• A **virion** is the extracellular form of a **virus** and contains either an RNA or a DNA genome (**Figure 9.1**). The virus genome is introduced into a new host cell by infection. The virus redirects the host metabolism to support virus replication.

**Why is it difficult to treat viral disease with drugs?**

- Virus - poison or venom (Latin)
- Acellular entities with genome enclosed in a protein coat (sometimes with membrane)
- Reproduce only within living cells
- Contain RNA or DNA, not both
- Cultured in living host or cell cultures

**History**

- 1000 - Pox vaccine in China
- 1798 - Jenners pox vaccine
- 1892 - Filtration of TMV through Chamberland filter
- 1898 - First filterable animal virus
- 1901 - First human virus (yellow fever)
- 1911 - Virus causing solid tumor (Rous sarcoma)
- 1933 - Human influenza
- 1948 - Culture of animal cells
- 1950s - Polio vaccine

**The origin of viruses**

- **Hypothesis 1**: Originated from small intracellular parasites? Viruses are radically different from procaryotes, no intermediate forms
- **Hypothesis 2**: Viruses are nucleic acids that are partially independent of cells, retrovirus contain sequences similar to that found in cells, plasmids and transposons
  - Probably originated many times during evolution
**Viral habitats**

- Plants, Bacteria, Fungi, Eucaryotic cells, soil, fresh and salt water
- Sea water contains $10^9$ to $10^{12}$ viral particles per liter
- This is mostly bacteriophages important for control of bacterial growth (responsible for 1/3 of bacterial death)
- Important for flow of genes between bacteria in oceans
- Possible increase of ability to degrade toxic pollutants and antibiotic resistance

**Virus cultivation**

- Injection in suitable host
- Innoculation of embryonated eggs
- Innoculation of cultured cells
- Virus can be assembled by transfection of cells with the individual viral genes

**Virus purification**

- Differential centrifugation
- Gradient centrifugation
- Precipitation with ammonium sulfate or polyethylene glycol
- Precipitation of contaminants with organic solvents
- Enzymatic degradation of contaminants

- Viruses are classified by replication strategy as well as by type of host (Table 9.1).
9.2 Nature of the Virion, p. 232

- In the virion of the naked virus, only nucleic acid and protein are present, with the nucleic acid on the inside; the whole unit is called the nucleocapsid (Figure 9.3).

- One or more lipoprotein layers surround the nucleocapsid in enveloped viruses. The nucleocapsid is symmetrical, with a precise number and arrangement of structural subunits surrounding the virus nucleic acid (Figure 9.4).
Viruses can replicate only in certain types of cells or in whole organisms. Bacterial viruses \textit{(bacteriophages)} have proved useful as model systems because the host cells are easy to grow and manipulate in culture. Many animal and plant viruses also can be grown in cultured cells.

9.4 Quantification of Viruses, p. 236

Although it requires only a single virion to initiate an infectious cycle, not all virions are equally infectious. The plaque assay is one of the most accurate ways to measure virus infectivity (Figure 9.6).

Plaques are clear zones that develop on lawns of host cells. Theoretically, each plaque results from infection by a single virus particle. The virus plaque is analogous to the bacterial colony.
• The virus life cycle can be divided into five stages: attachment (adsorption), penetration (injection), protein and nucleic acid synthesis, assembly and packaging, and virion release (Figure 9.8).

• The attachment of a virion to a host cell is a highly specific process involving complementary receptors on the surface of a susceptible host cell and its infecting virus (Figure 9.10).

• Resistance of the host to infection by the virus can involve restriction-modification systems that recognize and destroy foreign double-stranded DNA.
• The Baltimore Classification scheme has seven classifications of viruses (Table 9.2).

• Before replication of viral nucleic acid can occur, messenger RNA molecules transcribed from the virus genome encode new virus proteins.

• In some RNA viruses, the viral RNA itself is the mRNA; in others, the virus genome is a template for the formation of viral mRNA. In certain cases, essential transcriptional enzymes are contained in the virion (Figure 9.11).
• By convention, mRNA is said to be in the plus (+) configuration. Its complement is said to be in the minus (−) configuration. This nomenclature is also used to describe the configuration of the genome of a single-stranded virus, whether its genome contains RNA or DNA.

• For example, a virus that has a single-stranded RNA genome with the same orientation as its mRNA is said to be a positive-strand RNA virus. A virus whose single-stranded RNA genome is complementary to its mRNA is said to be a negative-strand RNA virus.

• Bacterial viruses are very diverse (Figure 9.12). The best-studied bacteriophages infect enteric bacteria such as *Escherichia coli* and are structurally quite complex, containing heads, tails, and other components.

9.9 Virulent Bacteriophages and T4, p. 243

• After a virion of T4 attaches to a host cell and the DNA penetrates the cytoplasm, the expression of viral genes is regulated to redirect the host synthetic machinery to the reproduction of viral nucleic acid and protein. Lysis then assembles and releases new virions from the cell.

• T4 has a double-stranded DNA genome that is circularly permuted and terminally redundant (Figure 9.13).
• The T4 genome can be divided into three parts, encoding early proteins, middle proteins, and late proteins (Figure 9.15).

9.10 Temperate Bacteriophages, p. 245

• Bacteriophage T4 is a virulent virus. Temperate viruses, although also able to kill cells through a lytic cycle, can undergo a different life cycle resulting in a stable genetic relationship with the host.

• These viruses can enter into a state in which most virus genes are not expressed and the virus genome, called a provirus (or prophage), is replicated in synchrony with the host chromosome. This is the lysogenic pathway.

• Host cells can harbor viral genomes without harm if the expression of the viral genes can be controlled. This is the situation found in lysogens.
• If this control is lost, however, the virus enters the **lytic pathway** and produces new virions, eventually lysing the host cell. **Figure 9.16** shows an overall view of the life cycle of a temperate bacteriophage.

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**9.11 Bacteriophage Lambda, p. 246**

• Lambda is a double-stranded DNA temperate phage. Regulation of lytic versus lysogenic events in lambda is controlled by several promoters and regulatory proteins.

• The cl protein (the lambda repressor) causes repression of lambda lytic events; the Cro protein controls activation of lytic events. Although the genome of lambda is linear, it circularizes inside the cell, where DNA synthesis occurs by a rolling circle mechanism (**Figure 9.18**).
• Many animal viruses are enveloped, picking up portions of the host cytoplasmic membrane as they leave the cell.

• Not all infections of animal host cells result in cell lysis or death; latent or persistent infections are common, and some animal viruses can cause cancer (Figure 9.24).
9.13 Retroviruses, p. 251

- **Retroviruses** are RNA viruses that replicate through a DNA intermediate (Figure 9.25). The retrovirus called human immunodeficiency virus (HIV) causes AIDS.

- The retrovirus virion contains an enzyme, reverse transcriptase, that copies the information from its RNA genome into DNA, a process called reverse transcription (Figure 9.26).

- The DNA becomes integrated into the host chromosome in the same way as it does in a temperate virus. The retrovirus DNA can be transcribed to yield mRNA (and new genomic RNA), or it may remain in a latent state.
Amantadine

- Mechanisms of Action
  - Inhibits uncoating of viral RNA
  - May also block viral assembly
- Used to prevent spread of influenza A2
- Adverse reactions
  - Dizziness, nervousness, confusion, hallucinations, hypotension
  - CNS: releases dopamine, dopamine agonist

Zanamivir

- Neuraminidase inhibitor
- Inhibits replication of influenza A and B
- Early use reduces severity and duration of influenza symptoms

Replication of HSV

Replication of Herpesvirus

Influenza can be treated with neuraminidase inhibitors
Acyclovir

- **Mechanism:**
  - Activated by viral thymidine kinase
  - AcycloGTP inhibits viral DNA polymerase

- **Uses:**
  - Herpes simplex
  - Varicella-Zoster

- **Adverse Reactions:**
  - IV: local irritation, phlebitis, nephrotoxicity
  - Oral: headache, vertigo, diarrhea, nausea, vomiting, arthralgia
Replication of Herpesvirus

Ribavirin

- **Mechanism:**
  - Metabolized to a monophosphate which inhibits synthesis of guanine nucleotides - RNA and DNA synthesis is inhibited
- **Broad spectrum:**
  - Respiratory syncytial virus, influenza
  - Hepatitis C, Myxovirus, paromyxovirus, adenovirus, herpes virus, poxviruses,