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Chapter 7

Viruses

Section 7.1 Viruses and the meaning of life

The question whether or not “viruses are alive” has caused considerable debate over many years. Yet, the question is effectively without substance because the answer depends entirely on the definition of life or the state of “being alive” that is bound to be arbitrary.

Eugene V. Koonin and Petro Starokadomsky [1]

The first edition of this book, published 7 years ago, includes the following ill-conceived statement: “Viruses lack key features that distinguish life from nonlife. They depend entirely on host cells for replication; they do not partake in metabolism, and do not yield energy; they cannot adjust to changes in their environment (i.e., no homeostasis), nor can they respond to stimuli. Most scientists consider viruses to be mobile genetic elements that travel between cells (such as transposons are mobile genetic elements that travel within a cell)” [2].

As nonliving organisms, dependent entirely on host cells for their continued existence, viruses have done extremely well for themselves [3]. Every class of living organism hosts viruses. Viruses are literally everywhere in our environment, and are the most abundant life form in the oceans, in terms of numbers of organisms [4]. The number of different species of viruses seems to far exceed the species of eukaryotes, bacteria, and archaea [5, 6]. A single class of newly characterized aquatic viruses, the Megaviridae, appears to have more species and more phylogenetic diversity than all of the bacterial and archaean species found in ocean water [7].

Viruses have been on earth for a very long time [8, 9]. The evidence suggesting that viruses preceded the appearance of other classes of living organisms is based in part on the observation that some archaeans, bacteria, and eukaryotes have homologous genes that code for capsid proteins, such as would be derived from a class of viruses. The simplest explanation for homology for a viral-type gene, in all extant cellular forms of life, is that an ancient gene came from viral species that lived at a time that preceded the emergence of newer forms of life [10]. Over the aeons, retroviruses have had a chance to insert lots of DNA fragments into eukaryotic species. At least 8% of the human genome is composed of fragments of RNA viruses [11–13] [Glossary **Capsid**].

Over the past 7 years, the evidence and the arguments, supporting viruses as living organisms, has won a great deal of support. Consider the following points:

Viruses replicate and create virocells

Viruses employ the replicative machinery that they find in host cells, manufacturing viral assembly plants in the process. After infection, host cells forego many of their normal functions, and the newly synthesized viral products produce disturbances in cellular physiology (so-called cytopathic effects). The host cells become something more akin to a viral factory than to eukaryotic organisms, and these new living entities are referred to as virocells, indicating that the virus has created its own form of cellular life [Glossary [Virion](#)].

Viruses exhibit chemical, structural, and physiological diversity

Viruses display great diversity in their range of hosts, habitat, size, genes, mechanisms of infection, and capsids. Unlike eukaryotes, viruses have a range of genomic types, which include: double-stranded DNA; single-stranded DNA; double-stranded RNA; positive sense single-stranded RNA; negative sense single-stranded RNA, single-stranded RNA with a reverse transcriptase, and double-stranded DNA with a reverse transcriptase.

Viruses of each type breed true, meaning that a virus of any type will replicate to produce viruses of the same type. Thus, the types of viruses, determined by their genomic structure and replicative modes, can be organized as biological classes.

Viruses do not lead a totally intracellular life

Viruses are accused of having no life outside of their host cells. It has long been assumed that extracellular viral existence is relegated to long-term storage: a lifeless viral genome double-wrapped in a protein capsid, and an envelope that is mostly purloined from the cell membranes of a former host.

It has been recently demonstrated that some viruses enjoy life outside of their hosts. The Acidianus Tailed Virus can be cold-stored at room temperature for long periods, without changing their morphology. When the temperature rises they undergo a structural transformation, forming bipolar tails [14]. This tells us that viruses can react to external stimuli and perform biological activities, much as free-living organisms do.

Viruses evolve and speciate

It has long been accepted that there are different distinctive species of viruses. The definition of a viral species, as suggested in 1985, is essentially the same definition as any other species of living organism: an evolving gene pool [15]. Despite the high mutation rate of viral genomes, there is sufficient stability in their genomes, particularly in genes that code for constitutive proteins, to establish a phylogenetic lineage for classes of viruses, by examining relatively conserved genomic sequences [16].

Presumably, much of the stability of viral species is imposed by host organisms. How so? All viruses must replicate within a host, and the process by

which a eukaryotic cell is infected and transformed into a virocell is very complex. Viruses are forced to adapt some level of host preference, and must fine-tune all their functions to the available conditions within the host [17]. Thus, for viruses to successfully replicate, they must evolve into relatively stable species. And this is what we observe when we study viruses [Glossary [Evolvability](#)].

Virus speciation yields phylogenetic lineages (i.e., descendant families)

In 2017, the ICTV (International Committee on Taxonomy of Viruses) recognized 9 orders, 131 families, 46 subfamilies, 803 genera, and 4853 different viral species [18]. The number of known viral species (4853) is thought to represent a tiny fraction of the total number. In the next section, “Viral Phylogeny” we will discuss the various concepts and methods that have led to a rudimentary phylogeny of the viruses.

Viruses participate in the evolution of eukaryotic organisms

Some of the greatest evolutionary leaps among eukaryotic organisms can be attributed to genes taken from noneukaryotes (e.g., mitochondria and chloroplasts). The viruses have also contributed to eukaryotic evolution, and it's fair to say that if it were not for viral genes, you would not be reading this book (it would be left to some octopus or insect to finish out the chapter).

Specifically, at least four major advancements can be attributed to retroviral genes inserted into ancient eukaryotic genomes:

- 1. The acquisition of adaptive immunity in Class Gnathostomata (the jawed vertebrates), and every descendant class [19] [Glossary [Adaptive immunity](#)].
- 2. The acquisition of the placenta in Class Theria (i.e., the placental mammals plus the marsupials, which have a rudimentary placenta).
- 3. The maintenance of pluripotent stem cells, important in embryogenesis, is achieved, in part, with transcripts of stem cell-specific long terminal repeat retrotransposons, themselves derived from retroviral sequences [20, 21] [Glossary [Transposon](#)].
- 4. In Class Mus (containing the common house mouse), an MuERV-L retrovirus capsid gene domesticated to code an antiviral factor [22, 23].

We should note that the adaptation of retroviruses does not always have purely beneficial consequences for the individual members of a species. Oncogenes, many of which have a retroviral origin, are genes that play a key role in driving cells toward a cancer phenotype. Oncogenes are highly conserved genes, indicating a beneficial role for the species (otherwise, they would not be conserved). Nonetheless, oncogenes clearly have a deleterious effect on some individuals within the species (i.e., by causing cancer). One particularly striking example occurs in a polycythemia strain of mice carrying the Friend murine leukemia virus. All the mice of this particular strain have polycythemia, a condition characterized by a sustained increase in the number of circulating red blood cells. It seems that the resident virus codes for a nonfunctional Env (viral envelope) gene. The protein coded by the degenerate

Env gene serves as a mimic for the normal erythropoietin gene of the mouse, causing an increase in red cell production (i.e., polycythemia) [24, 25].

Participating in eukaryotic evolution, and accounting in no small way for the generation of new species and new strains of species, as viruses certainly do, are itself a biological function, and another indicator of viral life.

Life is what we choose to make of it.

Are viruses living organisms, or are they simply sequences of nucleic acid that have the wherewithal to move from cell to cell. Much of the debate focuses around the definition of life [1, 26]. How we define life is somewhat arbitrary, and we can certainly produce a definition of life that includes the viruses, if that is what we choose. There's no urgency to the matter. Once our robots become self-replicating, we'll need to address the definition of life anew. When that time comes, perhaps robots will take the lead and create a definition for life that includes organic viruses and software viruses.

Who is the better class of organism: virus or human?

For a moment, let's put our tongues in our cheeks and pretend that we are viruses [8]. As viruses, what would we think of humans and other eukaryotic organisms? Would we be willing to accept humans as fellow living organisms, or would we point to the following list of disqualifiers to conclude that humans just don't make the grade?

- 1. Humans cannot replicate (they merely procreate).

In an effort to strengthen their species' gene pool, humans undergo a strange mating process in which the chromosomes of both parents are hopelessly jumbled together to produce an offspring that is unique, and unlike either the father or the mother. In doing so, humans miss out on the replicative process, performed with the greatest enthusiasm by every virus.

Self-replication is one of the fundamental features of life. Because humans cannot replicate themselves, they barely qualify as living organisms. At least, this is what the viruses think.

- 2. Humans do not react in a manner that preserves the survival of their own species.

Humans have created a variety of weapons that are fully capable of wiping out all of human life. Viruses generally respect one another's right to co-exist.

- 3. We can thank viruses for the existence of humans.

Viruses are constantly donating DNA to humans, and humans have used this DNA to evolve [12]. In point of fact, if there were no viruses, there would be no DNA replication, no adaptive immune system, no placentas, and no humans [27].

We also see that viral species acquire genes from their hosts, and that viruses retain these genes as they evolve. Presumably, the acquisition of host genes confers some survival advantage upon the virus. Nonetheless, viruses are a self-sufficient class of organism, and no specific instance comes to mind wherein a viral species depended on a human gene for its survival.

–4. Humans may have descended from viruses.

Nobody really knows much about the earliest forms of life, and there is plenty of room for conjecture. It's quite feasible that the earliest genetic material consisted of sequences of RNA, and that these RNA molecules moved between the earliest forms of cells. If this were the case, then the earliest genomes were essentially RNA viruses, and this would place humans as direct, but distant descendants of viruses.

There is a current theory, among many competing theories, that the first eukaryotic nucleus was a giant virus that was not totally successful in transforming its proto-eukaryotic host into a virocell [8, 28, 29]. A hybrid giant virus/virocell/proto-eukaryote may have stabilized and replicated to form an early, nucleated cell; the first eukaryote.

–5. Humans serve viruses; not vice versa.

We are taught to think of viruses as fragments of nucleic acids wrapped by a capsid (i.e., the virion). To a virus, extracellular existence must be akin to a state of suspended animation. Virions come back to life when they invade a eukaryotic cell and create a virocell; a living organism consisting of the hijacked eukaryotic cell whose nuclear machinery is redirected to synthesize viral progeny. If every eukaryotic cell is conceptualized as a potential virocell, then every eukaryotic species is a potential slave owned by the viral kingdom. The viruses probably think they're doing us a favor. Frankly, most of the cells in a metazoan body lead a vegetative existence, doomed to a fully differentiated, postmitotic, and short existence. Viruses re-animate postmitotic cells, and create a thriving center for viral life from a lackluster population of eukaryotic cells, as virocells.

Section 7.2 Viral phylogeny

How is it that you keep mutating and can still be the same virus?

Chuck Palahniuk, in his novel, *Invisible Monsters*

If we accept that viruses are living organisms, on equal footing with bacteria, archaeans, and eukaryotes, then we must accept the challenge of creating a classification of viruses based on phylogeny (descent from evolving ancestral species), and abandon viral groupings based solely on phenetics (i.e., based on physical similarities). **There is a problem with the notion of a purely phylogenetic classification of viruses; it may be impossible** [Glossary [Phenetics](#)].

Let's take a look at a few of the impediments to establishing a viral phylogeny that is comprehensive, testable, and credible.

-1. Large number of known and unknown viral species

Simply put, the greater the number of species, the more work is required to prepare a taxonomy. Every new species requires a certain irreducible amount of study, and if new species are being discovered at a rate that exceeds our ability to describe and classify known species, then the list of unassigned species will become infinitely long over time.

-2. Lack of any accepted concept of a “root” virus

The classification of cellular organisms is built on the premise that each of the major classes (i.e., bacteria, archaeans, and eukaryotes) has a root or founder class, with a hypothesized set of class-defined features, from which all subclasses descended. In the case of viruses, we really have no way of describing the ancestor of all extant viruses, and we do not have a strong reason to assume that all the viruses we see today came from any single class of viruses.

Furthermore, we define viruses as being obligatory parasites, requiring one of the major classes of cellular organisms for a host. If this were the case, then viruses, as we have come to define them, could not have existed prior to the existence of host organisms to parasitize. Hence, if viruses existed prior to the emergence of cellular life, then the root of the viruses was not a virus, insofar as they could not have parasitized cellular hosts. If the root of the viruses was not a virus, then it may have been almost anything, and we could not rule out the existence of multiple root organisms, accounting for the widely varying versions of viral genomes that we observe today.

Games of phylogenetic logic are harmless fun, but they illustrate how it is impossible to create a top-down classification of viruses, if we know nothing about the biological features that would define the top class.

-3. High rate of mutation in viruses

For the most part, viruses do not repair their genomes. A notable exception is the megavirus *Cafeteria roenbergensis* [30]. Presumably, we will find that other megaviruses have DNA repair pathways, but the small, simple viruses have rates of mutation in DNA and RNA, with no mechanism to repair the damage. This means that genome-damaged viruses have two choices: to die or to live with, and replicate, their mutations. Consequently, viral genomes tend to degenerate quickly, producing lots of variants. Species mutability is particularly prevalent among the RNA viruses (e.g., influenza virus, Newcastle disease virus, and foot and mouth disease virus).

Mutational variations of a virus seldom produce a new species. Instead, variations produce diversity in the viral gene pool of the species. If new mutations do not produce an alteration in the specificity of host organisms, or in the construction of the virocell, then the variant viral replicants resulting from mutations will usually preserve their membership in the same viral species [Glossary [Virocell](#)].

Still, all those viral genomic variants complicate the job of the viral taxonomist. Basically, the high rate of mutation in viruses yields lots of genomic variation among viral populations, making it easy for bioinformaticians to detect species diversity where none exists. We can easily imagine a situation wherein new species are discovered, and old species are declared extinct, because we simply do not have the time and manpower to carefully examine every genomic variant for the structural and physiologic features that determine its correct taxonomic classification. Bioinformaticians off-handedly refer to the variant genomes, resulting from mutations and replication errors, as quasispecies [31]. For the traditional taxonomist who is trying to create a simple phylogenetic classification of viruses, the vague concept of “quasispecies” must be particularly exasperating.

–4. Multiparental lineage of viruses

Viral reassortment is a process wherein whole segments (the equivalent of viral chromosomes) are exchanged between two viruses infecting the same cell. Viral reassortment has been observed in four classes of segmental RNA viruses: Bunyaviridae, Orthomyxoviridae, Arenaviridae, and Reoviridae. Following reassortment, a new species of virus may appear, and this new species will contain segments of two parental species. This poses a serious problem for traditional taxonomists, who labor under the assumption that each new species has one and only one parental species [32]. It is the uniparental ancestry of biological classifications that accounts for their simplicity, and for the concept of lineage, wherein the ancestry of any species can be computed from an uninterrupted line of classes stretching from the species level to the root level. When a species has more than one parent, then its lineage is replaced by an inverted tree. The tree branches outwards with each class reaching to more than one parent class, iteratively, producing a highly complex ancestry wherein the individual classes have mixed heritage.

Bioinformaticians have no problem creating multiparental classifications, and have used them to organize and model for biological processes (e.g., pathways), and molecular components (e.g., genes and proteins) [33]. They call such constructs ontologies, and have an assortment of computational tools to construct, deconstruct, and analyze complex representations of class relationships.

The pros and cons of single-parent class relationships versus multiparent class relationships have been argued at great length in the bioinformatics literature and cannot be fully explored here [34, 35]. Suffice it to say that no matter how many species we must accommodate, a simple classification will always provide an ordered set of class relationships that can be fully absorbed by the human mind. Ontologies are highly complex, often uncomputable, and chaotic (e.g., providing different analytic solutions with repeated analyses of the same data) [34]. It remains to be seen whether the ontologic model can be usefully applied to viral classifications.

Hope for a viral classification, based on phylogeny

Despite these four listed impediments to viral classification, there is reason to hope that there will one day be a complete set of viral classes and a simple set of lineages that connect each viral class to a defined “root” organism. A sense of hopefulness is based, in no small part, on observations of the physical world. Despite our sense that anything is possible in the vastness of space, we see an awful lot of sameness throughout the universe. Wherever we aim our telescopes, we see galaxies, most of which are flat and spiral, often having about the same size, and composed of the same objects: stars, planets, gas, dust, and black holes. A small set of physical laws impose stability everywhere at once, and the result is the somewhat repetitious universe in which we live. Likewise, despite the large number of species living on our planet, they are all variations of a few common themes that can be encapsulated under a simple classification.

About a half billion years ago, the early metazoan classes (i.e., animals) evolved at a rapid rate, producing dozens of body plans that we can examine in ancient shale deposits. This period, which lasted about 40 million years or so, is known as the Cambrian Explosion. The same body plans that evolved during the Cambrian explosion account for nearly all of the classes of animals that live today. This is to say that since the Cambrian, no new body plans have gained entry into the metazoan world. Much has been written about the Cambrian explosion, much of it focused on why metazoan body plans are so few, and why the world lacks newly evolved entries [36]. We have observed as a general rule of biology, that no matter how easy it may be for a class of organisms to speciate, there always seems to be a limited number of general classes into which all the species can be assigned. It is as though the evolutionary process itself confines classes to a smaller and smaller repertoire of available designs.

When we think that we have encountered a class of life that is too complex for simple classification, we are usually proven wrong. For example, in the first two-thirds of the 20th century, the classification of bacteria was considered a hopeless task, insofar as bacteria of different classes were known to exchange DNA among themselves, in a general process known as horizontal gene transfer. If bacteria were constantly exchanging genetic material, then it seemed that every bacteria was an amalgam of other bacteria and could not be sensibly classified. Be that as it may, bacteria were found to have a convincing phylogenetic order, based on the ancestral lineage of highly conserved species of rRNA that distinguished the bacteria from archaeal bacteria and further distinguished the classes and subclasses of bacteria [37, 38].

In the case of viruses that mutate at a high rate, that exchange large pieces of their DNA, that extract DNA from their host organisms, and that produce an uncountably large number of diverse species, one might think that a classification would be an impossible task. Not so. Instead, we are finding fundamental molecular motifs that can be used to classify viruses into biological groups that share phylogenetic origins [39, 16]. For example, despite the sequence variations that

occur in rapidly mutating viruses, scientists are finding that the three-dimensional folds of protein molecules are conserved, and that viruses can be grouped into the so-called fold families, which can in turn be grouped into fold super families, that preserve phylogenetic relationships among viral lineages [39].

Among the retroviruses, it has been shown that viral ancestral lineages can be determined by looking at inherited variations in the so-called “global” genomic properties (e.g., translational strategies, motifs in Gag and Pol genes and their associated enzymes) [16].

We shouldn't be surprised that viruses, like every other class of organism, falls into a rather limited set of phylogenetic classes. Because all viruses are parasitic, we can see why all viral species are constrained to evolve in a manner that maintains their host compatibility [17].

A demonstration of host-specific constraints on viruses is found by examining the specificity of viruses for the highest classes of organisms. Virus infections are found in Class Archaea, Class Bacteria, and Class Eukaryota, but there is no instance in which any single class of viruses is capable of infecting more than one of these classes of cellular organisms. Furthermore, within a class of cellular organisms, there are only rare instances of classes of virus that can infect distantly related subclasses. For example, there are virtually no viruses that can infect both Class Animalia and Class Plantae (rare exceptions are claimed [40]). Furthermore, as the host evolves, so must the virus. Hence, we might expect to find ancestral lineages of viruses that shadow the lineage of their host organisms.

The relatively recent discovery of NCLDV (nucleocytoplasmic large DNA viruses, popularly known as giant viruses) has greatly expanded our notion of viral existence [45, 46]. The life of an NCLDV is not much different from that of obligate intracellular bacteria (e.g., *Rickettsia*). The NCLDVs, with their large genomes and complex sets of genes, have provided taxonomists with an opportunity to establish ancestral lineages among some of these viruses [45, 46].

At this time, the classification of viruses is somewhat crude. Anything you choose as a classifying principle fails to biologically unify the subclasses. For example, if you classify viruses by their genomic molecules (i.e., DNA or RNA, single strandedness or double strandedness), you will find that subclasses with the same genomic type will have dissimilar structures: envelope, size, shape, proteins, and capsid. When we list viruses based on method of contagion, by persistence within host (i.e., acute, chronic, latent, or persistent), toxicity (lytic, immunogenic), or by target cell specificity, no consistent taxonomic correlation is found.

Though we cannot as yet classify viruses strictly by their evolutionary lineage, we can usefully group viruses based on the physical characteristics of their genomes. The Baltimore Classification divides viruses into seven groups based on whether their genome is DNA, RNA, single stranded, or double stranded, the sense of the single strand, and the presence or absence of a reverse transcriptase. Here are the classes of the pathogenic viruses. This classification,

though nonphylogenetic in concept, has the great advantage of being comprehensive: every known virus can be assigned to a group within the Baltimore Classification.

Group I, double-stranded DNA

Group II, single-stranded DNA

Group III, double-stranded RNA

Group IV, positive sense single-stranded RNA

Group V, negative sense single-stranded RNA ssRNA

Group VI, single-stranded RNA with a reverse transcriptase

Group VII, double-stranded DNA with a reverse transcriptase

It is worth repeating that when we use the Baltimore Classification (or any alternate viral classification, for that matter) we must grudgingly accept the fact that biologically relevant features of grouped viruses will cross taxonomic boundaries. Consider the arboviruses. Arbovirus is a shortened name for Arthropod borne virus. The arboviruses fall into several different groups of viruses. The principle vectors of the arboviruses are mosquitoes, ticks. Mosquito-borne arboviruses are members of Class Bunyaviridae (Group V), Flaviviridae (Group IV), or Togaviridae (Group IV). Tick-borne arboviruses are members of Class Bunyaviridae (Group V), Flaviviridae (Group IV), or Reoviridae (Group III). Over 500 arboviruses, infecting a variety of animals, have been described [47]. The arboviruses, organized by their transmission vectors, as shown below, cross multiple viral groups.

Mosquito-borne viruses.

Bunyaviridae (Group V)

La Crosse encephalitis virus

California encephalitis virus

Rift Valley fever virus

Flaviviridae (Group IV)

Japanese encephalitis virus

Australian encephalitis virus

St. Louis encephalitis virus

West Nile fever virus

Dengue fever virus

Yellow fever virus

Zika fever virus

Togaviridae (Group IV)

Eastern equine encephalomyelitis virus

Western equine encephalomyelitis virus

Venezuelan equine encephalomyelitis virus

Chikungunya virus

O'Nyong-nyong fever virus

Ross River fever virus

Barmah Forest virus

Tick-borne viruses.

Bunyaviridae (Group V)

Crimean-Congo hemorrhagic fever virus

Flaviviridae (Group IV)

Tick-borne encephalitis virus

Powassan encephalitis virus

Deer tick encephalitis virus

Omsk hemorrhagic fever virus

Kyasanur forest disease virus (Alkhurma virus)

Langat virus

Reoviridae (Group III)

Colorado tick fever virus

The term “arbovirus” excludes viruses transmitted by nonarthropod vectors, such as rodents and bats[48] [Glossary Bat].

Rodent-borne viruses (roboviruses)

Arenaviridae (Group V)

Lassa fever

Venezuelan hemorrhagic fever (Guanarito virus)

Argentine hemorrhagic fever (Junin virus)

Bolivian hemorrhagic fever (Machupo virus)

Lujo virus

Bunyaviridae (Group V)

Puumala virus

Andes virus

Sin Nombre virus

Hantavirus

Bat-borne viruses [48] [Glossary Bat].

Filoviridae (Group V)

Ebola hemorrhagic fever

Marburg hemorrhagic fever

Rhabdoviridae (Group V)

Australian bat lyssavirus

Rabies virus

Mokola virus

Duvenhage virus

Lagos bat virus

Duvenhage virus

It would seem that we do not know enough about the origin and phylogeny of the different classes of viruses to create a true classification, wherein viruses of a class share a common set of inherited relationships. There is, however, hope for a future in which viruses can be organized by phylogenetic principles. Highly innovative work in the field of viral phylogeny is proceeding, from a

variety of different approaches, including: inferring retroviral phylogeny by sequence divergences of nucleic acids and proteins in related viral species [16]; tracing the acquisition of genes in DNA viruses [41]; and dating viruses by the appearance of viral-specific antibodies in ancient host cells [12]. Because viruses evolve very rapidly, it is possible to trace the evolution of some viruses, with precision, over intervals as short as centuries or even decades [39, 42–44]. It should be noted that before the advent of ribosomal sequence analysis, and as recently as the early 1970s, bacterial phylogeny was considered a hopeless field [37]. Bacteria were grouped by morphology, nutritional requirements, and enzymatic reactions (e.g., hemolysis, coagulase, etc.) without much attention to phylogenetic relationships. The field of viral phylogeny is quickly catching up with the phylogeny of living organisms.

Section 7.3 Group I viruses: Double-stranded DNA

What trap is this? Where were its teeth concealed?

Philip Larkin, from his poem “Myxomatosis”

Group I, dsDNA

Herpesvirales

Herpesviridae

Epstein-Barr virus
 Herpes simplex virus type
 Herpes simplex virus type
 Herpes virus varicella
 Herpesvirus simiae
 Human herpesvirus type
 Human herpesvirus type
 Human herpesvirus type
 Cytomegalovirus

Unassigned

Nonenveloped

Adenoviridae

Human adenoviruses A through G

Papillomaviridae

Human papillomavirus

Polyomaviridae

BK polyomavirus

JC polyomavirus

Simian virus

Nucleocytoplasmic large DNA viruses (NCLDV viruses)

Poxviridae

Orthopoxvirus

- Buffalopox virus
- Cowpox virus
- Monkeypox virus
- Vaccinia virus
- Variola major virus
- Variola minor virus
- Parapoxvirus
 - Orf
 - Milker
- Molluscipoxvirus
 - Molluscum contagiosum virus
- Yatapoxvirus
 - Tanapoxvirus
 - Yaba monkey tumor virus
- Mimiviridae
 - Mimivirus
 - Acanthamoeba polyphaga mimivirus
- Group II, ssDNA
- Group III, dsRNA
- Group IV (+)ssRNA
- Group V (-)ssRNA
- Group VI, ssRNA-RT
- Group VII, dsDNA-RT

The Group I viruses all have a double-stranded DNA genome. Aside from this property, these viruses vary greatly. Some species have envelopes; others do not. Some species have circular genomes; others have linear genomes. The size of the viral genome can vary as much as 50-fold among different species of the group. The host range covers the range of living organisms. Bacteria, archaeans, eukaryotes are infected by one or the other Group I viruses. The group has been subclassed based on shared morphologic properties, six of these subclasses contain human pathogens: Adenoviridae, Herpesviridae, Poxviridae, Papillomaviridae, Polyomaviridae, and Mimiviridae.

Most of the DNA transforming viruses (i.e., DNA viruses that cause cancer) belong to Group I: Polyomaviruses, Adenoviruses, Papillomaviruses, and Herpesviruses (including Epstein Barr virus). One exception is Hepatitis B virus, which belongs to Group VIII. Unlike the retroviruses (Group VI), which contain genes that are homologous with cancer-causing oncogenes, the DNA transforming viruses do not contain oncogenes. The Group I DNA transforming viruses seem to cause cancer through a mechanism related to their ability to induce replication in their host cells [Glossary [Hepatitis viruses](#)].

- Group I, dsDNA
 - Herpesvirales
 - Herpesviridae

Epstein-Barr virus
 Herpes simplex virus type
 Herpes simplex virus type
 Herpes virus varicella
 Herpesvirus simiae
 Human herpesvirus type
 Human herpesvirus type
 Human herpesvirus type
 Cytomegalovirus

Members of Class Herpesviridae are commonly known as herpesviruses. These viruses produce acute disease characterized by lytic (i.e., cytopathic) effects in infected cells; and latent disease, characterized by recurrences of disease, sometimes spanning the life of the host. After cells are infected by virus particles, the viral genome migrates to the host nucleus, where replication and transcription of the viral genes occurs. After a latent phase, viruses may precipitate a lytic phase, manifesting as clinical disease. The recurring disease may be clinically distinct from the initial infection (e.g., chicken pox, the initial varicella virus infection, is followed decades later by shingles). Some of the herpesviruses are DNA transforming viruses.

The human herpesviruses are: Epstein-Barr virus, Herpes simplex viruses, Varicella virus, and Human herpesviruses 6, 7, and 8, and Cytomegalovirus.

Epstein-Barr virus infects almost all adults. Its persistence makes it one of the most prevalent human pathogens. It manifests acutely as mononucleosis, a pharyngitis accompanied by lymphocytosis (increases lymphocytes in the peripheral blood) with morphologic alterations in infected lymphocytes. Splenomegaly and hepatomegaly may occur. The generalized symptoms of the disease, particularly fatigue, may extend for months or longer, and some cases of mononucleosis recur. Epstein-Barr virus is a DNA transforming virus and accounts for several cancers, including Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma, and central nervous system lymphoma. A role for the virus in several autoimmune diseases has been suggested.

Herpes simplex type 1 causes cold sores, and Herpes simplex types 2 causes genital herpes. Both diseases may recur after initial infection.

As mentioned, Herpes virus varicella-zoster causes chickenpox on first infection and herpes zoster, also known as shingles, on reactivation.

Herpesvirus simiae, also known as B virus, infects macaque monkeys, without causing severe disease. In rare circumstances, humans may become infected with this virus, from the monkey reservoir. Human infection typically results in a severe encephalopathy.

Human herpesvirus type 6 (HHV6) and type 7 (HHV7) produce exanthem subitum, also known as roseola infantum and as sixth disease. Readers should not confuse sixth disease with fifth disease. Fifth disease, also known as erythema infectiosum and slapped face disease, is caused by

Parvovirus B19. These diseases take their names from an historical diagnostic dilemma faced by pediatricians, who regularly encountered six clinical syndromes of childhood rashes. Four of the childhood rashes had known etiologies. The fifth and sixth rashes, both caused by organisms that were not yet identified, were referred to as “fifth disease” and “sixth disease.” Subsequently, the viral causes of these two diseases were discovered, but the numeric names held.

Human herpesvirus type 8 (HHV8) is a DNA transforming virus that can cause Kaposi sarcoma, primary effusion lymphoma, and some forms of Castleman disease. Kaposi sarcoma is a cancer characterized by focal proliferations of small blood vessels, occurring most often in the skin. Immunosuppressed patients (e.g., transplant recipients), who are carriers of the latent HHV8 virus, may develop Kaposi sarcoma within a few months of immunosuppression. Interestingly, if immunosuppression is halted, the Kaposi sarcoma may regress [49]. It is presumed that sustained viral replication is necessary for early tumor growth.

Cytomegalovirus infects about half of the world population, with most individuals suffering no ill effects. Once infected, the virus usually persists for the life of the individual. In a minority of cases, particularly among immunocompromised individuals (e.g., organ transplant recipients and AIDS patients) and newborns, the virus may produce severe neurologic disease. The disease is known as cytomegalic inclusion body disease, and, as the name suggests, cytoplasmic and nuclear inclusion bodies characterize actively infected cells. When the virus is transmitted transplacentally, by mothers infected during their pregnancy, the newborn may suffer developmental damage to the brain and other organs (Fig. 7.1).

```

Group I, dsDNA
  Unassigned
    Nonenveloped
      Adenoviridae
        Human adenoviruses A through G
      Papillomaviridae
        Human papillomavirus
      Polyomaviridae
        BK polyomavirus
        JC polyomavirus
        Simian virus
  
```

Class Adenoviridae contains the human adenoviruses of which there are 57 types, with different clinical syndromes associated with specific subtypes of the virus. Most adenoviral diseases present clinically as respiratory illness, conjunctivitis (i.e., viral conjunctivitis), or gastroenteritis. Infections may present clinically as tonsillitis (simulating strep throat), pharyngitis (croup), otitis media,

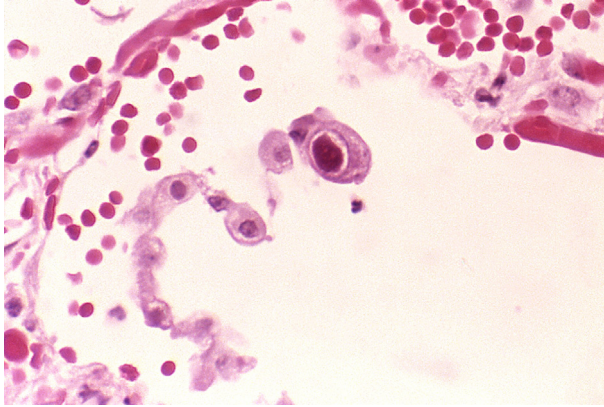


FIG. 7.1 Cytomegalovirus infection of the lung. Near the top, center of the image is an infected pneumocyte with a highly enlarged nucleus. The bulk of the nucleus is occupied by a dense inclusion, sometimes called Cowdry body, containing viral nucleocapsids. Surrounding the inclusion is a clear zone. Such nuclear inclusions, observed with all species of herpes viruses that infect humans, have long served as an important clue to the diagnosis and the pathogenesis of viral diseases. (Source, a public domain image provided by the U.S. Centers for Disease Control and Prevention Public Health Image Library.)

pneumonia, meningoencephalitis, and hemorrhagic cystitis. Adenoviruses are commonly spread by aerosolized droplets, and are particularly stable in the external environment.

Human papillomaviruses cause skin warts, laryngeal warts, and genital warts. Warts are benign tumors composed of proliferating squamous cells. In some cases, these human papillomavirus-induced warts progress to become invasive squamous cell carcinomas (Fig. 7.2).

Class Polyomaviridae contains several viruses that infect humans: BK polyomavirus, JC polyomavirus, and Simian virus 40.

The BK polyomavirus rarely causes disease in infected patients, and the majority of humans carry the latent virus. Latency can shift to lytic infection after immunosuppression, producing a clinical nephropathy.

The JC polyomavirus persistently infects the majority of humans, but it is not associated with disease in otherwise healthy individuals. Rarely, in immunocompromised patients, JC polyomavirus may produce progressive multifocal leukoencephalopathy. The virus targets myelin-producing oligodendrocytes in the brain to produce areas of demyelination and necrosis.

Simian virus 40 (SV40) infects monkeys and humans, but there is no evidence at this time confirming a role in human disease.

Group I, dsDNA

Unassigned

Nucleocytoplasmic large DNA viruses (NCLDV viruses)

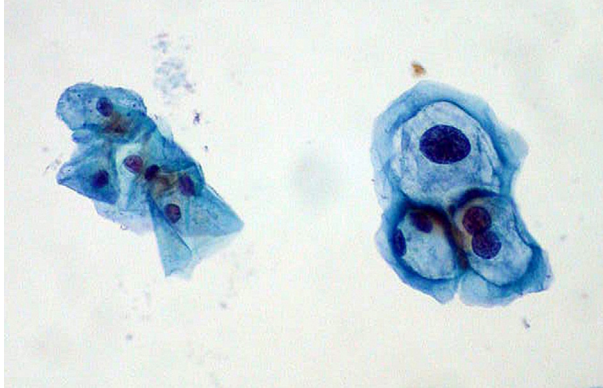


FIG. 7.2 Koilocytosis. The clump of flat epithelial cells on the left is normal squamous cells that line the uterine cervix. The clump of three cells on the right is squamous epithelial cells demonstrating koilocytosis, a cytopathic effect produced by human papillomavirus infection. Notice that the nuclei are enlarged, appearing approximately 2-3 times as large as normal nuclei (on left). Surrounding each nucleus (right clump) is an abnormal zone of pale cytoplasm, typical of koilocytosis. Beyond the pale zone is a thinner zone of normal-appearing cytoplasm extending out to the cell membrane. (Source, Wikipedia, from a public domain image contributed by Euthman.)

- Poxviridae
 - Orthopoxvirus
 - Buffalopox virus
 - Cowpox virus
 - Monkeypox virus
 - Vaccinia virus
 - Variola major virus
 - Variola minor virus
 - Parapoxvirus
 - Orf
 - Milker
 - Molluscipoxvirus
 - Molluscum contagiosum virus
 - Yatapoxvirus
 - Tanapoxvirus
 - Yaba monkey tumor virus
 - Yaba

Members of Class Orthopoxvirus produce disease characterized by pustules of the skin, and lymphadenopathy.

The smallpox virus is remarkable for its extremely narrow host range: humans only. The virus infects the skin and the mucosa of the upper respiratory tract, where it produces a pustular, weeping, and rash. In the respiratory mucosa, the rash interferes with breathing. If the disease becomes hemorrhagic, the

prognosis worsens. Smallpox is reputed to have killed about 300 million people in the 20th century, prior to the widespread availability of an effective vaccine. Smallpox has been referred to as the greatest killer in human history. Its mortality rate was 30%–35%, which is significantly less than some of the hemorrhagic viruses (e.g., Ebola virus, Group V, has a mortality rate of nearly 90%). No doubt, death rates climbed because the disease was easily communicable via aerosols, fomites, bodily fluids, or direct contact with patients with rash.

Currently, smallpox has the distinction of being the only infection of humans which has been declared “eradicated.” It should be noted that there are a few closed societies for which the status of smallpox in the population is unknown (e.g., North Korea). Aside from the remarkable success of vaccination, eradication was no doubt made possible because smallpox has no animal reservoir. At this time, vaccination is not routinely performed and is reserved primarily as an antiterror measure, for personnel entering a zone where there is a bioweapons threat.

Variola minor is a virus closely related to Variola major that produces a milder disease. These diseases are known by various names including alastrim, cottonpox, milkpox, whitepox, and Cuban itch. Infection with Variola minor is thought to produce cross-resistance to Variola Major (and vice versa).

Vaccinia virus is the laboratory-grown poxvirus, of obscure heritage, that does not precisely correspond to known viruses that reside outside the laboratory or clinic (i.e., not quite cowpox, not quite variola). Vaccinations with vaccinia virus have been known to produce, in rare cases, a variety of clinical disorders, ranging from vaccinia (localized pustular eruptions) to generalized vaccinia, to progressive vaccinia, to vaccinia gangrenosum, and to vaccinia necrosum. Other conditions associated with vaccinations include eczema vaccinatum and postvaccinial encephalitis).

Smallpox vaccination, aside from eradicating mankind's greatest killer, may have heretofore unrecognized public health value. The number of currently known pathogenic organisms, their variant subtypes, their ability to mutate, and the emergence of newly encountered pathogens make it impossible to develop vaccines for every organism that infects humans. Consequently, vaccine experts are searching for vaccines that confer immunity, partial or full, for several different pathogens or for several variants of a single pathogen [50]. An interesting development in this field is that the smallpox vaccine may confer limited protection against HIV (human immunodeficiency virus) infection. Both viruses enhance their infectivity by exploiting a receptor, CCR5, on the surface of white blood cells. This shared mode of infection may contribute to the cross-protection against HIV that seems to come from smallpox vaccine. It has been suggested that the emergence of HIV in the 1980s may have resulted, in part, from the cessation of smallpox vaccinations in the late 1970s [51].

Buffalopox, cowpox, and monkeypox produce diseases in animal reservoirs and rarely infect humans. Human infections occur from close contact with infected animals and manifest much like smallpox, but milder.

Members of Class Parapoxvirus infect vertebrates, particularly sheep, goats, cattle, and red squirrels. Orf virus causes “sore mouth” or “scabby mouth” disease of sheep and goats. Humans, though rarely infected, may develop painful hand sores. A similar condition can occur in humans who handle the udders of cows infected with Milker's nodule virus.

Class Molluscipoxvirus contains one species infectious in humans, *Molluscum contagiosum* virus. *Molluscum contagiosum* is an eruption of wart-like skin lesions that are easily diagnosed on histological examination by their distinctive cellular inclusions (so-called molluscum bodies). There are no known animal reservoirs. Infection is spread from human to human. Treatment is not always necessary, as individual lesions will regress within two months. However, auto-inoculation of the virus may produce new skin lesions, thus prolonging the disease.

Members of Class Yatapoxvirus infect primates in equatorial Africa. Infections can spread to humans by insect vectors. Tana poxvirus produces a pock-forming skin infection, with fever and lymphadenopathy in infected humans (i.e., like a mild form of smallpox). The Yaba monkey tumor virus produces histiocytomas in monkeys. Histiocytomas are proliferative lesions of fibrous tissue that yield tumor-like nodules. These virally induced histiocytomas in monkeys grow rapidly following infection, and then regress over the ensuing month [52]. Yaba monkey tumor virus and Yaba-like disease virus, like all members of Class Yatapoxvirus, are considered potential human pathogens.

Group I, dsDNA

Unassigned

Nucleocytoplasmic large DNA viruses (NCLDV viruses)

Mimiviridae

Mimivirus

Acanthamoeba polyphaga mimivirus

Class Mimiviridae, discovered in 1992, occupies a niche that seems to span the biological gulf separating living organisms from viruses. Members of Class Mimiviridae are complex, larger than some bacteria, with enormous genomes (by viral standards), exceeding a million base pairs and encoding upwards of 1000 proteins. The large size and complexity of Class Mimiviridae exemplifies the advantage of a double-stranded DNA genome. DNA is much more chemically stable than RNA, and can be faithfully replicated, even when its length exceeds a billion base pairs. A double-stranded DNA genome can be protected by DNA repair enzymes, and by external modifications to the DNA structure. Class Megaviridae is a newly reported (October 2011) class of viruses, related to Class Mimiviridae, but larger [45].

As previously noted, the life of a mimivirus is not very different from that of obligate intracellular bacteria (e.g., *Rickettsia*). The discovery of Class Mimiviridae inspires biologists to reconsider the “nonliving” status relegated to viruses and compels taxonomists to examine the placement of viruses within the phylogenetic development of prokaryotic and eukaryotic organisms.

Acanthamoeba polyphaga mimivirus is a possible human pathogen. Some patients with pneumonia have been shown to have antibodies against the virus [53].

Though Myxoma virus is not a human pathogen, it seems appropriate to include some mention of this member of Class Poxviridae, due to the role humans have played in its history. Myxoma virus produces a fatal disease, myxomatosis, in rabbits. The disease is characterized by the rapid appearance of skin tumors (myxomas), followed by severe conjunctivitis, systemic symptoms, and fulminant pneumonia. Death usually occurs in 2-14 days after infection. In 1952, a French virologist, hoping to reduce the rabbit population on his private estate, inoculated a few rabbits with Myxoma virus. The results were much more than he had bargained for. Within two years, 90% of the rabbit population of France had succumbed to myxomatosis.

European rabbits, introduced to Australia in the 19th century, became feral and multiplied. By 1950 the rabbit population of Australia was about 3 billion. Seizing upon the Myxoma virus as a solution to rabbit overpopulation, the Australians launched a Myxoma virus inoculation program. In less than 10 years, the Australian rabbit population was reduced by 95% [54]. Nearly 3 billion rabbits died, a number very close to the number of humans living on the planet in the mid-1950s. This plague on rabbits was unleashed by a committee of humans who decided that it was proper to use a lethal rabbit virus as a biological weapon. Without commenting on the moral implications of animal eradication efforts, it is worth noting that rabbits are not the only mammals that can be exterminated by a pathogenic virus. Humans should take heed.

Infectious Genera

Adenoviridae species

- **Lineage.** dsDNA viruses, no RNA stage: Adenoviridae: Mastadenovirus: unclassified Human adenoviruses: Human adenovirus sp.
- **Infection.** Human adenoviruses (produce infections of respiratory tract, pharyngitic and pneumonic, plus conjunctival, gastroenteritic, or bacteremic infections)

Human adenovirus A, types 12, 18, 31

Human adenovirus B, types 3, 7, 11, 14, 16, 21, 34-35, 50, 55

Human adenovirus C, types 1, 2, 5-6, 57

Human adenovirus D, types 8-10, 13, 15, 17, 19-20, 22, 23-30, 32-33, 36-39, 42-49, 51, 53-54, 56

Human adenovirus E, type 4

Human adenovirus F, types 40-41

Human adenovirus G, type 52

Herpesviridae

- **Lineage.** dsDNA viruses, no RNA stage: Herpesvirales: Herpesviridae: Gammaherpesvirinae: Lymphocryptovirus: Human gammaherpesvirus 4 (Epstein-Barr virus)

- **Infection.** Epstein-Barr virus (include infections such as mononucleosis, and neoplasms such as Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma, and central nervous system lymphoma, as well as various autoimmune diseases)
- **Infection.** Herpes simplex types 1 (cold sores)
- **Infection.** Herpes simplex types 2 (genital herpes)
- **Infection.** Herpes virus varicella-zoster (chickenpox on first infection, herpes zoster or shingles on re-activation)
- **Infection.** Herpesvirus simiae, also known as B virus (encephalopathy)
- **Infection.** Human herpesvirus type 6, HHV6 (exanthem subitum, roseola infantum, sixth disease)
- **Infection.** Human herpesvirus type 7, HHV7 (exanthem subitum, roseola infantum, sixth disease; suggested but disputed cause of pityriasis rosea)
- **Infection.** Human herpesvirus type 8, HHV8 (Kaposi sarcoma, primary effusion lymphoma, Castleman's disease)
- **Infection.** Cytomegalovirus, also known as Human herpesvirus 5 (cytomegalic inclusion body disease)

Orthopoxvirus

- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Orthopoxvirus: Variola virus
- **Infection.** Variola major (smallpox)
- **Infection.** Variola minor (alastrim, cottonpox, milkpox, whitepox, and Cuban itch)
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Orthopoxvirus: Vaccinia virus
- **Infection.** Vaccinia virus (vaccinia, generalized vaccinia, progressive vaccinia, vaccinia gangrenosum, vaccinia necrosum, eczema vaccinatum, postvaccinial encephalitis)
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Orthopoxvirus: Vaccinia virus: Buffalopox virus
- **Infection.** Buffalopoxvirus (Buffalopox)
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Orthopoxvirus: Monkeypox virus
- **Infection.** Monkeypox virus (Monkeypox)
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Orthopoxvirus: Cowpox virus
- **Infection.** Cowpox virus (Cowpox)

Molluscipoxvirus

- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Molluscipoxvirus: Molluscum contagiosum virus
- **Infection.** Molluscum contagiosum virus (Molluscum contagiosum)

Parapoxvirus

- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Parapoxvirus
- **Infection.** Milker's nodule virus (Milker's nodes)
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Parapoxvirus: Orf virus
- **Infection.** Orf virus (Orf, also known as ecthyma contagiosum)

Yatapoxvirus

- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Yatapoxvirus: Tanapox virus
- **Infection.** Tanapox virus (mild pock-forming skin infection) [52]
- **Lineage.** dsDNA viruses, no RNA stage: Poxviridae: Chordopoxvirinae: Yatapoxvirus: Yaba monkey tumor virus
- **Infection.** Yaba monkey tumor virus (regressing histiocytoma) [52]

Papillomaviridae

- **Lineage.** dsDNA viruses, no RNA stage: Papillomaviridae
- **Infection.** Human papillomavirus (warts, genital warts, laryngeal papillomas, squamous carcinoma)

Polyomaviridae

- **Lineage.** dsDNA viruses, no RNA stage: Polyomaviridae
- **Infection.** BK polyomavirus or BK virus (nephropathy in immune-compromised individuals)
- **Infection.** JC polyomavirus or JC virus (progressive multifocal leukoencephalopathy in immune-compromised individuals)
- **Infection.** Simian virus 40 or SV40 virus (highly controversial potential cause of human cancer)

Mimiviridae:

- **Lineage.** dsDNA viruses, no RNA stage: Mimiviridae: Mimivirus
- **Infection.** Acanthamoeba polyphaga mimivirus (pneumonia)

Section 7.4 Group II viruses: Single-stranded (+) sense DNA

Everything should be made as simple as possible, but not simpler.

Albert Einstein

Group I, dsDNA

Group II, ssDNA

Parvoviridae

Bocavirus

Human parvovirus B
 Group III, dsRNA
 Group IV (+)ssRNA
 Group V (-)ssRNA
 Group VI, ssRNA-RT
 Group VII, dsDNA-RT

Group II, The single-stranded DNA viruses, contains only one family of viruses that are pathogenic in humans: Class Parvoviridae. Class Parvoviridae contains environmentally resistant viruses that infect a wide range of animals. Parvoviruses are the smallest viruses currently known.

Group II, ssDNA
 Parvoviridae
 Bocavirus
 Human parvovirus B

Parvovirus B19 is the agent that causes fifth disease, so named because the disease was the fifth type of common childhood exanthem among six rashes listed in textbooks. Until the 1980s, the cause of this fifth listed exanthem was unknown; so it came to be known as “fifth disease.” Other names for fifth disease are erythema infectiosum and slapped face disease. Human herpesviruses 6 and 7 cause the sixth childhood rash, “sixth disease.” The rash of fifth disease results from an immune response of the host to the virus particles. Essentially, fifth disease is an allergic phenomenon, and not the direct, cytopathic effect of the virus.

Infection by parvovirus occurs from contact (usually via respiratory droplets) with actively infected hosts. The virus is known to infect humans and dogs. Serologic evidence indicates that at least half of the human population has been infected with parvovirus B19.

Members of Class Parvoviridae characteristically grow in rapidly dividing host cells, using host processes to support their own replication. The target cells for the parvovirus B19 are the dividing precursor erythroid cells. Another name for parvovirus B19 is erythrovirus B19, indicating the target cell for the virus. In the active stage of infection, huge amounts of virus are produced. Death or dysfunction of the target hematopoietic (blood precursor) cells can lead to a transient pancytopenia (i.e., anemia of all blood cell lineages). In rare cases, aplastic anemia may occur, in which most of the precursor erythroid cells are destroyed, leading to a massive decline in circulating mature forms. When aplastic anemia occurs, it usually occurs in individuals who have a concurrent condition that requires an excessive production of blood cells to maintain the normal blood profile of mature cells. These conditions include: autoimmune hemolytic anemia, sickle cell anemia, and inherited blood dyscrasias that increase the fragility of red blood cells or that decrease the life span of red blood cells. Basically, a coinfection with parvovirus B19 is the last straw for bone marrows that are barely keeping pace with the body's demand for erythrocytes.

The intense viremia that occurs in parvovirus B19 infection, and the small size of parvovirus particles, may predispose to cross-placental transmission occurring in some cases of infection in pregnant women. Though rare, parvovirus may cause miscarriage or hydrops fetalis (fluid accumulation in the fetus) with anemia.

Bocavirus has been associated with some cases of respiratory disease and diarrhea in young children. Though it is rarely detected in healthy persons, there is indication that it can occur in up to 9% of pediatric patients hospitalized with lower respiratory infections [55]. Bocavirus should not be confused with Bocas virus, a type of Coronavirus (Group IV).

SEN virus (SEN-V) is a newly discovered single-stranded nonenveloped DNA virus that has been found in the blood of donors and recipients of transfusion blood [56]. In addition, another Group II virus, TT virus, also known as Transfusion Transmitted virus or Torque teno virus, has been isolated from transfusion blood. TT virus is currently a suspected hepatitis virus. At this time, the pathogenicity of both SEN-V and TT viruses are in doubt; hence neither virus is included in the list of Group II virus pathogens.

Infectious Genera

Bocavirus

- **Lineage.** ssDNA viruses: Parvoviridae: Parvovirinae: Bocaparvovirus (Bocavirus)
- **Infection.** Bocavirus (respiratory disease and diarrhea in children)

Human parvovirus

- **Lineage.** ssDNA viruses: Parvoviridae: Parvovirinae: Erythroparvovirus: Primate erythroparvovirus 1: Human parvovirus B19
- **Infection.** Human parvovirus B19, alternately known as erythrovirus B19 (Fifth disease, erythema infectiosum, slapped face disease, transient hemolytic anemia, aplastic anemia)

Section 7.5 Group III viruses: Double-stranded RNA

What is essential is invisible to the eye.

Antoine de Saint-Exupery

- Group I, dsDNA
- Group II, ssDNA
- Group III, dsRNA
 - Reoviridae
 - Rotavirus
 - Coltivirus
 - Orbivirus
- Group IV (+)ssRNA

Group V (-)ssRNA
 Group VI, ssRNA-RT
 Group VII, dsDNA-RT

The Group III viruses have a double-stranded RNA genome. Replication of Group III viruses takes place exclusively in the cytoplasm, where the viral RNA codes for the proteins needed for viral replication. Viral proteins are synthesized using the host cell machinery (i.e., ribosomes).

Group III contains six major classes, of which only one contains organisms that are infectious to humans: Class Reoviridae. The name derives from “Respiratory enteric orphan” viruses. The term “orphan,” when applied to a virus indicates that no known diseases are associated with the virus. This is no longer the case for the Reoviruses.

Group III, dsRNA
 Reoviridae
 Rotavirus
 Coltivirus
 Orbivirus

The most clinically significant species in Class Reoviridae is rotavirus. In 2004, rotavirus infections accounted for about a half million deaths in young children, from severe diarrhea [57]. Most of the deaths occurred in developing countries. The death rate is expected to decline due to the introduction of an apparently safe and effective vaccine [57]. Rotavirus, when observed with transmission electron microscopy, resembles a wagon wheel. It was formerly known as gastroenteritis virus type B. It is passed from human to human by fecal-oral route (Fig. 7.3).

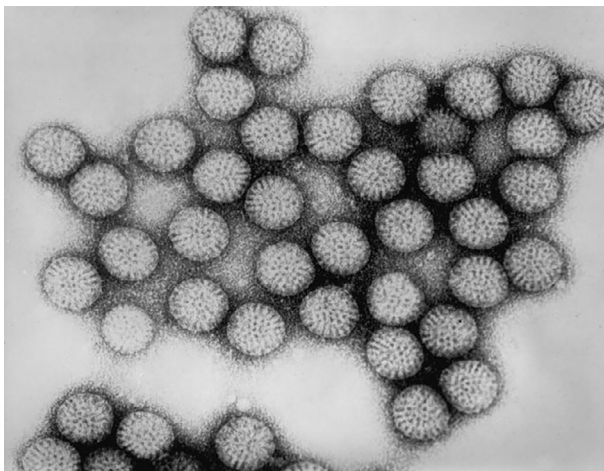


FIG. 7.3 Transmission electron micrograph of rotavirus particles. (Source, a public domain image provided by the U.S. Centers for Disease Control and Prevention, prepared by Dr. Erskine Palmer. Rotavirus_TEM_B82-Rotavirus_TEM_B82-.)

Aside from rotavirus, there are three genera that infect humans, of which two produce disease. The Orotoviruses infect vertebrates, including humans, but no disease has been linked to the infections. The two disease-producing infectious genera are Coltivirus and Orbivirus.

Colorado tick fever is endemic in the Rocky Mountains (in contradistinction to Rocky Mountain spotted fever, a rickettsial infection that has no restricted affinity for the Rocky Mountains). Coltivirus takes its name from the disease (i.e., COLorado TICK fever VIRus). As the name suggests, Colorado tick fever is carried by a tick (in this case, *Dermacentor andersoni*) and produces a fever. The fever is often accompanied by myalgia, headache, and photophobia. In a small percentage of children with Colorado tick fever, encephalitis may follow.

Orbiviruses have been implicated in several rather obscure fever-associated conditions: Kemerovo fever, found in Western Siberia and transmitted by ticks; Orungo fever, found in Central African and transmitted by mosquitoes; and Changuinola fever, found in Northern South America and transmitted by sand flies of Class Phlebotomus.

Human rotavirus

- **Lineage.** dsRNA viruses: Reoviridae: Sedoreovirinae: Rotavirus
- Human rotavirus (gastroenteritis, diarrhea)

Coltivirus

- **Lineage.** dsRNA viruses: Reoviridae: Spinareovirinae: Coltivirus
- Coltivirus (Colorado tick fever)

Orbivirus

- **Lineage.** dsRNA viruses: Reoviridae: Sedoreovirinae: Orbivirus
- Orbivirus (Colorado tick fever)

Section 7.6 Group IV viruses: Single-stranded (+) sense RNA

Simplicity is the ultimate sophistication.

Leonardo da Vinci

```

Group I, dsDNA
Group II, ssDNA
Group III, dsRNA
Group IV (+)ssRNA
  Nidovirales
    Coronaviridae
      SARS virus
      Torovirus species

```

Hepeviridae:

Hepatitis E

Caliciviridae:

Norovirus

Sapporo virus

Togaviridae

Alphavirus Viral diseases

Chikungunya

Eastern equine encephalomyelitis virus

Getah virus

Mayaro virus

Mucambo virus

O'nyong'nyong virus

Ross river virus

Barmah forest virus

Sagiyama virus

Semliki forest virus

Sindbis virus

Tonate virus

Venezuelan equine encephalomyelitis virus

Western equine encephalomyelitis virus

Rubivirus

Rubella virus

Flaviviridae

Hepacivirus

Hepatitis C

Flavivirus

Dengue virus types

Hepatitis G virus

Japanese B encephalitis virus

Murray Valley encephalitis virus

Rocio virus

Spondweni virus

St Louis encephalitis

Wesselsbron

West Nile virus

Yellow fever virus

Tick-borne virus group:

Absettarov

Hanzalova

Hypr

Kumlinge

Kyasanur forest disease

Louping ill

- Negishi
- Omsk
- Powassan
- Langat
- Russian spring summer encephalitis
- Hepatitis G virus group
- Hepatitis G virus
- Picornaviridae
 - Enterovirus:
 - Coxsackievirus
 - Echovirus
 - Poliovirus
 - Enterovirus
 - Rhinovirus A and B
 - Hepatovirus:
 - Hepatitis A
- Astroviridae
 - Astrovirus species
- Group V (-) ssRNA
- Group VI, ssRNA-RT
- Group VII, dsDNA-RT

The Group IV viruses have a positive sense RNA genome. Positive sense RNA can be translated directly into protein, without a DNA intermediate and without creating a complementary RNA strand. To replicate its genome, though, a complementary RNA strand is required. The positive RNA strand serves as a template for an RNA-dependent RNA polymerase, yielding a complementary RNA strand, to form a dimer with the template strand. The double-stranded RNA subsequently serves as the template for a new positive sense genome.

The positive-strand RNA genome is independently infectious, for most Group IV viruses. This means that in the absence of a capsid, envelope, or enclosed proteins, the RNA molecule, when inserted into a cell, is capable of using host cell machinery to construct additional viruses. Such viruses can be extremely small. In an experiment conducted in the late 1960s, Sol Spiegelman and his coworkers developed a method by which smaller and smaller viral RNA molecules could be isolated that were capable of replicating if provided with a specific RNA-dependent RNA polymerase and substrate nucleotides. A minimalist infectious viral genome was eventually selected which was only 220 nucleotides (bases) in length [58].

As discussed in the overview, we know very little about the phylogenetic relationship among viruses. Consequently, we subclassify the Group IV viruses based on structural similarities: symmetry of capsid, presence of absence of a viral envelope, and size. There are six subclasses of the Group IV single-stranded positive-sense RNA viruses: Picornaviridae, Togaviridae, Coronaviridae, Hepeviridae, Caliciviridae, Flaviviridae, and Astroviridae. As expected, within

each class, viruses share structural similarities; but there are no properties, other than the defining property of a (+)sense single-stranded RNA genome, that extends to all six classes of the Group IV viruses. For example, some classes have envelopes (i.e., Flaviviridae, Togaviridae, Coronaviridae), and others do not (i.e., Caliciviridae, Picornaviridae, Hepeviridae, and Astroviridae).

```

Group IV (+)ssRNA
  Nidovirales
    Coronaviridae
      SARS virus
    Torovirinae
      Human torovirus

```

Members of Class Nidovirales do not package polymerase in the viral particle. The genome is read directly using host enzymes. Class Nidovirales contains one subclass with viruses that infect humans: Class Coronaviridae. The coronaviruses are characterized by glycoprotein spikes (peplomers) that protrude from the envelope that encloses the round nucleocapsid. The arrangement of peplomers resembles a corona (hence, coronavirus).

SARS (severe acute respiratory syndrome) virus produces a severe flu-like illness, and is spread by close human contact. The earliest outbreak of SARS occurred in Southeast Asia, in 2002. Soon thereafter, cases occurred in distant locations, including Toronto, Canada, and Bangalore, India. The worldwide response to SARS was possibly the most intensive public health effort ever launched to stem an epidemic of a new, and potentially fatal, viral disease. By 2004, China, the epicenter of the fledgling epidemic, was declared SARS free.

Toroviruses infect a variety of mammals. Human torovirus is a rare cause of enteritis.

```

Group IV (+)ssRNA
  Hepeviridae:
    Hepatitis E

```

Class Hepeviridae is a tentative class, with just one genus and one species, the Hepatitis E virus. It is possible that the Hepatitis E virus will be reassigned to an existing subclass of Group IV or will be assigned to a newly named subclass.

Hepevirus should not be confused with the orthographically similar “herpesvirus.”

Also, readers should not confuse Class Hepeviridae (Hepatitis E virus) with Class Hepacivirus, a subclass of Class Flaviviridae that contains the Hepatitis C virus. Neither of these Group IV subclasses should be confused with Class Hepadnaviridae (Group VII).

```

Group IV (+)ssRNA
  Caliciviridae
    Norovirus
    Sapporo virus

```

Class Calciviridae contains small nonenveloped viruses, 35–40 nm in diameter, just a tad larger than members of Class Picornaviridae. They take their name from the Latin root, calyx, meaning goblet, referring to the cup-shaped capsid depressions. Members of Class Calciviridae cause acute gastroenteritis in humans.

Group IV (+)ssRNA

Togaviridae

Alphavirus Viral diseases

Chikungunya

Eastern equine encephalomyelitis virus

Getah virus

Mayaro virus

Mucambo virus

O'nyong'nyong virus

Ross river virus

Barmah forest virus

Sagiyama virus

Semliki forest virus

Sindbis virus

Tonate virus

Venezuelan equine encephalomyelitis virus

Western equine encephalomyelitis virus

Rubivirus

Rubella virus

Class Togaviridae is named for its distinctive coat (the “toga”). Togaviruses have a genome approximately 12 kbases in length, somewhat larger than the genome of Class Picornaviridae. Togaviruses live in the cytoplasm of their host cells, where viral replication and gene expression take place. Class Togaviridae contains two subclasses: Class Alphavirus and Class Rubivirus. All the members of Class Alphavirus are arboviruses (arthropod-borne viruses) spread by mosquitoes (primarily) or ticks. Class Rubivirus contains only one species that is infective in humans: Rubella virus, the cause of German measles. Rubella is spread directly from person to person, without an insect vector. Readers should not confuse Rubella virus with the measles virus, Rubeola. Rubeola virus is a paramyxovirus (Group V), unrelated to Rubella virus.

A few of the alphaviruses typify the group. Chikungunya is a disease that produces a clinical syndrome similar to that seen with Dengue virus (Class Flaviviridae), Ross river virus and Barmah forest virus; namely, an acute febrile phase followed by a prolonged arthralgic phase. Chikungunya fever is spread by the *Aedes* mosquito, and the reservoir is human (i.e., transmission is human to mosquito to human). In recent years, the incidence of Chikungunya has recently increased in Asia and Africa and is now an emerging disease in the Europe [47].

Ross river virus and Barmah forest virus produce clinically and geographically indistinguishable diseases, sometimes referred to collectively as epidemic

polyarthritis. The diseases are spread by various species of mosquito, and both are endemic to Australasia. They produce an acute influenza-like illness, followed by arthralgia. Joint pains may persist for many months. The reservoir for both viruses seems to be, primarily, marsupials.

Group IV (+)ssRNA

Flaviviridae

Hepacivirus

Hepatitis C

Flavivirus

Dengue virus types

Japanese B encephalitis virus

Murray Valley encephalitis virus

Rocio virus

Spondweni virus

St Louis encephalitis

Wesselsbron

West Nile virus

Yellow fever virus

Tick-borne virus group:

Absettarov virus

Hanzalova virus

Hypr virus

Kumlinge virus

Kyasanur forest disease virus

Louping ill

Negishi virus

Omsk virus

Powassan

Langat

Russian spring summer encephalitis

Hepatitis G virus group

Hepatitis G virus

The members of Class Flaviviridae are enveloped, spherical, and have a diameter of about 50 nm. Most members of Class Flaviviridae are arthropod-borne, being transmitted by a tick (Class Chelicerata) or a mosquito (Class Hexapoda). The subclasses of Class Flaviviridae that contain infectious viruses in humans are: Hepacivirus, Flavivirus, Tick-borne virus group, and Hepatitis G virus group.

Hepatitis C virus is the only member of Class Hepacivirus known to cause human disease. Hepatitis C is a common cause of hepatitis and chronic liver disease. It is spread from person to person by sexual transmission, by contact with infected blood, or blood products, and can be spread by contaminated needles. It can be transmitted to the infants born to infected mothers. People who develop hepatitis from this virus often develop chronic infection of the

liver, which varies from person to person in intensity and in the likelihood of progressing to cirrhosis. Over 1% of the US population is infected with Hepatitis C.

Class Flavivirus (from the Latin “flavus,” meaning yellow) is a subclass of Class Flaviviridae, both named for the yellow (jaundiced) skin resulting from infection with its most notorious species, Yellow fever virus. The flaviviruses include some of the most common and deadly viruses on earth, led by Yellow fever virus and Dengue fever virus. Among the flaviviruses are numerous encephalitis-producing viruses that have specific geographic distributions: Japanese encephalitis virus (mosquito-borne), Murray Valley encephalitis virus (mosquito-borne), St. Louis encephalitis virus (mosquito-borne), West Nile encephalitis virus (mosquito-borne), and a host of viruses collectively known as Tick-borne encephalitis viruses.

Yellow fever virus seems to have originated in Africa and spread to other continents in the mid-17th century. It is responsible for hundreds of thousands of deaths in North America alone. The disease is carried by primates, including humans, and transmitted from person to person by the bite of a mosquito (*Aedes aegypti*). It produces hepatitis and hemorrhaging (hence, it is included among the hepatitis viruses and the hemorrhagic fever viruses).

Yellow fever virus is associated with an impressive number of medical breakthroughs, being the first disease demonstrated to be transmitted by an arthropod, among the first diseases shown to be caused by a virus, and among the first infections controlled by a live vaccine. Effective methods of yellow fever prevention, through the eradication of the *Aedes aegypti* were developed in the 1890s, and an effective vaccine was developed in the 1930s. Today, there are about 200,000 cases of yellow fever worldwide, with about 30,000 deaths [59]. Most infections occur in Africa.

While the incidence of yellow fever has diminished over the past century, the incidence of dengue fever is increasing. Dengue, like yellow fever, is transmitted primarily by the *Aedes aegypti* mosquito. More than 50 million dengue virus infections occur each year worldwide. Most infections are asymptomatic or cause only mild disease, but a minority of infections are severe and may cause death. Typical cases exhibit fever and intense pain in muscles and joints (hence the alternate name of the disease, breakbone fever). Fevers can come and go. Capillary permeability is a common feature of the disease, and this may result in petechiae, the egress of fluid from the vascular compartment, shock (so-called Dengue shock syndrome), and hemorrhage (hemorrhagic syndrome). Severe cases of dengue, if untreated, may have a fatality rate approaching 20%. Like yellow fever, Dengue is included in the group of hemorrhagic viruses.

The Hepatitis G virus group, in Class Flaviviridae, contains only one species, Hepatitis G virus, which had been traditionally included among the named hepatitis viruses. Hepatitis G is now considered to be an “orphan virus” (i.e., a virus that has no associated disease). The Hepatitis G virus is found in a small percentage of donated blood units.

Group IV (+)ssRNA
 Picornaviridae
 Enterovirus:
 Coxsackievirus
 Echovirus
 Poliovirus
 Enterovirus
 Rhinovirus A and B
 Hepatovirus:
 Hepatitis A

Members of Class Picornaviridae have a small RNA genome, as small as 7 kbases (i.e., 7000 nucleotides) in length. The picornaviruses include two subclasses: Enterovirus and Hepatovirus.

Members of Class Enterovirus are among the most prevalent human pathogens. In active infections, the virus can often be recovered from feces and respiratory secretions. Poliovirus, spread by contaminated fecal material, produces a paralytic syndrome characterized by inflammation and destruction of the anterior horn cells of the spinal cord. Many poliovirus infections do not result in disease, but disease-free infected individuals are carriers, transiently producing infective virus. Aside from poliovirus, many of the enteroviruses display neurotropism, producing aseptic meningitis and flacid paralysis [60].

There are a huge number of serotypes in Class Enterovirus, spread among the Coxsackievirus, Echovirus, and Enterovirus genera. They produce nonspecific flu-like illnesses, and various strains produce distinctive syndromes such as hand-foot-mouth disease, herpangina, and hemorrhagic conjunctivitis, and Bornholm disease (epidemic pleurodynia). Enterovirus infections are common pediatric maladies. Infections in newborns can be severe, with hepatitis, encephalitis, and sepsis.

Class Enterovirus also includes Genus Rhinovirus, which contains more than 100 variant strains. The rhinoviruses account for most instances of the common cold.

Class Hepatovirus contains Hepatitis A, a cause of hepatitis. As you would expect from a member of Class Enterovirus, Hepatitis A is typically spread by the fecal-oral route. The resulting hepatitis is acute, and generally subsides without sequelae. Unlike Hepatitis B and C, Hepatitis A does not progress to chronic hepatitis and cirrhosis.

Group IV (+)ssRNA
 Astroviridae
 Astrovirus species

Members of Class Astroviridae, like those of Class Picornaviridae and Class Caliciviridae, lack an envelope. The class contains one species that is pathogenic in humans: Astrovirus. Astrovirus causes enteritis. Infections are especially common in children, accounting for more than 5% of enteritis cases in the pediatric age group.

Infectious Genera

Enterovirus

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Picornavirales: Picornaviridae: Enterovirus
- **Infection.** Coxsackievirus (flu-like illness, hand-food-mouth disease, herpangina, hemorrhagic conjunctivitis, aseptic meningitis; in newborns, myocarditis, meningoencephalitis, hepatitis)
- **Infection.** Echovirus, Enteric Cytopathic Human Orphan virus (flu-like illness, aseptic meningitis; in newborns, severe myocarditis hepatitis, and systemic infection)
- **Infection.** Poliovirus (polio)
- **Infection.** Enterovirus 68–109 (flu-like illnesses and other syndromes associated with Coxsackievirus and Echovirus)
- **Infection.** Rhinovirus (common cold)

Hepatovirus

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Picornavirales: Picornaviridae: Hepatovirus
- **Infection.** Hepatitis A (hepatitis A)

Alphavirus

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Togaviridae: Alphavirus
- **Infection.** Chikungunya virus, a member of Semliki Forest virus complex (Chikungunya fever, rash, arthritis)
- **Infection.** Eastern equine encephalomyelitis virus (Encephalitis)
- **Infection.** Getah virus (asymptomatic in humans)
- **Infection.** Mayaro virus, a member of Semliki Forest virus complex (rash, arthritis)
- **Infection.** Mucambo virus (encephalitis)
- **Infection.** O'nyong'nyong virus, a member of Semliki Forest virus complex (rash, arthritis)
- **Infection.** Ross river virus, a member of Semliki Forest virus complex (epidemic polyarthritis)
- **Infection.** Barmah forest virus (epidemic polyarthritis)
- **Infection.** Sagiyama virus, a subtype of Ross River virus (asymptomatic in humans)
- **Infection.** Semliki forest virus, a member of Semliki Forest virus complex (rash, arthritis)
- **Infection.** Sindbis virus (Sindbis fever, rash, arthritis)
- **Infection.** Tonate virus (encephalitis)
- **Infection.** Venezuelan equine encephalomyelitis virus (encephalitis, often causing, in humans, a flu-like illness with high fever and headache)
- **Infection.** Western equine encephalomyelitis virus (Western equine encephalomyelitis)

Rubivirus

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Togaviridae: Rubivirus
- **Infection.** Rubella virus (German measles)

Coronaviridae

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Nidovirales: Coronidovirineae: Coronaviridae
- **Infection.** SARS virus
- **Infection.** Torovirus species (gastroenteritis)

Hepeviridae

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Hepeviridae
- **Infection.** Hepatitis E (hepatitis)

Caliciviridae

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Caliciviridae
- **Infection.** Norovirus, formerly Norwalk virus (epidemic gastroenteritis)
- **Infection.** Sapporo virus (mild gastroenteritis in children)

Hepacivirus

- **Lineage.** ssRNA positive-strand viruses, no DNA stage: Flaviviridae: Hepacivirus
- **Infection.** Hepacivirus C (Hepatitis C)

Flavivirus

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Flaviviridae: Flavivirus
- **Infection.** Dengue virus types 1–4 (dengue fever; severe form is called dengue hemorrhagic fever)
- **Infection.** Japanese encephalitis virus (encephalitis, with less than 1% of human infections leading to disease)
- **Infection.** Murray Valley encephalitis virus (Murray Valley encephalitis, formerly known as Australian encephalitis)
- **Infection.** Rocio virus (meningoencephalitis)
- **Infection.** Spondweni virus (acute febrile illness)
- **Infection.** St Louis encephalitis (encephalitis)
- **Infection.** Wesselsbron virus (fever, flu-like illness, most infections are subclinical)
- **Infection.** West Nile virus (West Nile fever)
- **Infection.** Yellow fever virus (yellow fever)

Tick-borne encephalitis group of flaviviruses

- **Infection.** Absettarov virus (encephalitis)
- **Infection.** Hanzalova virus (encephalitis)
- **Infection.** Hypr virus (encephalitis)
- **Infection.** Kumlinge virus (fever and encephalitis)
- **Infection.** Kyasanur forest disease virus (hemorrhagic fever)
- **Infection.** Louping ill virus (tick-borne encephalitis)
- **Infection.** Negishi virus (encephalitis)
- **Infection.** Omsk virus (hemorrhagic fever)
- **Infection.** Powassan virus (tick-borne encephalitis)
- **Infection.** Langat virus (tick-borne encephalitis)
- **Infection.** Russian spring summer encephalitis virus (encephalitis)

Hepatitis G virus group

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Flaviviridae: Pegivirus: Pegivirus C: GB virus C
- **Infection.** Hepatitis G virus, alternately GB virus CF (“orphan virus” not associated with any human disease)

Astroviridae:

- **Lineage.** ssRNA viruses: ssRNA positive-strand viruses, no DNA stage: Astrovirid
- **Infection.** Astrovirus species (gastroenteritis)

Section 7.7 Group V viruses: Single-stranded (–) sense RNA

An inefficient virus kills its host. A clever virus stays with it.

James Lovelock

Group I, dsDNA
Group II, ssDNA
Group III, dsRNA
Group IV (+) ssRNA
Group V (-) ssRNA
 Mononegavirales (nonsegmented)
 Paramyxoviridae
 Henipavirus
 Hendra virus
 Nipah virus
 Rubulavirus
 Mumps virus
 Parainfluenza types

- Morbillivirus
 - Measels virus
- Avulavirus
 - Newcastle disease virus
- Metapneumovirus
- Pneumovirus
 - Respiratory syncytial virus
- Parainfluenza Types
- Rhabdoviridae
 - Lyssavirus
 - Duvenhage
 - Rabies virus
 - Vesiculovirus
 - Vesicular stomatitis
 - Chandipura
- Filoviridae
 - Marburg virus
 - Marburg virus
 - Ebolavirus
 - Ebola Reston
 - Ebola Siena
 - Ebola Sudan
 - Ebola Zaire
- Bornaviridae
 - Bornavirus
- Unassigned Classes
- Arenaviridae
 - Mammarenavirus
 - Lassa_virus complex:
 - Lassa virus
 - Lujo virus
 - Lymphocytic choriomeningitis virus
 - Mobala virus
 - Mopeia virus
 - Tacaribe-virus complex:
 - Amapari virus
 - Chapare virus
 - Flexal virus
 - Guanarito virus
 - Junin virus
 - Latino virus
 - Machupo virus
 - Oliveros virus
 - Parana virus

- Pichinde virus
- Piritai virus
- Sabia virus
- Tacaribe virus
- Tamiami virus
- Whitewater Arroyo virus
- Bunyaviridae
 - Akabane virus
 - Bunyamwera virus
 - California encephalitis virus
- Hantavirus
 - Hantavirus Belgrade virus
 - Hantavirus Hantaan virus
 - Hantavirus Prospect Hill virus
 - Hantavirus Puumala virus
 - Hantavirus Seoul virus
 - Hantavirus Sin Nombre virus
- Nairovirus
 - Nairovirus Bhanja virus
 - Nairovirus Crimean virus
 - Nairovirus Hazara virus
 - Oropouche virus
 - Phlebovirus
 - Rift Valley Fever
 - Pappataci fever virus
- Orthomyxoviridae
 - Influenza
 - Thogotovirus
 - Tick-borne orthomyxoviridae Dhori
 - Tick-borne orthomyxoviridae Thogoto
- Unassigned genus
- Deltavirus
 - Hepatitis delta virus
- Group VI, ssRNA-RT
- Group VII, dsDNA-RT

Single-stranded RNA viruses are grouped into viruses with a positive sense, negative sense, and ambisense.

Positive sense RNA viruses are those that have the same direction as human mRNA. Positive sense virus genes can be translated (to yield protein) with the same cellular machinery that translates mRNA. These are the Group IV viruses.

Negative sense RNA is complementary to mRNA. Negative sense RNA must be converted to positive sense RNA or to DNA before it becomes biologically available for translation or replication, respectively.

The Group V viruses are single-stranded negative sense RNA viruses that use an RNA-dependent RNA polymerase, packaged within the virus particle, to produce positive sense RNA, within the host cell. The Group VI viruses are single-stranded negative sense RNA viruses that use an RNA-dependent DNA polymerase (so-called reverse transcriptase), packaged within the virus particle, to produce a complementary strand of DNA. The synthesized strand of DNA is subsequently used as a template to yield a double-stranded DNA molecule that contains the genetic information from the viral genome.

The ambisense single-strand RNA viruses contain at least one positive sense RNA segment admixed with negative sense RNA. Genomically, an ambisense virus is a concatenation of a Group IV virus (positive sense single-stranded) and a negative sense virus. Nevertheless, transcription in ambisense viruses is coupled with translation of the viral genome to a complementary RNA strand, a process that is characteristic of the Group V viruses [61]. Consequently, the ambiviruses are currently included in the “unassigned” subclasses of the Group V viruses.

Among the Group V RNA viruses pathogenic to humans, there is one assigned class of viruses, Class Monongavirales, which includes the following subclasses: Bornaviridae, Filoviridae, Paramyxoviridae, and Rhabdoviridae. The remaining Class V viruses belong to unassigned subclasses (i.e., with no named taxonomic superclass) or unassigned genera (i.e., belonging to no assigned class). The unassigned viruses include the ambisense viruses. The unassigned classes are: Arenaviridae, Bunyaviridae, and Orthomyxoviridae. Deltavirus is an unassigned genus.

The Group V viruses are numerous, and it would be unproductive to describe each virus in detail. The following discussion will include viral disorders that typify their class or that highlight recent findings that might have been omitted from previously published virology texts. A listing of the Group V viruses, along with their associated diseases and clinical conditions, arranged by subclass, is provided at the end of this section.

- Group V (-)ssRNA
 - Mononegavirales (nonsegmented)
 - Paramyxoviridae
 - Henipavirus
 - Hendra virus
 - Nipah virus
 - Rubulavirus
 - Mumps virus
 - Parainfluenza types
 - Morbillivirus
 - Measels virus
 - Avulavirus
 - Newcastle disease virus
 - Metapneumovirus

- Pneumovirus
 - Respiratory syncytial virus
- Parainfluenza Types
- Rhabdoviridae
 - Lyssavirus
 - Duvenhage
 - Rabies virus
- Vesiculovirus
 - Vesicular stomatitis
 - Chandipura
- Filoviridae
 - Marburg virus
 - Marburg virus
 - Ebolavirus
 - Ebola Reston
 - Ebola Siena
 - Ebola Sudan
 - Ebola Zaire
- Bornaviridae
 - Bornavirus

Class Paramyxoviridae includes the viruses that cause measles (Rubeola or Morbilli virus) and mumps. Measles remains one of the most fatal virus disease, in terms of deaths worldwide. In 2001, measles virus accounted for about 745,000 deaths. Class Paramyxoviridae also includes several viruses that account for many respiratory diseases, particularly in children: the parainfluenza viruses, respiratory syncytial virus, and (somewhat less severe, clinically) human metapneumovirus.

Class Rhabdoviridae includes Rabies virus, a species of lyssavirus (from Lyssa, the Greek goddess of madness).

Class Filoviridae includes Ebola virus, Marburg virus. Members of Class Filoviridae infect primates (including humans) and produce potentially fatal viral hemorrhagic fevers.

Class Bornaviridae contains one species that infects humans, Borna virus. This virus, which infects a variety of animals, is neurotropic, producing nervous system inflammation (e.g., meningoencephalitis), neurologic impairment (e.g., ataxia), and behavior disorders (e.g., excitation or depression) in infected animals.

The role of Bornavirus in humans is undetermined at this time, but Bornavirus infections have been implicated as a cause of mental illnesses in humans, including bipolar disorder. It is the only member of Class Mononegavirales that replicates inside the host nucleus. Bornavirus has recently gained scientific attention as the only nonretrovirus that has been shown to integrate (permanently) into the mammalian genome [11]. Inherited

fragments of bornavirus have been found in various types of mammals, suggesting that bornavirus is not new [12].

Group V (-)ssRNA

Arenaviridae

Mammarenavirus

Lassa_virus complex:

Lassa virus

Lujo virus

Lymphocytic choriomeningitis virus

Mobala virus

Mopeia virus

Tacaribe-virus complex:

Amapari virus

Chapare virus

Flexal virus

Guanarito virus

Junin virus

Latino virus

Machupo virus

Oliveros virus

Parana virus

Pichinde virus

Piritital virus

Sabia virus

Tacaribe virus

Tamiami virus

Whitewater Arroyo virus

Bunyaviridae

Akabane virus

Bunyamwera virus

California encephalitis virus

Hantavirus

Hantavirus Belgrade virus

Hantavirus Hantaan virus

Hantavirus Prospect Hill virus

Hantavirus Puumala virus

Hantavirus Seoul virus

Hantavirus Sin Nombre virus

Nairovirus

Nairovirus Bhanja virus

Nairovirus Crimean virus

Nairovirus Hazara virus

Oropouche virus

Phlebovirus
 Rift Valley Fever
 Pappataci fever virus
 Orthomyxoviridae
 Influenza
 Thogotovirus
 Tick-borne orthomyxoviridae Dhori
 Tick-borne orthomyxoviridae Thogoto

Along with the bunyaviruses, the viruses in Class Arenaviridae account for the majority of roboviruses (rodent-borne viruses). In general, each arenavirus infects a specific species of rodent. Rodents occasionally transmit the virus to humans, either through aerosolized excreta (e.g., urine, feces) or by direct contact of infectious material with cuts and abrasions in human skin. Most of the diseases caused by bunyaviruses are encephalitides, hemorrhagic fevers, or nonhemorrhagic fevers; the severity vary with the viral species and host resistance.

The arenaviruses have been separated by geographic locale into two groups: New World Viruses and Old world viruses. Old world arenaviruses and their approximate locales are: Ippy virus (Central African Republic), Lasssa virus (West Africa), Lymphocytic choriomeningitis virus (worldwide), Mobala virus (Central African Republic), and Mopeia virus (Mozambique).

The New World arenaviruses and their approximate locales are: Amapari virus (Brazil), Flexal virus (Brazil), Guanarito virus (Venezuela), Junin virus (Argentina), Latino virus (Bolivia), Machupo virus (Bolivia), Oliveros virus (Argentina), Parana virus (Paraguay), Pichinde virus (Columbia), Pirital virus (Venezuela), Sabia virus (Brazil), Tacaribe virus (Trinidad), Tamiami virus (Florida, USA), and Whitewater Arroyo virus (New Mexico, USA). Several of the arenaviruses isolated from humans have not, as yet, been associated with human disease; these species are omitted from the list of infectious diseases associated caused by arenaviruses (vida infra).

One member of Class Arenaviridae, Lassa virus, the cause of Lassa fever, should not be confused with Lyssa virus, a member of Class Rhabdoviridae and the cause of rabies.

Class Bunyaviridae along with Class Arenaviridae account for the majority of Roboviruses (rodent-borne viruses). In addition, like the virus syndromes produced by members of Class Arenaviridae, the members of Class Bunyaviridae tend to produce fever syndromes, hemorrhagic fever syndromes, or meningoencephalitides.

Class Orthomyxoviridae includes Influenza virus (types A, B, and C) and the thogotoviruses. Seasonal influenza kills between a quarter million and a half million people worldwide each year. In the United States seasonal

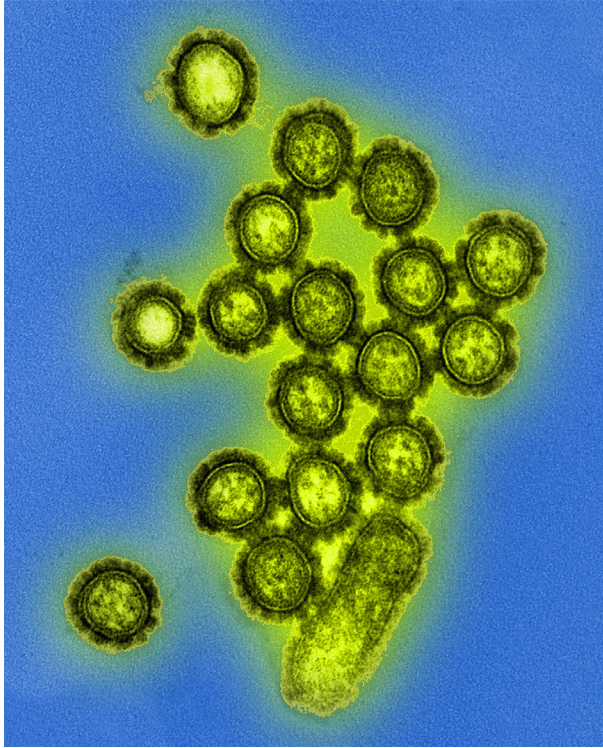


FIG. 7.4 H1N1 influenza (swine flu) viruses. (Source, a public domain image provided by the U.S. National Institute of Allergy and Infectious Diseases.)

influenza accounts for about 40,000 deaths annually. The 1917–18 influenza pandemic caused somewhere between 50 million and 100 million deaths (Fig. 7.4).

The thogotoviruses (Dhori virus and Thogoto virus) infect ticks, and ticks transmit the infection to humans. Thogotoviruses produce fever and encephalitis.

```

Group V (-)ssRNA
  Unassigned Classes
    Unassigned genus
      Deltavirus
        Hepatitis delta virus
  
```

Genus Deltavirus is a genus in Group V that has not been assigned a viral class. The genus contains one species, the Hepatitis D virus. The Hepatitis D virus cannot replicate on its own. Replication requires the presence of Hepatitis B virus in the same host cell. Coinfections of Hepatitis B and Hepatitis D viruses (sometimes referred to as Labrea fever) have a more severe clinical course than infections with

Hepatitis B alone (e.g., increased likelihood of developing liver failure, shortened time interval for initial infection to the development of cirrhosis, increased likelihood of developing liver cancer, and overall increased mortality rate).

Infectious Genera

Paramyxoviridae

- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Henipavirus: Hendra henipavirus (also known as equine morbillivirus)
- **Infection.** Hendra virus, a henipavirus transmitted by Pteropid fruit bats (pulmonary edema and hemorrhage, encephalitis)
- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Henipavirus: Nipah henipavirus
- **Infection.** Nipah, a henipavirus transmitted by Pteropid fruit bats (encephalitis, relapse encephalitis)
- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Morbillivirus: Measles morbillivirus
- **Infection.** Measles virus (measles, rubeola, morbilli)
- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Rubulavirus: Mumps rubulavirus
- **Infection.** Mumps virus (mumps)
- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Avulavirus: Avian avulavirus 1 (Newcastle disease virus)
- **Infection.** Newcastle disease virus, transmitted by infected birds (conjunctivitis and flu-like illness)
- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Paramyxoviridae: Respirivirus: Human respirovirus 1
- **Infection.** Human Parainfluenza virus 1, HPIV-1 (most common cause of croup; also other upper and lower respiratory tract illnesses typical)
- **Infection.** Human Parainfluenza virus 2, HPIV-2 (causes croup and other upper and lower respiratory tract illnesses)
- **Infection.** Human Parainfluenza virus 3, HPIV-3 (associated with bronchiolitis and pneumonia)
- **Infection.** Human Parainfluenza virus 4, HPIV-4 (mild respiratory infections, often clinically silent)

Pneumoviridae

- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Pneumoviridae: unclassified Pneumoviridae
- **Infection.** Respiratory syncytial virus, RSV (pneumonia, pneumovirus pneumonia)

- **Lineage.** ssRNA viruses: ssRNA negative-strand viruses: Mononegavirales: Pneumoviridae: Metapneumovirus
- **Infection.** Human metapneumovirus (mild respiratory illness in healthy individuals, occasionally severe respiratory illness in children, elderly, and immune-compromised individuals)

Rhabdoviridae: Lyssavirus

- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Rhabdoviridae: Lyssavirus: Duvenhage lyssavirus
- **Infection.** Duvenhage (rabies-like encephalitis)
- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Rhabdoviridae: Lyssavirus: Rabies lyssavirus
- **Infection.** Rabies virus (rabies, hydrophobia, lyssa)

Rhabdoviridae: Vesiculovirus

- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Rhabdoviridae: Vesiculovirus: unclassified Vesiculovirus: Vesicular stomatitis virus
- **Infection.** Vesicular stomatitis virus (flu-like illness in humans)
- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Rhabdoviridae: Vesiculovirus: Chandipura vesiculovirus: Chandipura virus
- **Infection.** Chandipura (encephalitis)

Filoviridae:

- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Filoviridae: Ebolavirus: Zaire ebolavirus: Ebola virus
- **Infection.** Ebola virus (Ebola hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Filoviridae: Marburg virus
- **Infection.** Marburg virus (Marburg hemorrhagic fever)

Bornaviridae:

- **Lineage.** ssRNA negative-strand viruses: Mononegavirales: Bornaviridae: Orthobornavirus
- **Infection.** Bornavirus, alternately Borna disease virus (Borna disease in mammals, possible cause of mental illness, including bipolar disorder in humans)

Mammarenavirus

- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Lassa mammarenavirus
- **Infection.** Lassa virus (Lassa fever, multisystem disease characterized by hyperpyrexia, coagulopathy, hemorrhaging, and necrosis of liver and spleen)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Lujo mammarenavirus
- **Infection.** Lujo virus (viral hemorrhagic fever)

- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Lymphocytic choriomeningitis mammarenavirus
- **Infection.** Lymphocytic choriomeningitis virus (lymphocytic choriomeningitis)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Chapare mammarenavirus
- **Infection.** Chapare virus (hemorrhagic fever) [62]
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Flexal mammarenavirus
- **Infection.** Flexal virus (flu-like illness)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Guanarito mammarenavirus
- **Infection.** Guanarito virus (Venezuelan hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Argentinian mammarenavirus
- **Infection.** Junin virus (Argentine hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Machupo mammarenavirus
- **Infection.** Machupo virus (Bolivian hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Oliveros mammarenavirus
- **Infection.** Oliveros virus (severe hemorrhagic fever in South America) [63]
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Brazilian mammarenavirus (Sabio virus)
- **Infection.** Sabia virus (Brazilian hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Whitewater Arroyo mammarenavirus
- **Infection.** Whitewater Arroyo virus (hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Wenzhou mammarenavirus
- **Infection.** Wenzhou virus (transmitted by rodents and shrews, of undetermined human pathogenicity)
- **Lineage.** ssRNA negative-strand viruses: Arenaviridae: Mammarenavirus: Mopeia mammarenavirus
- **Infection.** Mopeia virus (transmitted by *Mastomys natalensis* rodents, of undetermined human pathogenicity)

Bunyaviridae:

- **Lineage.** ssRNA negative-strand viruses: Bunyavirales: Peribunyaviridae: Orthobunyavirus: Bunyamwera orthobunyavirus: Bunyamwera virus
- **Infection.** Bunyamwera virus (headache systemic symptoms, and rash)

- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Peribunyaviridae: Orthobunyavirus: California encephalitis orthobunyavirus: California encephalitis virus
- **Infection.** California encephalitis virus (encephalitis)
- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Hantaviridae: Orthohantavirus
- **Infection.** Hantavirus Belgrade, also known as Hantavirus Dobrava-Belgrade (hemorrhagic fever with renal syndrome)
- **Infection.** Hantavirus Hantaan (Korean hemorrhagic fever, hemorrhagic fever with renal syndrome)
- **Infection.** Hantavirus Prospect Hill (not associated with human disease)
- **Infection.** Hantavirus Puumala (hemorrhagic fever with renal syndrome)
- **Infection.** Hantavirus Seoul (hemorrhagic fever with renal syndrome)
- **Infection.** Hantavirus Sin Nombre (formerly Muerto Canyon)
- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Nairoviridae: Orthonairovirus
- **Infection.** Nairovirus Bhanja (rare, flu-like illness ranging from mild to severe disease)
- **Infection.** Nairovirus Crimean (Congo haemorrhagic fever, Crimean-Congo hemorrhagic fever)
- **Infection.** Nairovirus Hazara (hemorrhagic fever)
- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Peribunyaviridae: Orthobunyavirus: Oropouche orthobunyavirus: Oropouche virus
- **Infection.** Oropouche virus (Oropouche fever, characterized by fever with systemic symptoms)

Phlebovirus:

- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Phenuiviridae: Phlebovirus: Rift Valley fever phlebovirus: Rift Valley fever virus
- **Infection.** RVF virus (Rift Valley fever)
- **Lineage.** ssRNA negative-strand viruses: Bunyvirales: Phenuiviridae: Phlebovirus: unclassified Phlebovirus: Sandfly fever Sicilian virus
- **Infection.** Pappataci fever virus (Pappataci fever, phlebotomus fever, sandfly fever, three-day fever)

Orthomyxoviridae:

- **Lineage.** ssRNA negative-strand viruses: Orthomyxoviridae: unclassified Orthomyxoviridae: unidentified influenza virus
- **Infection.** Influenza types A, B, and C (viral influenza)

Thogotovirus

- **Lineage.** ssRNA negative-strand viruses: Orthomyxoviridae: Thogotovirus: Dhori thogotovirus
- **Infection.** Tick-borne orthomyxoviridae Dhori (fever, encephalitis)

- **Lineage.** ssRNA negative-strand viruses: Orthomyxoviridae: Thogotovirus: Thogoto thogotovirus
 - **Infection.** Tick-borne orthomyxoviridae Thogoto (respiratory disease)
- Deltavirus:
- **Lineage.** ssRNA negative-strand viruses: Deltavirus: Hepatitis delta virus
 - **Infection.** Hepatitis delta virus (high mortality hepatitis when co-infected or superinfected with Hepatitis B virus)

Section 7.8 Group VI viruses: Single-stranded RNA reverse transcriptase viruses with a DNA intermediate in life cycle

The origin of retroviruses is lost in a prebiotic mist.

Patric Jern, Goran Sperber, Jonas Blomberg [16]

```
Group I, dsDNA
Group II, ssDNA
Group III, dsRNA
Group IV (+)ssRNA
Group V (-)ssRNA
Group VI, ssRNA-RT
  Retroviridae
    Deltaretrovirus
      Human T-cell lymphotropic virus
    Lentivirus
      Human immunodeficiency virus
Group VII, dsDNA-RT
```

Single-stranded RNA viruses can be positive sense or negative sense. Positive sense RNA, for example, eukaryotic mRNA and Group IV viruses, can be directly translated to produce protein. Negative sense RNA is complementary to mRNA. Negative sense RNA must be copy-converted to positive sense RNA or to DNA before becoming biologically available for translation or replication, respectively.

The Group VI viruses are single-stranded negative sense RNA viruses that use an RNA-dependent DNA polymerase (so-called reverse transcriptase), packaged within the virus particle to produce a complementary strand of DNA. The synthesized strand of DNA is subsequently used as a template to yield a double-stranded DNA molecule containing the genetic information from the viral genome. Group VI viruses can integrate this double-stranded DNA into the host genome. The Group VI viruses are referred to as retroviruses.

The Group V viruses, like the Group VI viruses, are single-stranded negative sense RNA viruses. These viruses do not employ reverse transcriptase. Instead,

they use an RNA-dependent RNA polymerase, packaged within the virus particle, to produce positive sense RNA within the host cell. The positive sense RNA is subsequently used to synthesize proteins.

Group VI viruses share their genetic legacy with the human genome. About 8% of human genes are retroviral. Human DNA of retroviral origin is referred to as endogenous retrovirus, or as a retroviral provirus. Retroviruses in the external environment, capable of infecting eukaryotic host cells, are referred to as exogenous retrovirus (i.e., a retrovirus that is outside the gene).

Despite the legacy of retroviruses within the genome of eukaryotic cells, there are only a few exogenous retroviruses that cause infectious disease in humans. The Group VI human pathogens are restricted to one class of retroviruses, Class Retroviridae, and to two genera within this class: Deltaretrovirus and Lentivirus.

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Group VI, ssRNA-RT
  Retroviridae
    Deltaretrovirus
      Human T-cell lymphotropic virus
    Lentivirus
      Human immunodeficiency virus

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Genus Deltaretrovirus contains four human t-cell lymphotropic viruses: HTLV-1, HTLV-2, HTLV-3, and HTLV-4. Of these four viruses that infect humans, only HTLV-1 virus has been associated with human disease. Infection with HTLV-1 greatly increases the risk of developing adult T-cell leukemia/lymphoma, with about 1 out of every 25 infected individuals eventually developing the disease). HTLV-1 has also been implicated as a cause of a human myelopathic condition, tropical spastic paraparesis. Although millions of individuals have been infected by HTLV-1, worldwide, fewer than 2% of infected individuals will develop an HTLV-1 associated myelopathic condition.

Readers should be careful not to confuse Class Deltaretrovirus (a class of Group VI retroviruses) with Class Deltavirus, a Group V single-strand RNA negative-strand virus containing Hepatitis delta virus.

Genus Lentivirus contains the HIV, which produces HIV infection and the syndrome of associated diseases known as AIDS.

Readers should not confuse HTLV-III, a virus discovered in 2005, and which is not known at this time to produce disease in infected humans, with an early name (long since abandoned) that was assigned to the HIV virus.

Infectious Genera

Deltaretrovirus

- **Lineage.** Ortervirales: Retroviridae: Orthoretrovirinae: Deltaretrovirus: unclassified Deltaretrovirus: Untyped Human T-lymphotropic virus: Human T-cell lymphotropic virus

- **Infection.** HTLV-1 (some cases of T-cell leukemia and T-cell lymphoma in adults, HTLV-1 associated myelopathy/tropical spastic paraparesis or HAM/TSP)

Lentivirus

- **Lineage.** Ortervirales: Retroviridae: Orthoretrovirinae: Lentivirus: Primate lentivirus group: unclassified Primate lentivirus group: Human immunodeficiency virus
- **Infection.** Human immunodeficiency virus (HIV infection and AIDS)

Section 7.9 Group VII viruses: Double-stranded DNA reverse transcriptase viruses

The human genome is a living document of ancient and now extinct viruses.

Michael Emerman and Harmit Malik [12]

Group I, dsDNA
Group II, ssDNA
Group III, dsRNA
Group IV (+)ssRNA
Group V (-)ssRNA
Group VI, ssRNA-RT
Group VII, dsDNA-RT
Hepadnaviridae
Orthohepadnavirus
Hepatitis B

Group VII viruses are double-stranded DNA viruses that can integrate their DNA into the host genome, using a reverse transcriptase enzyme. The reverse transcriptase enzyme acts upon RNA, transcribed from viral DNA, as the template for genomic DNA. Hence, the Group VII viruses are an unusual type of retrovirus that do not belong to Class Retroviridae (Group VI), because the genome is double-stranded DNA. Likewise, the Group VII viruses are not classed within the double-stranded DNA viruses (Group I) because their replication requires the synthesis of an RNA intermediate.

Group VII, dsDNA-RT
Hepadnaviridae
Orthohepadnavirus
Hepatitis B

Group VII has one class of viruses that is pathogenic in humans: Class Hepadnaviridae. Hepadnaviruses (short for HEPATIC DNA VIRUS) have a small, circular DNA genome. Class Hepadnaviridae contains one viral species that is pathogenic in humans: hepatitis B virus.

Hepatitis B infects more than 200 million people, worldwide, causing 2 million deaths each year. Deaths are due to acute or chronic hepatitis or due to ensuing conditions such as cirrhosis and hepatocellular carcinoma. Infection is spread from infected persons through contact with body fluids (e.g., sexual intercourse, through inoculation with contaminated needles or tattoo instruments, or through the use of contaminated blood transfusion products) [Glossary [Blood contamination](#)].

As a virus that can insert part of its genome into host DNA, you might expect that it would be oncogenic (able to produce cancers). You would be correct. Hepatocellular carcinoma occurs in about 10% of infected patients who develop chronic hepatitis. Hepatitis B is the only DNA transforming virus that is not a Group I virus. Sections of the viral genome, inserted into host DNA, persist in cells of the hepatocellular carcinomas that eventually develop.

In addition to causing hepatitis B, the hepatitis B virus is essential for the replication of hepatitis delta virus. Hepatitis delta virus (Hepatitis D virus) is an RNA virus of Group V. As previously noted, the hepatitis delta virus is a defective virus that cannot replicate without the help of the hepatitis B virus, which produces the protein coat for hepatitis delta virus. A coinfection with hepatitis B and hepatitis D produces a more aggressive disease than that produced with hepatitis B alone [64].

Infectious Genera

Hepadnaviridae

- **Lineage.** Retro-transcribing viruses: Hepadnaviridae: Orthohepadnavirus: Hepatitis B virus
- **Infection.** Hepatitis B (acute hepatitis, chronic hepatitis, cirrhosis, hepatocellular carcinoma)

Glossary

Adaptive immunity Immunity in which the response adapts to the specific chemical properties of foreign antigens. Adaptive immunity is a system wherein somatic T cells and B cells are produced, each with a unique and characteristic immunoglobulin (in the case of B cells) or T-cell receptor (in the case of T cells). Through a complex presentation and selection system, a foreign antigen elicits the replication of a B cell that produces an antibody whose unique immunoglobulin attachment site matches the antigen. Antigen-antibody complexes may deactivate and clear circulating antibodies, or may lead to the destruction of the organism that carries the antigen (e.g., virus or bacteria).

The process of producing unique proteins requires that recombination and hypermutation take place within a specific gene region. Recombinations yield on the order of about a billion unique somatic genes, starting with one germinal genome. This process requires the participation of recombination-activating genes (RAGs). The acquisition of an immunologically active recombination-activating gene from a retrovirus is presumed to be the key evolutionary event that led to the development of the adaptive immune system. This event, which occurred in one of the early species of gnathostomes (jawed vertebrates),

established the adaptive immune system in all jawed vertebrates and their descendants. As one might expect, inherited mutations in RAG genes cause immune-deficiency syndromes [65, 66].

Bat A bat is not a flying mouse and is not a member of Class Rodentia, flying or otherwise. Bats are mammals of Class Chiroptera. With forelimbs that have evolved into wings, they are the only mammals capable of sustained, self-propelled flight. Their relevance in this book stems from their status as viral vectors. Currently, bat populations of many species are being decimated by *Geomyces destructans*, a fungus in Class Ascomycota, the cause of white-nose syndrome. Apparently, the fungal infection, which grows in cold conditions, awakens bats from their deep hibernation; starvation results.

Blood contamination When a blood donor is infected with a pathogenic organism, the disease can be passed to the recipient. Examples of organisms and diseases that can be spread through blood transfused blood or blood components include:

Human Immunodeficiency Virus
 Human T-Lymphotropic Viruses type I and type II
 Hepatitis A
 Hepatitis B
 Hepatitis C
 Hepatitis E
 Cytomegalovirus
 Epstein-Barr Virus
 Human Parvovirus B19
 Human Herpesvirus 6
 Human Herpesvirus 8
 TT virus or Transfusion Transmitted Virus or Torque teno virus [67]
 SEN Virus [56]
 CJD and vCJD
 Syphilis
 Malaria [68]
 Chagas Disease
 African trypanosomiasis
 Toxoplasmosis
 Leishmaniasis
 Babesiosis
 Rocky Mountain Spotted Fever
 Ehrlichiosis

Capsid The protein shell of a virus that encloses the genetic material of the virus when the virus is outside its host cell. The capsid aids the virus with its attachment to the target host cell, and with the penetration of the viral genome into the host cell.

Evolvability Evolution by natural selection is not a physiological process, like respiration or replication. The theory of evolution is little more than a restatement of a probabilistic truism, in biological terms. Namely, organisms that are most likely to survive will be the organisms most likely to reproduce. Biologists speak in terms of evolvability to indicate certain factors that may tip the evolutionary scales in an organism's favor.

For the most part, these features all involve mechanisms by which new or modified genetic material that may serve as the source of new genes, is obtained. These would include:

- Having mechanisms for horizontal gene transfer
- Having mechanisms for increasing the rate of mutation under environmentally stressful circumstances (e.g., radiation, heat, cold)
- Tendency toward endoduplication of genes
- Having large, diverse gene pool
- Presence of pseudogenes and junk DNA

Hepatitis viruses Several of the viruses that cause hepatitis are provided with names that are easy to remember but impossible to reconcile as a coherent biological class. These are Hepatitis A, B, C, D, E, F, and G. Pathogenic viruses that attack any particular organ need not all belong to the same biological class, and the named hepatitis viruses are no exception, belonging to Groups IV, V, and VII. In addition, not all pathogenic viruses that infect the liver belong to the named hepatitis viruses. Yellow fever virus, which has killed millions of people throughout history, is a Group IV hepatitis virus.

Here is a list of the named hepatitis viruses:

- Hepatitis A virus is a member of Class Picornaviridae (Group IV).
- Hepatitis B virus is a member of Class Hepadnaviridae (Group VII).
- Hepatitis C virus is a member of Class Flaviviridae (Group IV), the same class that contains yellow fever virus, which also produces hepatitis.
- Hepatitis D is a member of an unassigned class in Group V.
- Hepatitis E virus is a member of class Hepeviridae (Group IV).
- Hepatitis F virus is a hypothetical organism, supposedly responsible for some cases of hepatitis that cannot be diagnosed under any of the nonimaginary taxa.
- Hepatitis G virus is now thought to be the same virus as GB virus C, a virus not known to produce any human disease.

Phenetics An approach to classification wherein objects are grouped together based on a shared set of physical features. In this book, we make the argument that phenetics is an improper approach for biological classifications insofar as two distantly related species may share a physical similarity (e.g., ability to fly or aquatic life) without having any close ancestral relationship, without having a close genetic relationship, and without sharing many metabolic pathways. As the biologist George Gaylord Simpson put it, “Individuals do not belong in the same taxon because they are similar, but they are similar because they belong to the same taxon” [69].

Transposon Also called transposable element, and informally known as jumping gene. The name “transposable element” would seem to imply that a fragment of the genome (i.e., the transposable element) physically moves from one point in the genome to another. This is not the case. What actually happens (in the case of Class II transposons) is that a copy of the DNA sequence of the transposon is inserted elsewhere in the genome, resulting in the sequence now occupying two different locations in the genome. In the case of Class II transposons, the DNA sequence of the transposon is translated into RNA, then reverse-transcribed as DNA, and reinserted at another location; likewise resulting in two of the same sequence in two locations in the genome [70]. You can see how transposable elements might bloat the genome with repeated elements. Some transposons are the ancient remnants of retroviruses and other horizontally transferred genes that insinuated their way into the eukaryotic genome. Because transposon DNA is not necessary for cell survival, the sequences of transposons are not conserved, and mutations occurring over time yield

degenerate sequences that no longer function as retroviruses. A role for transposons in the altered expression of genes in cancer cells has been suggested [71].

Virion The infective form of a virus outside the host cell. Viruses can be thought of as having two alternating forms: the virion and the virocell.

Virocell The name given to a host cell that has been commandeered by a virus to devote its cellular machinery to the mass production of virus particles. When we think of viruses as living organisms, it is best to envisage the virocell, which consists of a viral factory built from the wreckage of the host cells; and not the virion, which is simply a vehicle for transporting a virus safely from host to host.

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