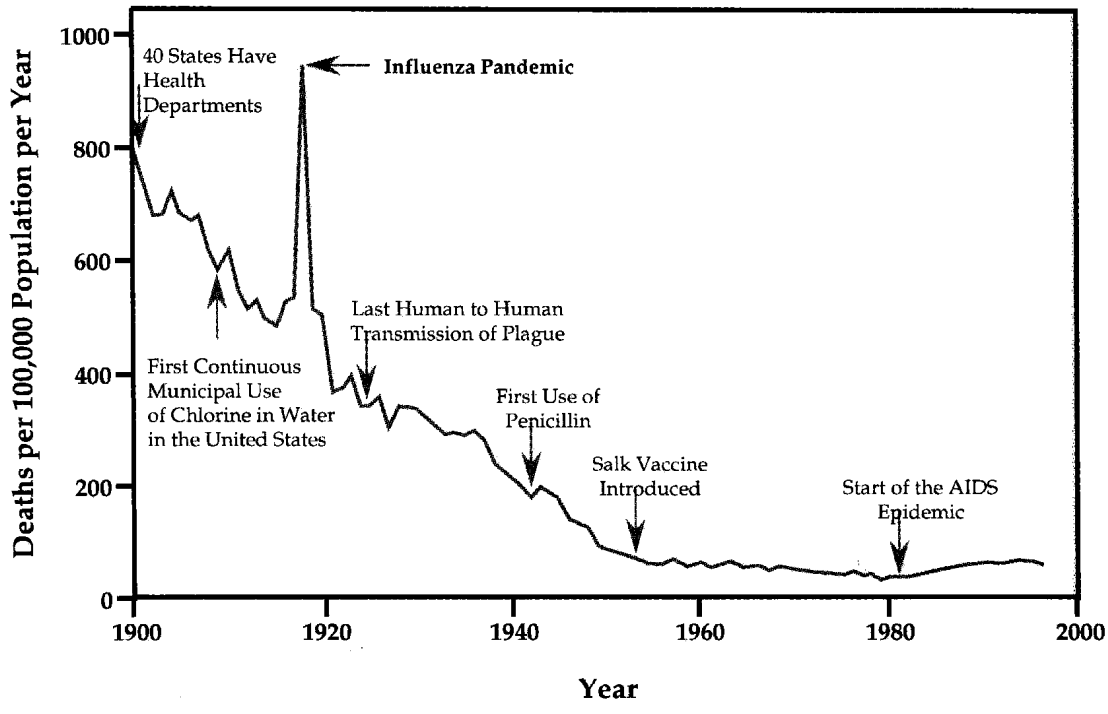

FIGURE 1.1 Death rate from infectious disease in the United States, 1900–1996. The death rate has dropped over this century from around 800 deaths per 100,000 population per year to about 50. Significant milestones in public health are shown. After dropping steadily for 80 years, interrupted only by the influenza pandemic of 1918–1919, the death rate began to rise in 1980 with the advent of the AIDS epidemic. From *Morbidity and Mortality Weekly Report (MMWR)*, Vol. 48, No. 29, p. 621 (1999).

viral diseases continue to plague humans, as do infectious diseases caused by bacteria, protozoa, fungi, and multicellular parasites. Deaths worldwide due to infectious disease are shown in Fig. 1.2, divided into six categories. In 1998 more than 3 million deaths occurred as a result of acute respiratory disease, many of which are caused by viruses. More than 2 million deaths were attributed to diarrheal diseases, about half of which are due to viruses. AIDS killed 2 million people worldwide in 1998, and measles is still a significant killer in developing countries. Recognition is growing that infectious diseases, of which viruses form a major component, have not been conquered by the introduction of vaccines and drugs. The overuse of antibiotics has resulted in an upsurge in antibiotic-resistant bacteria, and viral diseases continue to resist elimination.

The persistence of viruses is in part due to their ability to change rapidly and adapt to new situations. Human immunodeficiency virus (HIV) is the most striking example of the appearance of a virus that has recently entered the human population and caused a plague of worldwide importance. The arrival of this virus in the United States caused a significant rise in the number of deaths from infectious disease, as seen in Fig. 1.1. Other, previously undescribed viruses also continue to emerge as serious pathogens. Sin Nombre virus caused a 1994 outbreak in the United States of hantavirus pulmonary syndrome with a 50% case fatality rate, and it is now recognized as being widespread in North America. Junin virus, which causes Argentine hemorrhagic fever, and related viruses have become a more serious problem in South America with the spread of farming. Ebola virus, responsible for several small African epidemics with a case fatality rate of 70%, was first described in the 1970s. Nipah virus, previously unknown, appeared in 1998 and caused 258 cases of encephalitis, with a 40% fatality rate, in Malaysia and Singapore. As faster and more extensive travel becomes ever more routine, the potential for rapid spread of all viruses increases. The possibility exists that any of these viruses could become more widespread, as has HIV since its appearance in Africa perhaps half a century ago, and as has West Nile virus, which spread to the Americas in 1999.

Newly emerging viruses are not the only ones to plague humans, however. Many viruses that have been known for a long time, and for which vaccines may exist, continue to cause widespread problems. Respiratory syncytial virus, as an example, is a major cause of pneumonia in infants. Despite much effort, it has not yet been possible to develop an effective vaccine. Even when vaccines exist, problems may continue. For example, influenza virus changes rapidly and the vaccine for it must be reformulated yearly. Because the major reservoir for influenza is birds, it is not possible to eradicate the virus. Thus, to control influenza would

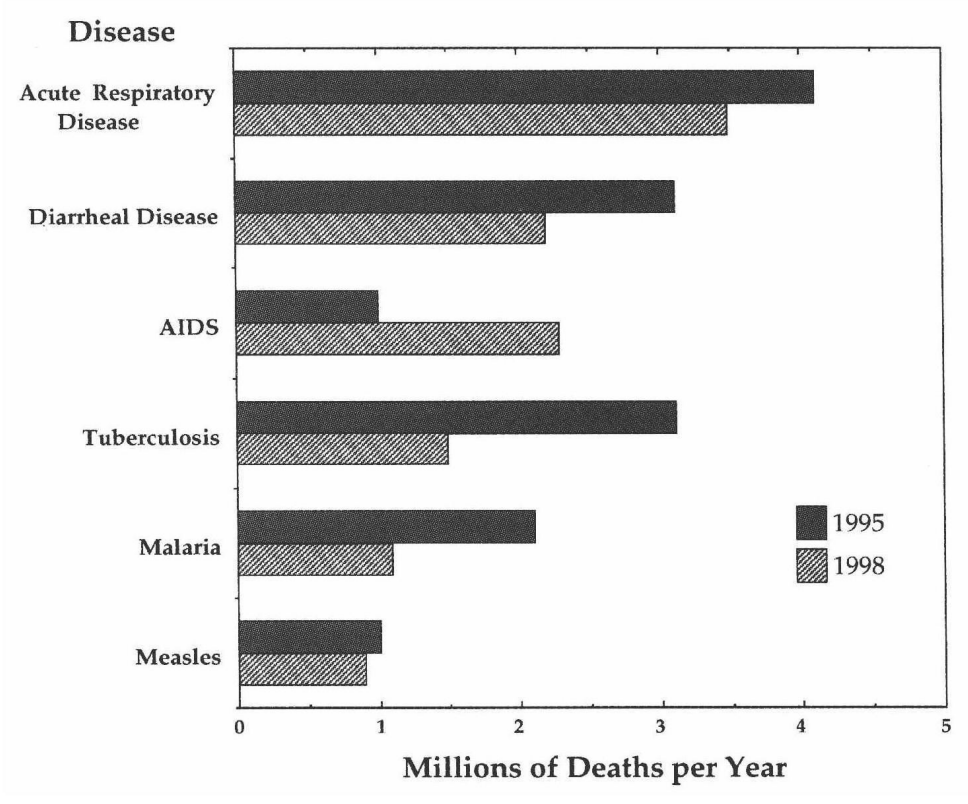

FIGURE 1.2 Six leading infectious diseases as causes of death. Data are the totals for all ages worldwide in 1995 and in 1998. The data came from the World Health Organization web site: http://www:who.int/infectious-disease-report/pages/graph5.html.

require that the entire population be immunized yearly. This is a formidable problem and the virus continues to cause annual epidemics with a significant death rate (Chapter 4). Although primarily a killer of the elderly, the potential of influenza to kill the young and healthy was shown by the worldwide epidemic of influenza in 1918 in which 20–100 million people died worldwide. In the United States, perhaps 1% of the population died during the epidemic (Fig. 1.1). Continuing study of virus replication and virus interactions with their hosts, surveillance of viruses in the field, and efforts to develop new vaccines as well as other methods of control are still important.

The other side of the coin is that viruses have been useful to us as tools for the study of molecular and cellular biology. Further, the development of viruses as vectors for the expression of foreign genes has given them a new and expanded role in science and medicine, including their potential use in gene therapy (Chapter 9). As testimony to the importance of viruses in the study of biology, numerous Nobel Prizes have been awarded in recognition of important advances in biological science that resulted from studies that involved viruses (Table 1.1). To cite a few examples, Max Delbrück received the prize for pioneering studies in what is now called molecular biology, using bacteriophage T4. Cellular oncogenes were first discovered from their presence in retroviruses that could transform cells in culture, a discovery that resulted in a prize for Francis Peyton Rous for his discovery of transforming retroviruses, and for Michael Bishop and Harold Varmus, who were the first to show that a transforming retroviral gene had a cellular counterpart. As a third example, the development of the modern methods of gene cloning have relied heavily on the use of restriction enzymes and recombinant DNA technology, first developed by Daniel Nathans and Paul Berg working with SV40 virus, and on the use of reverse transcriptase, discovered by David Baltimore and Howard Temin in retroviruses. As another example, the study of the interactions of viruses with the immune system has told us much about how this essential means of defense against disease functions, and this resulted in a prize for Rolf Zinkernagel and Peter Doherty. The study of viruses and their use as tools has told us as much about human biology as it has told us about the viruses themselves.

In addition to the interest in viruses that arises from their medical and scientific importance, viruses form a fascinating evolutionary system. There is debate as to how ancient are viruses. Some argue that RNA viruses contain remnants of the RNA world that existed before the invention of DNA. All would accept the idea that viruses have been present for hundreds of millions of years and have helped to shape the

TABLE 1.1 Nobel Prizes Involving Virology[a]

Year	Names	Nobel citation; *virus group or family*
1946 [chemistry]	Wendell Stanley	Isolation, purification, and crystallization of tobacco mosaic virus; *Tobamovirus*
1951	Max Theiler	Development of yellow fever vaccine; *Flaviviridae*
1954	John F. Enders Thomas Weller Frederick C. Robbins	Growth and cultivation of poliovirus; *Picornaviridae*
1958	Joshua Lederberg	Transforming bacteriophages
1965	Francois Jacob André Lwoff Jacques Monod	Operons; bacteriophages
1966	Francis Peyton Rous	Discovery of tumor-producing viruses; *Retroviridae*
1969	Max Delbrück Alfred D. Hershey Salvador E. Luria	Mechanism of virus infection in living cells; bacteriophages
1975	David Baltimore Howard M. Temin Renato Dulbecco	Discoveries concerning the interaction between tumor viruses and the genetic material of the cell; *Retroviridae*
1976	D. Carleton Gajdusek Baruch S. Blumberg	New mechanisms for the origin and dissemination of infectious diseases; Blumberg with *Hepadnaviridae*, Gajdusek with prions
1978[b]	Daniel Nathans	Application of restriction endonucleases to the study of the genetics of SV40; *Polyomaviridae*
1980 [chemistry]	Paul Berg	Studies of the biochemistry of nucleic acids, with particular regard to recombinant DNA (SV40); *Polyomaviridae*
1982 [chemistry]	Aaron Klug	Development of crystallographic electron microscopy and structural elucidation of biologically important nucleic acid–protein complexes; *Tobamovirus* and *Tymovirus*
1988[b]	George Hitchings Gertrude Elion	Important principles of drug treatment using nucleotide analogs (acyclovir)
1989	J. Michael Bishop Harold E. Varmus	Discovery of the cellular origin of retroviral oncogenes; *Retroviridae*
1993	Phillip A. Sharp Richard J. Roberts	Discoveries of split (spliced) genes; *Adenoviridae*
1996	Rolf Zinkernagel Peter Doherty	Presentation of viral epitopes by major histocompatibility complex molecules
1997	Stanley Prusiner	Prions

[a]All prizes listed are in physiology or medicine except those three marked [chemistry].
[b]In these two instances, the prize was shared with unlisted recipients whose work did not involve viruses.

evolution of their hosts. Viruses are capable of very rapid change, both from drift due to nucleotide substitutions that may occur at a rate 10^6-fold greater than that of the plants and animals that they infect, and from recombination that leads to the development of entirely new families of viruses. This makes it difficult to trace the evolution of viruses back more than a few millennia or perhaps a few million years. The development of increasingly refined methods of sequence analysis, and the determination of more structures of virally encoded proteins, which change far more slowly than do the amino acid sequences that form the structure, have helped identify relationships among viruses that were not at first obvious. The coevolution of viruses and their hosts remains a study that is intrinsically interesting and has much to tell us about human biology.

The Nature of Viruses

Viruses are subcellular, infectious agents that are obligate intracellular parasites. They infect and take over a host cell in order to replicate. The mature, extracellular virus particle is called a virion. The virion contains a genome that may be DNA or RNA wrapped in a protein coat called a capsid or nucleocapsid. Some viruses have a lipid envelope surrounding the nucleocapsid (they are "enveloped"). In such viruses, glycoproteins encoded by the virus are embedded in the lipid envelope. The function of the capsid or envelope is to protect the viral genome while it is extracellular and to promote the entry of the genome into a new, susceptible cell. The structure of viruses is covered in detail in Chapter 2.

The nucleic acid genome of a virus contains the information needed by the virus to replicate and produce new virions after its introduction into a susceptible cell. Virions bind to receptors on the surface of the cell, and by processes described below the genome is released into the cytoplasm of the cell, sometimes still in association with protein ("uncoating"). The genome then redirects the cell to the replication of itself and to the production of progeny virions. The cellular machinery that is in place for the production of energy (synthesis of ATP) and for macromolecular synthesis, such as translation of mRNA to produce proteins, is essential.

It is useful to think of the proteins encoded in viral genomes as belonging to three major classes. First, most viruses encode enzymes required for replication of the genome and the production of mRNA from it. RNA viruses must encode an RNA polymerase or replicase, since cells do not normally replicate RNA. Most DNA viruses have access to the cellular DNA replication machinery in the nucleus, but even so, many encode new DNA polymerases for the replication of their genomes. Even if they use cellular DNA polymerases, many DNA viruses encode at least an initiation protein for genome replication. An overview of the replication strategies used by different viruses is presented below, and details of the replication machinery used by each virus are given in the chapters that describe individual viruses. Second, viruses must encode proteins that are used in the assembly of progeny viruses. For simpler viruses, these may consist of only one or a few structural proteins that assemble with the genome to form the progeny virion. More complicated viruses may encode scaffolding proteins that are required for assembly but are not present in the virion. In some cases, viral proteins required for assembly may have proteolytic activity. Assembly of viruses is described in Chapter 2. Third, the larger viruses encode proteins that interfere with defense mechanisms of the host. These defenses include, for example, the immune response and the interferon response of vertebrates, which are highly evolved and effective methods of controlling and eliminating virus infection; and the DNA restriction system in bacteria, so useful in molecular biology and genetic engineering, that prevents the introduction of foreign DNA. Vertebrate defenses against viruses, and the ways in which viruses counter these defenses, are described in Chapter 8.

It is obvious that viruses that have larger genomes and encode larger numbers of proteins, such as the herpesviruses (family Herpesviridae), have more complex life cycles and assemble more complex virions than viruses with small genomes, such as poliovirus (family Picornaviridae). The smallest known nondefective viruses have genomes of about 3 kb (1 kb = 1000 nucleotides in the case of single-stranded genomes or 1000 base pairs in the case of double-stranded genomes). These small viruses may encode as few as three proteins (for example, the bacteriophage MS2). At the other extreme, the largest known RNA viruses, the coronaviruses (family Coronaviridae), have genomes somewhat larger than 30 kb, whereas the largest DNA viruses, poxviruses belonging to the genera Entomopoxvirus A and C (family Poxviridae), have genomes of up to 380 kb. These large DNA viruses encode hundreds of proteins. It is the larger viruses that can afford the luxury of encoding proteins that interfere effectively with host defenses such as the immune system. It is worthwhile remembering that even the largest viral genomes are small compared to the size of the bacterial genome (2000 kb) and miniscule compared to the size of the human genome (2×10^6 kb).

There are other subcellular infectious agents that are even "smaller" than viruses. These include satellite viruses, which are dependent for their replication on other viruses; viroids, small (~300 nucleotide) RNAs that are not translated and have no capsid; and prions, infectious agents whose identity remains controversial, but which may consist of only protein. These agents are covered in Chapter 7.

CLASSIFICATION OF VIRUSES

The Many Kinds of Viruses

Three broad classes of viruses can be recognized, which may have independent evolutionary origins. One class, which includes the poxviruses and herpesviruses among many others, contains DNA as the genome, whether single stranded or double stranded, and the DNA genome is replicated by direct DNA → DNA copying. During infection, the viral DNA is transcribed by cellular and/or viral RNA polymerases, depending on the virus, to produce mRNAs for translation into viral proteins. The DNA genome is replicated by DNA polymerases that can be of viral or cellular origin. Replication of the genomes of most eukaryotic DNA viruses and assembly of progeny viruses occur in the nucleus, but the poxviruses replicate in the cytoplasm.

A second class of viruses contains RNA as their genome and the RNA is replicated by direct RNA → RNA copying. Some RNA viruses, such as yellow fever virus (family Flaviviridae) and poliovirus, have a genome that is a messenger RNA, defined as plus-strand RNA. Other RNA viruses, such as measles virus (family Paramyxoviridae) and rabies virus (family Rhabdoviridae), have a genome that is anti-messenger sense, defined as minus strand. The arenaviruses (family Arenaviridae) and some of the genera belonging to the family Bunyaviridae have a genome that has regions of both messenger and anti-messenger sense

and are called ambisense. The replication of these viruses follows a minus-sense strategy, however, and they are classified with the minus-sense viruses. Finally, some RNA viruses, for example, rotaviruses (family Reoviridae), have double-strand RNA genomes. In the case of all RNA viruses, virus-encoded proteins are required to form a replicase to replicate the viral RNA, since cells do not possess (efficient) RNA → RNA copying enzymes. In the case of the minus-strand RNA viruses and double-strand RNA viruses, these RNA synthesizing enzymes also synthesize mRNA and are packaged in the virion, because their genomes cannot function as messengers. Replication of the genome proceeds through RNA intermediates that are complementary to the genome in a process that follows the same rules as DNA replication.

The third class of viruses encodes the enzyme reverse transcriptase (RT), and these viruses have an RNA → DNA step in their life cycle. The genetic information encoded by these viruses thus alternates between being present in RNA and being present in DNA. Retroviruses (e.g., HIV, family Retroviridae) contain the RNA phase in the virion; they have a single-stranded RNA genome that is present in the virus particle in two copies. Thus, the replication of their genome occurs through a DNA intermediate (RNA → DNA → RNA). The hepadnaviruses (e.g., hepatitis B virus, family Hepadnaviridae) contain the DNA phase as their genome, which is circular and largely double stranded. Thus their genome replicates through an RNA intermediate (DNA → RNA → DNA). Just as the minus-strand RNA viruses and double-strand RNA viruses package their replicase proteins, the retroviruses package active RT, which is required to begin the replication of the genome in the virions. Although in many treatments the retroviruses are considered with the RNA viruses and the hepadnaviruses with the DNA viruses, we consider these viruses to form a distinct class, the RT-containing class, and in this book references to RNA viruses, or to DNA viruses are not meant to apply to the retroviruses.

All viruses, with one exception, are haploid; that is, they contain only one copy of the genomic nucleic acid. The exception is the retroviruses, which are diploid and contain two identical copies of the single-stranded genomic RNA. The nucleic acid genome may consist of a single piece of DNA or RNA or may consist of two or more nonidentical fragments. The latter can be considered analogous to chromosomes and can reassort during replication. In the case of animal viruses, when a virus has more than one genome segment, all of the different segments are present within a single virus particle. In the case of plant viruses with multiple genome segments, it is quite common for the different genome segments to be separately encapsidated into different particles. In this case, the infectious unit is multipartite: Infection to produce a complete replication cycle requires simultaneous infection by particles containing all of the different genome segments. Although this does not seem to pose a problem for the transmission of plant viruses, it must pose a problem for the transmission of animal viruses since such animal viruses have not been found. This difference probably arises because of different modes of transmission, the fact that many plant viruses grow to exceptionally high titers, and the fact that many plants grow to very high density.

The ICTV Classification of Viruses

The International Committee on Taxonomy of Viruses (ICTV), a committee organized by the Virology Division of the International Union of Microbiological Societies, is attempting to devise a uniform system for the classification and nomenclature of all viruses. Viruses are classified into species on the basis of a close, but not necessarily identical, relationship. The decision as to what constitutes a species is arbitrary because a species usually contains many different strains that may differ significantly (10% or more) in nucleotide sequence. Whether two isolates should be considered as being the same species rather than representing two different species can be controversial. Virus species that exhibit close relationships are then grouped into a genus. Species within a genus usually share significant nucleotide sequence identity demonstrated by antigenic cross reaction or by direct sequencing of the genome. Genera are grouped into families, which can be considered the fundamental unit of virus taxonomy. Classification into families is based on the type and size of the nucleic acid genome, the structure of the virion, and the strategy of replication used by the virus, which is determined in part by the organization of the genome. Groupings into families are not always straightforward because little or no sequence identity is present between members of different genera. However, uniting viruses into families attempts to recognize evolutionary relationships and is valuable for organizing information about viruses.

Higher taxonomic classifications have not been recognized for the most part. To date only three orders have been established that group together a few families. Taxonomic classification at higher levels is difficult because viruses evolve rapidly and it can be difficult to prove that any two given families are descended from a common ancestor, although it is almost certain that higher groupings based on common evolution do exist and will be elucidated with time. Viral evolution involves not only sequence divergence, however, but also the widespread occurrence of recombination during the rise of the modern families, a feature that blurs the genetic relationships between viruses. Two families may share, for example, a related polymerase gene but have structural protein genes that appear unrelated; how should such viruses be classified?

The ICTV has recognized almost 4000 viruses as species (more than 30,000 strains of viruses exist in collections around the world), and classified these 3954 species into 203 genera belonging to 56 families plus 30 "floating" genera that have not yet been assigned to a family. An overview of these families, in which viruses that cause human disease are emphasized, is shown in Table 1.2. Included in the table is the type of nucleic acid that serves as the genome, the genome size, the names of many families, and the major groups of hosts infected by viruses within each grouping. For many families the names and detailed characteristics are not shown here, but a complete listing of families can be found in the reports of the ICTV on virus taxonomy or in *The Encyclopedia of Virology* (2nd

TABLE 1.2 Major Virus Families

Nucleic acid	Genome size	Segments	Family	Major hosts (number of members infecting that host)[a]	
DS DNA	130–375 kbp	1	Poxviridae	Vertebrates (38), insects (25), plus 15 U[b]	
	170–190 kbp	1	Asfariviridae	Vertebrates (1)	
	170–400 kbp	1	Iridoviridae	Vertebrates (11), insects (6)	
	120–220 kbp	1	Herpesviridae	Vertebrates (56 + 65T)[c]	
	90–230 kbp	1	Baculoviridae	Insects (17 + 7T)	
	36–48 kbp	1	Adenoviridae	Vertebrates (26 + 35T)	
	5 kbp	1	Polyomaviridae	Vertebrates (12)	
	6.8–8.4 kbp	1	Papillomaviridae	Vertebrates (7 + 88T)	
	Various	1	Several families	Bacteria (42 + 368T)	
SS DNA	6–8 kb	1	Parvoviridae	Vertebrates (31), insects (7), plus 15U	
	Various	1	Several families	Bacteria (43 + 38T), plants (98 + 11T)	
DS RNA	20–30 kbp	10–12	Reoviridae	Vertebrates (174 + 22T), insects (66), plants (10)	
	5.9 kbp	2	Birnaviridae	Chickens (1), fish (2), drosophila (1)	
	4.6–7.0 kbp	1 or 2	Three families	Fungi (7 + 7T), plants (30 + 15T), protozoans (14)	
SS(+) RNA	28–33 kb	1	Coronaviridae	Vertebrates (16 + 1T)	
	13–16 kb	1	Arteriviridae	Vertebrates (4)	
	10–13 kb	1	Togaviridae	Vertebrates (insect vectors) (23)	
	10–12 kb	1	Flaviviridae	Vertebrates (some insect vectors) (57 + 6T)	
	7–8.5 kb	1	Picornaviridae	Vertebrates (16 + 137T)	
	7–8 kb	1	Astroviridae	Vertebrates (6)	
	8 kb	1	Caliciviridae	Vertebrates (6 plus 8T)	
	Various	1	Many families	Plants (331 + 219T)	
SS (–) RNA	15–16 kb	1	Paramyxoviridae	Vertebrates (31 + 2T)	
	13 kb	1	Filoviridae	Vertebrates (5)	
	13–16	1	Rhabdoviridae	Vertebrates (23 + 81T), plants (14 + 61T)	
	9 kb	1	Bornaviridae	Vertebrates (1)	
	13 kb	8	Orthomyxoviridae	Vertebrates (5)	
	12–23 kb	3	Bunyaviridae	Vertebrates and insect vectors (91 + 66T), plants (2)	
	11 kb	2	Arenaviridae	Vertebrates (19 + 2T)	
SS RNA RT	7–10 kb	dimer	Retroviridae	Vertebrates (59 + 2T)	DNA intermediate
DS DNA RT	3 kbp	1	Hepadnaviridae	Vertebrates (5 + 2T)	RNA intermediate
	8 kbp	1	Caulimoviridae	Plants (26 + 8T)	RNA intermediate

Source: This is according to Granoff and Webster (1999).

[a]Where underlined, humans are among the vertebrates infected.

[b]U = assigned to the family, but not to any particular genus within the family.

[c]T = tentatively assigned to a particular genus.