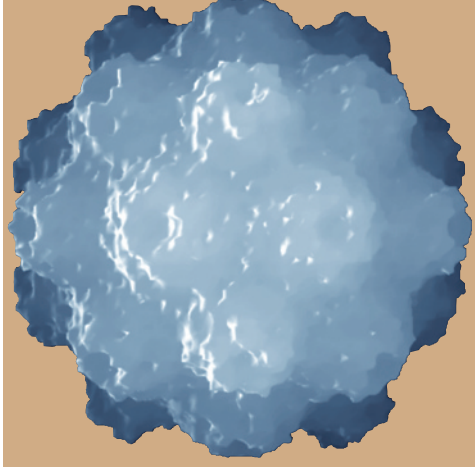
Virology and Viral Disease



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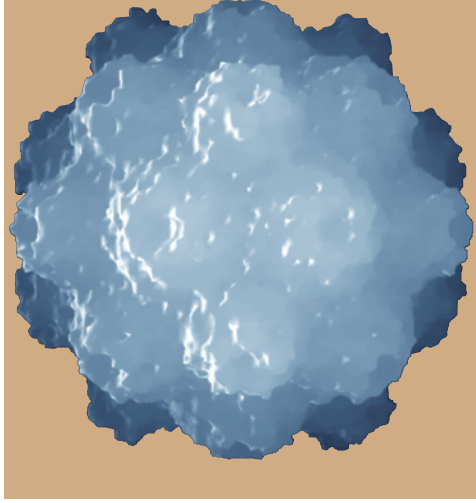
Introduction – The Impact of Viruses on Our View of Life



CHAPTER 1

- THE SCIENCE OF VIROLOGY
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THE SCIENCE OF VIROLOGY

The study of viruses has historically provided and continues to provide the basis for much of our most fundamental understanding of modern biology, genetics, and medicine. Virology has had an impact on the study of biological macromolecules, processes of cellular gene expression, mechanisms for generating genetic diversity, processes involved in the control of cell growth and development, aspects of molecular evolution, the mechanism of disease and response of the host to it, and the spread of disease in populations.

In essence, viruses are collections of genetic information directed toward one end: their own replication. They are the ultimate and prototypical example of "**selfish genes**." The viral genome contains the "blueprints" for virus replication enciphered in the genetic code, and must be decoded by the molecular machinery of the cell that it infects to gain this end. Viruses are; thus, obligate intracellular parasites dependent on the metabolic and genetic functions of living cells.

Given the essential simplicity of virus organization – a genome containing genes dedicated to self replication surrounded by a protective protein shell – it has been argued that viruses are nonliving collections of biochemicals whose functions are derivative and separable from the cell. Yet this generalization does not stand up to the increasingly detailed information accumulating describing the nature of viral genes, the role of viral infections on evolutionary change, and the evolution of cellular function. A view of viruses as constituting a major

subdivision of the **biosphere** as ancient as and fully interactive and integrated with the three great branches of cellular life becomes more strongly established with each investigational advance.

It is a major problem in the study of biology at a detailed molecular and functional level that almost no generalization is sacred, and the concept of viruses as simple parasitic collections of genes functioning to replicate themselves at the expense of the cell they attack does not hold up. Many generalizations will be made in the survey of the world of viruses introduced in this book, most if not all will be ultimately classified as being useful, but unreliable tools for the full understanding and organization of information.

Even the size range of viral genomes, generalized to range from one or two genes to a few hundred at most (significantly less than those contained in the simplest free living cells), cannot be supported by a close analysis of data. While it is true that the vast majority of viruses studied range in size from smaller than the smallest organelle to just smaller than the simplest cells capable of energy metabolism and protein synthesis, the mycoplasma and simple unicellular algae, the recently discovered **Mimivirus** (distantly related to **poxviruses** such as smallpox or **variola**) contains nearly 1000 genes and is significantly larger than the smallest cells. With such caveats in mind it is still appropriate to note that despite their limited size, viruses have evolved and appropriated a means of propagation and replication that ensures their survival in free-living organisms that are generally between 10 and 10,000,000 times their size and genetic complexity.

The effect of virus infections on the host organism and populations – viral pathogenesis, virulence, and epidemiology

Since a major motivating factor for the study of virology is that viruses cause disease of varying levels of severity in human populations and in the populations of plants and animals which support such populations, it is not particularly surprising that virus infections have historically been considered episodic interruptions of the well being of a normally healthy host. This view was supported in some of the earliest studies on bacterial viruses, which were seen to cause the destruction of the host cell and general disruption of healthy, growing populations of the host bacteria. Despite this, it was seen with another type of bacterial virus that a persistent, **lysogenic**, infection could ensue in the host population. In this case, stress to the lysogenic bacteria could release infectious virus long after the establishment of the initial infection.

These two modes of infection of host populations by viruses, which can be accurately modeled by mathematical methods developed for studying predator–prey relationships in animal and plant populations, are now understood to be general for virus–host interactions. Indeed, persistent infections with low or no levels of viral disease are universal in virus–host ecosystems that have evolved together for extended periods – it is only upon the introduction of a virus into a novel population that widespread disease and host **morbidity** occurs.

While we can, thus, consider severe virus-induced disease to be evidence of a recent introduction of the virus into the population in question, the accommodation of the one to the other is a very slow process requiring genetic changes in both virus and host, and it is by no means certain that the accommodation can occur without severe disruption of the host population – even its extinction. For this reason, the study of the replication and propagation of a given virus in a population is of critical importance to the body politic, especially in terms of formulating and implementing health policy. This is, of course, in addition to its importance to the scientific and medical communities.

The study of effects of viral infection on the host is broadly defined as the study of viral **pathogenesis**. The sum total of the virus-encoded functions that contribute to virus propaga-

tion in the infected cell, in the host organism, and in the population is defined as *pathogenicity* of that virus. This term essentially describes the genetic ability of members of a given specific virus population (which can be considered to be genetically more or less equivalent) to cause a disease and spread through (**propagate** in) a population. Thus, a major factor in the pathogenicity of a given virus is its genetic makeup or **genotype**.

The basis for severity of the symptoms of a viral disease in an organism or a population is complex. It results from an intricate combination of expression of the viral genes controlling pathogenicity, physiological response of the infected individual to these pathogenic determinants, and response of the population to the presence of the virus propagating in it. Taken together, these factors determine or define the **virulence** of the virus and the disease it causes.

A basic factor contributing to virulence is the interaction among specific viral genes and the genetically encoded defenses of the infected individual. It is important to understand, however, that virulence is also affected by the general health and genetic makeup of the infected population, and in humans, by the societal and economic factors that affect the nature and extent of the response to the infection.

The distinction and gradation of meanings between the terms *pathogenesis* and *virulence* can be understood by considering the manifold factors involved in disease severity and spread exhibited in a human population subjected to infection with a disease-causing virus. Consider a virus whose genotype makes it highly efficient in causing a disease, the symptoms of which are important in the spread between individuals – perhaps a respiratory infection with accompanying sneezing, coughing, and so on. This ideal or optimal virus will incorporate numerous, random genetic changes during its replication cycles as it spreads in an individual and in the population. Some viruses generated during the course of a disease may, then, contain genes that are not optimally efficient in causing symptoms. Such a virus is of reduced virulence, and in the extreme case, it might be a virus that has accumulated so many mutations in pathogenic genes that it can cause no disease at all (i.e., has mutated to an **avirulent** or **apathogenic** strain). While an avirulent virus may not cause a disease, its infection may well lead to complete or partial **immunity** against the most virulent genotypes in an infected individual. This is the basis of **vaccination**, which is described in Chapter 8, Part II. But the capacity to generate an immune response and the resulting generation of **herd immunity** also means that as a virus infection proceeds in a population, its virulence either must change or the virus must genetically adapt to the changing host.

Other factors not fully correlated with the genetic makeup of a virus also contribute to variations in virulence of a pathogenic genotype. The same virus genotype infecting two **immunologically naive** individuals (i.e., individuals who have never been exposed to any form of the virus leading to an immune response) can cause very different outcomes. One individual might only have the mildest symptoms because of exposure to a small amount of virus, or infection via a suboptimal route, or a robust set of immune and other defense factors inherent in his or her genetic makeup. Another individual might have a very severe set of symptoms or even death if he or she receives a large inoculum, or has impaired immune defenses, or happens to be physically stressed due to malnutrition or other diseases.

Also, the same virus genotype might cause significantly different levels of disease within two more or less genetically equivalent populations that differ in economic and technological resources. This could happen because of differences in the ability of one society's support net to provide for effective medical treatment, or to provide for isolation of infected individuals, or to have available the most effective treatment protocols.

Taken in whole, the study of human infectious disease caused by viruses and other pathogens defines the field of **epidemiology** (in animals it is termed **epizoology**). This field requires a good understanding of the nature of the disease under study and the types of medical and other

remedies available to treat it and counter its spread, and some appreciation for the dynamics and particular nuances and peculiarities of the society or population in which the disease occurs.

The interaction between viruses and their hosts

The interaction between viruses (and other infectious agents) and their hosts is a dynamic one. As effective physiological responses to infectious disease have evolved in the organism and (more recently) have developed in society through application of biomedical research, viruses themselves respond by exploiting their naturally occurring genetic variation to accumulate and select mutations to become wholly or partially resistant to these responses. In extreme cases, such resistance will lead to periodic or episodic reemergence of a previously controlled disease – the most obvious example of this process is the periodic appearance of human influenza viruses caused disease.

The accelerating rate of human exploitation of the physical environment and the accelerating increase in agricultural populations afford some viruses new opportunities to "break out" and spread both old and novel diseases. Evidence of this is the ongoing **acquired immune deficiency syndrome (AIDS)** epidemic, as well as sporadic occurrences of viral diseases, such as hemorrhagic fevers in Asia, Africa, and southwestern United States. Investigation of the course of a viral disease, as well as societal responses to it, provides a ready means to study the role of social policies and social behavior of disease in general.

The recent worldwide spread of AIDS is an excellent example of the role played by economic factors and other aspects of human behavior in the origin of a disease. There is strong evidence to support the view that the causative agent, **human immunodeficiency virus (HIV)**, was introduced into the human population by an event fostered by agricultural encroachment of animal habitats in equatorial Africa. This is an example of how economic need has accentuated risk.

HIV is not an efficient pathogen; it requires direct inoculation of infected blood or body fluids for spread. In the Euro-American world, the urban concentration of homosexual males with sexual habits favoring a high risk for venereal disease had a major role in spreading HIV and resulting in AIDS throughout the male homosexual community. A partial overlap of this population with intravenous drug users and participants in the commercial sex industry resulted in spread of the virus and disease to other portions of urban populations. The result is that in Western Europe and North America, AIDS has been a double-edged sword threatening two disparate urban populations: the relatively affluent homosexual community and the impoverished heterosexual world of drug abusers – both highly concentrated urban populations. In the latter population, the use of commercial sex as a way of obtaining money resulted in further spread to other heterosexual communities, especially those of young, single men and women.

An additional factor is that the relatively solid medical and financial resources of a large subset of the "economic first world" resulted in wide use of whole blood transfusion, and more significantly, pooled blood fractions for therapeutic use. This led to the sudden appearance of AIDS in hemophiliacs and sporadically in recipients of massive transfusions due to intensive surgery. Luckily, the incidence of disease in these last risk populations has been reduced owing to effective measures for screening blood products.

Different societal factors resulted in a different distribution of HIV and AIDS in equatorial Africa and Southeast Asia. In these areas of the world, the disease is almost exclusively found in heterosexual populations. This distribution of AIDS occurred because a relatively small concentration of urban commercial sex workers acted as the source of infection of working men

living apart from their families. The periodic travel by men to their isolated village homes resulted in the virus being found with increasing frequency in isolated family units. Further spread resulted from infected women leaving brothels and prostitution to return to their villages to take up family life.

Another overweening factor in the spread of AIDS is technology. HIV could not have spread and posed the threat it now does in the world of a century ago. Generally lower population densities and lower concentrations of individuals at risk at that time would have precluded HIV from gaining a foothold in the population. Slower rates of communication and much more restricted travel and migration would have precluded rapid spread; also the transmission of blood and blood products as therapeutic tools was unknown a century ago.

Of course, this dynamic interaction between pathogen and host is not confined to viruses; any pathogen exhibits it. The study and characterization of the genetic accommodations viruses make, both to natural resistance generated in a population of susceptible hosts and to human-directed efforts at controlling the spread of viral disease, provide much insight into evolutionary processes and population dynamics. Indeed, many of the methodologies developed for the study of interactions between organisms and their environment can be applied to the interaction between pathogen and host.

The history of virology

The historic reason for the discovery and characterization of viruses, and a continuing major reason for their detailed study, involves the desire to understand and control the diseases and attending degrees of economic and individual distress caused by them. As studies progressed, it became clear that there were many other important reasons for the study of viruses and their replication.

Since viruses are parasitic on the molecular processes of gene expression and its regulation in the host cell, an understanding of viral genomes and virus replication provides basic information concerning cellular processes in general.

The whole development of molecular biology and molecular genetics is largely based on the deliberate choice of some insightful pioneers of "pure" biological research to study the replication and genetics of viruses that replicate in bacteria: the bacteriophages. (Such researchers include Max Delbrück, Salvadore Luria, Joshua Lederberg, Gunther Stent, Seymour Benzer, Andre Lwoff, François Jacob, Jacques Monod, and many others.)

The bacterial viruses (**bacteriophage**) were discovered through their ability to destroy human enteric bacteria such as *Escherichia coli*, but they had no clear relevance to human disease. It is only in retrospect that the grand unity of biological processes from the most simple to the most complex can be seen as mirrored in replication of viruses and the cells they infect.

The biological insights offered by the study of viruses have led to important developments in biomedical technology and promise to lead to even more dramatic developments and tools. For example, when infecting an individual, viruses target specific tissues. The resulting specific symptoms, as already noted, define their pathogenicity. The normal human, like all vertebrates, can mount a defined and profound response to virus infections. This response often leads to partial or complete immunity to reinfection. The study of these processes was instrumental to gaining an increasingly clear understanding of the immune response and the precise molecular nature of cell–cell signaling pathways. It also provided therapeutic and preventive strategies against specific virus-caused disease. The study of virology has and will continue to provide strategies for the **palliative treatment** of metabolic and genetic diseases not only in humans, but also in other economically and aesthetically important animal and plant populations.

Examples of the impact of viral disease on human history

There is archeological evidence in Egyptian mummies and medical texts of readily identifiable viral infections, including genital papillomas (warts) and poliomyelitis. There are also somewhat imperfect historical records of viral disease affecting human populations in classical and medieval times. While the recent campaign to eradicate smallpox has been successful and it no longer exists in the human population (owing to the effectiveness of vaccines against it, the genetic stability of the virus, and a well-orchestrated political and social effort to carry out the eradication), the disease periodically wreaked havoc and had profound effects on human history over thousands of years. Smallpox epidemics during the Middle Ages and later in Europe resulted in significant population losses as well as major changes in the economic, religious, political, and social life of individuals. Although the effectiveness of vaccination strategies gradually led to decline of the disease in Europe and North America, smallpox continued to cause massive mortality and disruption in other parts of the world until after World War II. Despite its being eradicated from the environment, the attack of September 11, 2001 on the World Trade Center in New York has lead some government officials to be concerned that the high virulence of the virus and its mode of spread might make it an attractive agent for **bioterrorism**.

Other virus-mediated epidemics had equally major roles in human history. Much of the social, economic, and political chaos in native populations resulting from European conquests and expansion from the fifteenth through nineteenth centuries was mediated by introduction of infectious viral diseases such as measles. Significant fractions of the indigenous population of the western hemisphere died as a result of these diseases.

Potential for major social and political disruption of everyday life continues to this day. As discussed in later chapters of this book, the "Spanish" influenza (H1N1) epidemic of 1918–19 killed tens of millions worldwide and, in conjunction with the effects of World War I, came very close to causing a major disruption of world civilization. Remarkable medical detective work using virus isolated from cadavers of victims of this disease frozen in Alaskan permafrost has lead to recovery of the complete genomic sequence of the virus and reconstruction of the virus itself (some of the methods used will be outlined in Part V). While we may never know all the factors that caused it to be so deadly, it is clear that the virus was derived from birds passing it directly to humans. Further, a number of viral proteins have a role in its virulence. Ominously, there is no reason why another strain of influenza could not arise with a similar or more devastating aftermath or **sequela** – indeed as of the spring/summer of 2005 there is legitimate cause for concern because a new strain of avian influenza (H5N1) has been transmitted to humans. At the present time, human transmission of H5N1 influenza has not been confirmed, but further adaptation of this new virus to humans could lead to its establishing itself as a major killer in the near future.

A number of infectious diseases could become established in the general population as a consequence of their becoming drug resistant, human disruption of natural ecosystems, or introduced as weapons of bioterrorism. As will be discussed in later chapters, a number of different viruses exhibiting different details of replication and spread could, potentially, be causative agents of such diseases.

Animal and plant pathogens are other potential sources of disruptive viral infections. Sporadic outbreaks of viral disease in domestic animals, for example, vesicular stomatitis virus in cattle and avian influenza in chickens, result in significant economic and personal losses. Rabies in wild animal populations in the eastern United States has spread continually during the past half-century. The presence of this disease poses real threats to domestic animals and through them occasionally, to humans. An example of an agricultural infection leading to severe economic disruption is the growing spread of the Cadang-cadang viroid in coconut palms of the

Philippine Islands and elsewhere in Oceania. The loss of coconut palms led to serious financial hardship in local populations.

Examples of the evolutionary impact of the virus–host interaction

There is ample genetic evidence that the interaction between viruses and their hosts had a measurable impact on evolution of the host. Viruses provide environmental stresses to which organisms evolve responses. Also, it is possible that the ability of viruses to acquire and move genes between organisms provides a mechanism of gene transfer between lineages.

Development of the immune system, the cellular-based antiviral **interferon (IFN)** response, and many of the inflammatory and other responses that multicellular organisms can mount to ward off infection is the result of successful genetic adaptation to infection. More than this, virus infection may provide an important (and as yet underappreciated) basic mechanism to affect the evolutionary process in a direct way.

There is good circumstantial evidence that the specific origin of placental mammals is the result of an ancestral species being infected with an immunosuppressive proto-retrovirus. It is suggested that this immunosuppression permitted an immunological accommodation in the mother to the development of a genetically distinct individual in the placenta during a prolonged period of gestation!

Two current examples provide very strong evidence for the continued role of viruses in the evolution of animals and plants. Certain parasitic wasps lay their eggs in the caterpillars of other insects. As the wasp larvae develop, they devour the host, leaving the vital parts for last to ensure that the food supply stays fresh! Naturally, the host does not appreciate this attack and mounts an immune defense against the invader – especially at the earliest stages of the wasp's embryonic development. The wasps uninfected with a **polydnavirus** do not have a high success rate for their parasitism and their larvae are often destroyed. The case is different when the same species of wasp is infected with a polydnavirus that is then maintained as a persistent genetic passenger in the ovaries and egg cells of the wasps. The polydnavirus inserted into the caterpillar along with the wasp egg induces a systemic, immunosuppressive infection so that the caterpillar cannot eliminate the embryonic tissue at an early stage of development! The virus maintains itself by persisting in the ovaries of the developing female wasps.

A further example of a virus's role in development of a symbiotic relationship between its host and another organism can be seen in replication of the ***Chlorella* viruses**. These viruses are found at concentrations as high as 4×10^4 infectious units/ml in freshwater throughout the United States, China, and probably elsewhere in the world. Such levels demonstrate that the virus is a very successful pathogen. Despite this success, the viruses can only infect free algae; they cannot infect the same algae when the algae exist semi-symbiotically with a species of paramecium. Thus, the algae cells that remain within their symbiotes are protected from infection, and it is a good guess that existence of the virus is a strong selective pressure toward establishing or stabilizing the symbiotic relationship.

The origin of viruses

In the last decade or so, molecular biologists have developed a number of powerful techniques to amplify and sequence the genome of any organism or virus of interest. The correlation between sequence data, classical physiological, biochemical and morphological analyses and the geological record has provided one of the triumphs of modern biology. We now know that the biosphere is made up of three major superkingdoms, the **eubacteria**, the **eukaryotes** (nucleated

cells), and the **archaebacteria** – the latter only discovered through the **ribosomal** RNA (**rRNA**) sequence studies of Woese and his colleagues in the past 15 years or so. Further, analysis of genetic changes in conserved sequences of critical proteins as well as ribosomal RNA confirm that eukaryotes are more closely related to and, thus, derived from the ancestors of archaea than they are eubacteria.

Carefully controlled statistical analysis of the frequency and numbers of base changes in genes encoding conserved enzymes and proteins mediating essential metabolic and other cellular processes can be used to both measure the degree of relatedness between greatly divergent organisms, and provide a sense of when in the evolutionary time scale they diverged from a common ancestor. This information can be used to generate a **phylogenetic tree**, which graphically displays such relationships. An example of such a tree showing the degree of divergence of some index species in the three superkingdoms is shown in Fig. 1.1.

Although there is no geological record of viruses (they do not form fossils in any currently useful sense), the analysis of the relationship between the amino acid sequences of viral and cellular proteins and that of the nucleotide sequences of the genes encoding them provide ample genetic evidence that the association between viruses and their hosts is as ancient as the origin of the hosts themselves. Some viruses (e.g., retroviruses) integrate their genetic material into the cell they infect, and if this cell happens to be germ line, the viral genome (or its relict) can be maintained essentially forever. Analysis of the sequence relationship between various retroviruses found in mammalian genomes demonstrates integration of some types before major groups of mammals diverged.

While the geological record cannot provide evidence of when or how viruses originated, genetics offers some important clues. First, the vast majority of viruses do not encode genes for ribosomal proteins or genetic evidence of relicts of such genes. Second, this same vast majority

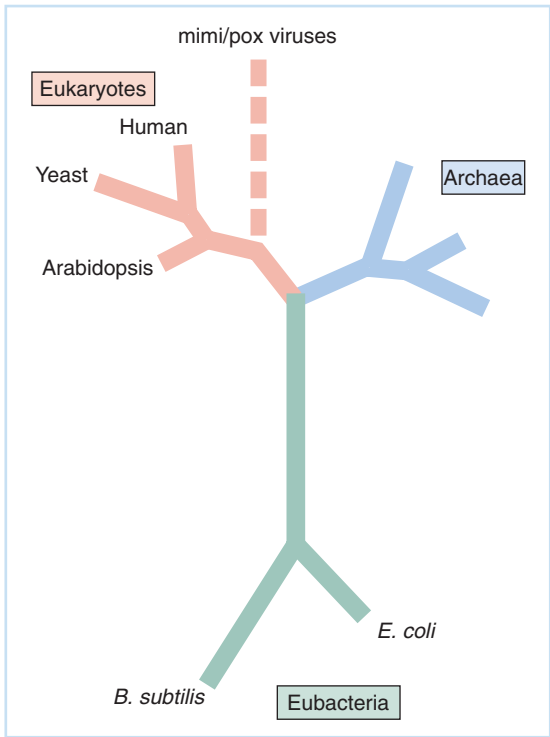

Fig. 1.1 A phylogenetic tree of selected species from the three superkingdoms of life, Eukaryotes, Eubacteria, and Archaea. The tree is based upon statistical analysis of sequence variation in seven universally conserved protein sequences: arginyl-t-RNA synthetase, methionyl-t-RNA synthetase, tyrosyl-t-RNA synthetase, RNA pol II largest subunit, RNA pol II second largest subunit, PCNA, and 5′–3′ exonuclease.(Figure based upon Raoult et al. The 1.2-megabase genome sequence of mimivirus. Science 2004;306:1344–1350.)

of viruses does not contain genetic evidence of ever having encoded enzymes involved in energy metabolism. This is convincing evidence that the viruses currently investigated did not evolve from free-living organisms. This finding distinctly contrasts with two eukaryotic organelles, the mitochondrion and the chloroplast, which are known to be derived from free-living organisms.

Genetics also demonstrates that a large number of virus-encoded enzymes and proteins have a common origin with cellular ones of similar or related function. For example, many viruses containing DNA as their genetic material have viral-encoded DNA polymerases that are related to all other DNA polyisomerases isolated from plants, animals, and archaea.

Statistical analysis of the divergence in three highly conserved regions of eukaryotic DNA polymerases suggests that the viral enzymes including both those from **herpesviruses**, and **poxviruses** and relatives (including mimiviruses) have existed as long as have the three superkingdoms themselves. Indeed, convincing arguments exist that the viral enzymes are more similar to the ancestral form. This, in turn, implies that viruses or virus-like self-replicating entities (**replicons**) had a major role, if not the major role, in the origin of DNA-based genetics. The phylogenetic tree of relationships between two forms of eukaryotic DNA polymerase (alpha and delta), and two forms of the enzyme found in archaebacteria as well as those of three groups of large DNA viruses and some other DNA viruses infecting algae and protests is shown Fig. 1.2.

Another example of the close genetic interweaving of early cellular and early viral life forms is seen in the sequence analysis of the reverse transcriptase enzyme encoded by retroviruses, which is absolutely required for converting retroviral genetic information contained in RNA to DNA. This enzyme is related to an important eukaryotic enzyme involved in reduplicating the telomeres of chromosomes upon cell division – an enzyme basic to the eukaryotic mode of genome replication. Reverse transcriptase is also found in cellular transposable genetic elements (**retrotransposons**), which are circular genetic elements that can move from one chromosomal location to another. Thus, the relationship between certain portions of the replication cycle of retroviruses and mechanisms of gene transposition and chromosome maintenance in cells are so intimately involved that it is impossible to say which occurred first.

A major complication to a complete and satisfying scheme for the origin of viruses is that a large proportion of viral genes have no known cellular counterparts, and viruses themselves may be a source of much of the genetic variation seen between different free-living organisms. In an extensive analysis of the relationship between groups of viral and cellular genes, L.P. Villarreal points out that the deduced size of the **Last Universal Common Ancestor (LUCA)** to eukaryotic and prokaryotic cells is on the order of 300 genes – no bigger than a large virus – and provides some very compelling arguments for viruses having provided some of the distinctive genetic elements that distinguish cells of the eukaryotic and prokaryotic kingdoms. In such a scheme, precursors to both viruses and cells originated in **pre-biotic** environment hypothesized to provide the chemical origin of biochemical reactions leading to cellular life.

At the level explored here, it is probably not that useful to expend great efforts to be more definitive about virus origins beyond their functional relationship to the cell and organism they infect. The necessarily close mechanistic relationship between cellular machinery and the genetic manifestations of viruses infecting them makes viruses important biological entities, but it does not make them organisms. They do not grow, they do not metabolize small molecules for energy, and they only "live" when in the active process of infecting a cell and replicating in that cell. The study of these processes, then, must tell as much about the cell and the organism as it does about the virus. This makes the study of viruses of particular interest to biologists of every sort.

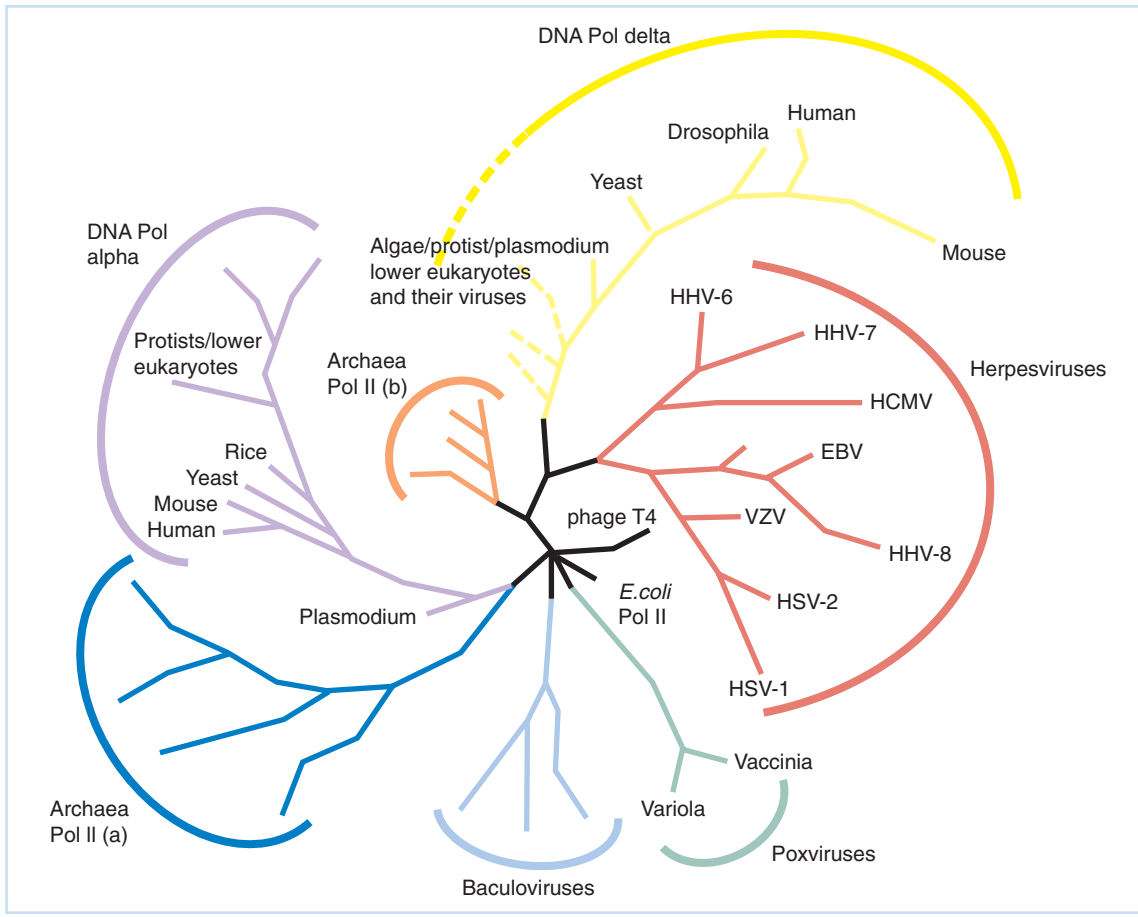

Fig. 1.2 A phylogenetic tree of selected eukaryotic and archaeal species along with specific large DNA-containing viruses based upon sequence divergence in conserved regions of DNA polymerase genes. (Figure based upon Villarreal and DeFilippis. A hypothesis for DNA viruses as the origin of eukaryotic replication proteins. Journal of Virology 2000;74:7079–7084.)

Viruses have a constructive as well as destructive impact on society

Often the media and some politicians would have us believe that infectious diseases and viruses are unremitting evils, but to quote Sportin' Life in Gershwin's *Porgy and Bess*, this "ain't necessarily so." Without the impact of infectious disease, it is unlikely that our increasingly profound understanding of biology would have progressed as it has. As already noted, much of our understanding of the mechanisms of biological processes is based in part or in whole on research carried out on viruses. It is true that unvarnished human curiosity has provided an understanding of many of the basic patterns used to classify organisms and fostered Darwin's intellectual triumph in describing the basis for modern evolutionary theory in his *Origin of Species*. Still, focused investigation on the microscopic world of pathogens needed the spur of medical necessity. The great names of European microbiology of the nineteenth and early twentieth centuries – Pasteur, Koch, Ehrlich, Fleming, and their associates (who did much of the work with which their mentors are credited) – were all medical microbiologists. Most of the justification for today's burgeoning biotechnology industry and research establishment is medical or economic.

Today, we see the promise of adapting many of the basic biochemical processes encoded by viruses to our own ends. Exploitation of viral diseases of animal and plant pests may provide

a useful and regulated means of controlling such pests. While the effect was only temporary and had some disastrous consequences in Europe, the introduction of **myxoma** virus – a pathogen of South American lagomorphs (rabbits and their relatives) – had a positive role in limiting the predations of European rabbits in Australia. Study of the adaptation dynamics of this disease to the rabbit population in Australia taught much about the coadaptation of host and parasite.

The exquisite cellular specificity of virus infection is being adapted to generate biological tools for moving therapeutic and palliative genes into cells and organs of individuals with genetic and degenerative diseases. Modifications of virus-encoded proteins and the genetic manipulation of viral genomes are being exploited to provide new and (hopefully) highly specific **prophylactic** vaccines as well as other therapeutic agents. The list increases monthly.

Viruses are not the smallest self-replicating pathogens

Viruses are not the smallest or the simplest pathogens able to control their self-replication in a host cell – that distinction goes to **prions**. Despite this, the methodology for the study of viruses and the diseases they cause provides the basic methodology for the study of all subcellular pathogens.

By the most basic definition, viruses are composed of a genome and one or more proteins coating that genome. The genetic information for such a protein coat and other information required for the replication of the genome are encoded in that genome. There are genetic variants of viruses that have lost information either for one or more coat proteins or for replication of the genome. Such virus-derived entities are clearly related to a parental form with complete genetic information, and thus, the mutant forms are often termed **defective virus particles**.

Defective viruses require the coinfection of a **helper virus** for their replication; thus, they are parasitic on viruses. A prime example is hepatitis delta virus, which is completely dependent on coinfection with hepatitis B virus for its transmission.

The hepatitis delta virus has some properties in common with a group of RNA pathogens that infect plants and can replicate in them by, as yet, obscure mechanisms. Such RNA molecules, called **viroids**, do not encode any protein, but can be transmitted between plants by mechanical means and can be pathogens of great economic impact.

Some pathogens appear to be entirely composed of protein. These entities, called prions, appear to be cellular proteins with an unusual folding pattern. When they interact with normally folded proteins of the same sort in neural tissue, they appear to be able to induce abnormal refolding of the normal protein. This abnormally folded protein interferes with neuronal cell function and leads to disease. While much research needs to be done on prions, it is clear that they can be transmitted with some degree of efficiency among hosts, and they are extremely difficult to inactivate. Prion diseases of sheep and cattle (**scrapie** and "mad cow" disease) recently had major economic impacts on British agriculture, and several prion diseases (**kuru** and **Creutzfeldt–Jacob disease [CJD]**) affect humans. Disturbingly, passage of sheep scrapie through cattle in England has apparently led to the generation of a new form of human disease similar to, but distinct from, CJD.

The existence of such pathogens provides further circumstantial evidence for the idea that viruses are ultimately derived from cells. It also provides support for the possibility that viruses had multiple origins in evolutionary time.

QUESTIONS FOR CHAPTER 1

1 Viruses are a part of the biosphere. However, there is active debate concerning whether they should be treated as living or nonliving.

(a) Briefly describe one feature of viruses that is also found in cell-based life forms.

(b) Briefly describe one feature of viruses that distinguishes them from cell-based life forms.

2 Why is it likely that viruses have not evolved from free-living organisms?

3 Give examples of infectious agents that are smaller self-replicating systems than viruses.

4 Ebola virus is a deadly (90% case-fatality rate for some strains) infectious agent. Most viruses, however, are not nearly as lethal. Given the nature of viruses, why would you expect this to be so?

5 Given that viruses are a part of the biosphere in which other organisms exist, what might be the kinds of selective pressure that viruses exert on evolution?

6 Viruses were originally discovered because of their size, relative to known bacterial cells. Tobacco mosaic virus was called a "filterable infectious agent" by this criterion. Why is size not a good defining feature for viruses? What is a better definition?