33

Viruses

Concept Outline

33.1 Viruses are strands of nucleic acid encased within a protein coat.

The Discovery of Viruses. The first virus to be isolated proved to consist of two chemicals, one a protein and the other a nucleic acid.

The Nature of Viruses. Viruses occur in all organisms. Able to reproduce only within living cells, viruses are not themselves alive.

33.2 Bacterial viruses exhibit two sorts of reproductive cycles.

Bacteriophages. Some bacterial viruses, called bacteriophages, rupture the cells they infect, while others integrate themselves into the bacterial chromosome to become a stable part of the bacterial genome.

Cell Transformation and Phage Conversion. Integrated bacteriophages sometimes modify the host bacterium they infect.

33.3 HIV is a complex animal virus.

AIDS. The animal virus HIV infects certain key cells of the immune system, destroying the ability of the body to defend itself from cancer and disease. The HIV infection cycle is typically a lytic cycle, in which the HIV RNA first directs the production of a corresponding DNA, and this DNA then directs the production of progeny virus particles.

The Future of HIV Treatment. Combination therapies and chemokines offer promising avenues of AIDS therapy.

33.4 Nonliving infectious agents are responsible for many human diseases.

Disease Viruses. Some of the most serious viral diseases have only recently infected human populations, the result of transfer from other hosts.

Prions and Viroids. In some instances, proteins and "naked" RNA molecules can also transmit diseases.

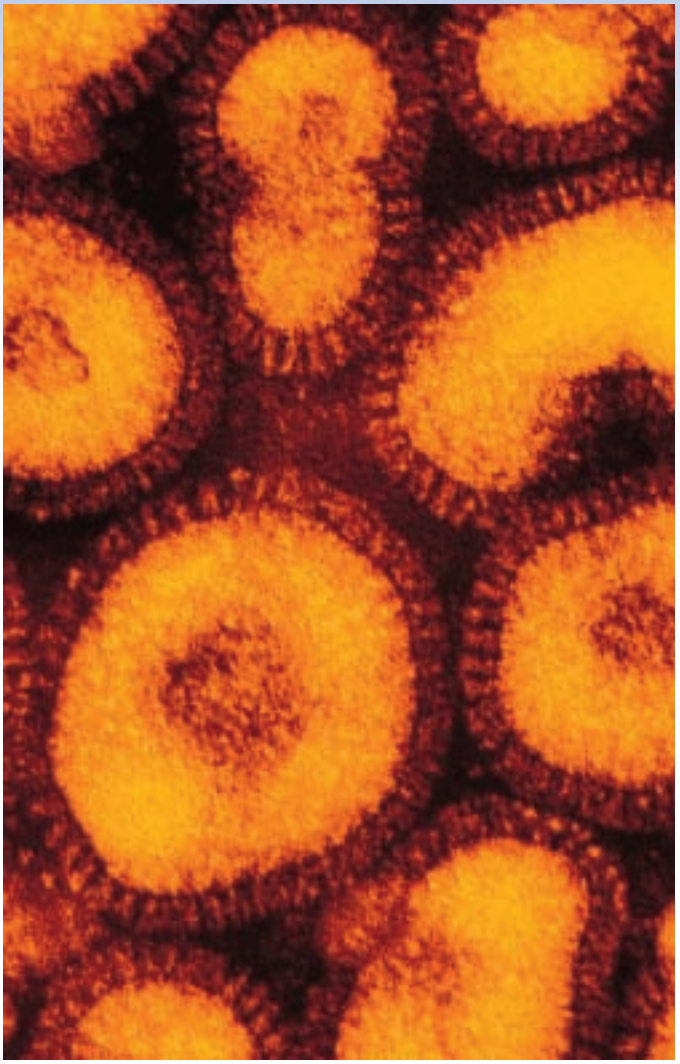


FIGURE 33.1
Influenza viruses. A virus has been referred to as "a piece of bad news wrapped up in a protein." How can something as "simple" as a virus have such a profound effect on living organisms? (30,000×)

We start our exploration of the diversity of life with viruses. Viruses are genetic elements enclosed in protein and are not considered to be organisms, as they cannot reproduce independently. Because of their disease-producing potential, viruses are important biological entities. The virus particles you see in figure 33.1 produce the important disease influenza. Other viruses cause AIDS, polio, flu, and some can lead to cancer. Many scientists have attempted to unravel the nature of viral genes and how they work. For more than four decades, viral studies have been thoroughly intertwined with those of genetics and molecular biology. In the future, it is expected that viruses will be one of the principal tools used to experimentally carry genes from one organism to another. Already, viruses are being employed in the treatment of human genetic diseases.

33.1 Viruses are strands of nucleic acid encased within a protein coat.

The Discovery of Viruses

The border between the living and the nonliving is very clear to a biologist. Living organisms are cellular and able to grow and reproduce independently, guided by information encoded within DNA. The simplest creatures living on earth today that satisfy these criteria are bacteria. Even simpler than bacteria are viruses. As you will learn in this section, viruses are so simple that they do not satisfy the criteria for "living."

Viruses possess only a portion of the properties of organisms. Viruses are literally "parasitic" chemicals, segments of DNA or RNA wrapped in a protein coat. They cannot reproduce on their own, and for this reason they are not considered alive by biologists. They can, however, reproduce within cells, often with disastrous results to the host organism. Earlier theories that viruses represent a kind of halfway point between life and nonlife have largely been abandoned. Instead, viruses are now viewed as detached fragments of the genomes of organisms due to the high degree of similarity found among some viral and eukaryotic genes.

Viruses vary greatly in appearance and size. The smallest are only about 17 nanometers in diameter, and the largest are up to 1000 nanometers (1 micrometer) in their greatest dimension (figure 33.2). The largest viruses are barely visible with a light microscope, but viral morphology is best revealed using the electron microscope. Viruses are so small that they are comparable to molecules in size; a hydrogen atom is about 0.1 nanometer in diameter, and a large protein molecule is several hundred nanometers in its greatest dimension.

Biologists first began to suspect the existence of viruses near the end of the nineteenth century. European scientists attempting to isolate the infectious agent responsible for hoof-and-mouth disease in cattle concluded that it was smaller than a bacterium. Investigating the agent further, the scientists found that it could not multiply in solution—it could only reproduce itself within living host cells that it infected. The infecting agents were called viruses.

The true nature of viruses was discovered in 1933, when the biologist Wendell Stanley prepared an extract of a plant virus called *tobacco mosaic virus* (TMV) and attempted to purify it. To his great surprise, the purified TMV preparation precipitated (that is, separated from solution) in the form of crystals. This was surprising because precipitation is something that only chemicals do—the TMV virus was acting like a chemical off the shelf rather than an organism. Stanley concluded that TMV is best regarded as just that—chemical matter rather than a living organism.

Within a few years, scientists disassembled the TMV virus and found that Stanley was right. TMV was not cellular but rather chemical. Each particle of TMV virus is in fact a mixture of two chemicals: RNA and protein. The TMV virus has the structure of a Twinkie, a tube made of an RNA core surrounded by a coat of protein. Later workers were able to separate the RNA from the protein and purify and store each chemical. Then, when they reassembled the two components, the reconstructed TMV particles were fully able to infect healthy tobacco plants and so clearly *were* the virus itself, not merely chemicals derived from it. Further experiments carried out on other viruses yielded similar results.

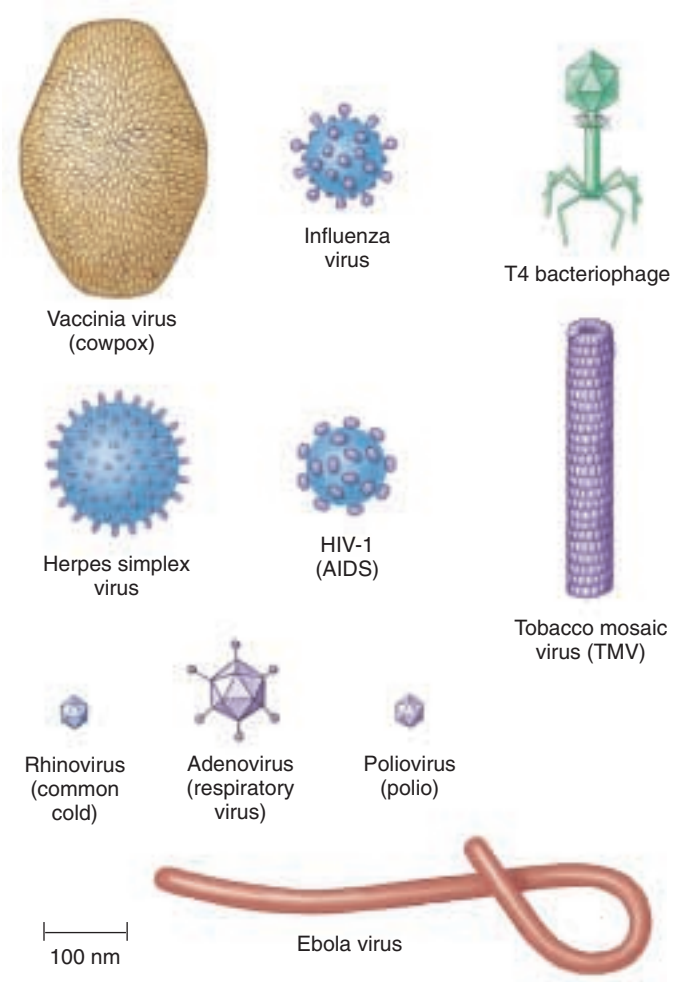


FIGURE 33.2
Viral diversity. A sample of the extensive diversity and small size viruses is depicted. At the scale these viruses are shown, a human hair would be nearly 8 meters thick.

Viruses are chemical assemblies that can infect cells and replicate within them. They are not alive.

The Nature of Viruses

Viral Structure

All viruses have the same basic structure: a core of nucleic acid surrounded by protein. Individual viruses contain only a single type of nucleic acid, either DNA or RNA. The DNA or RNA genome may be linear or circular, and single-stranded or double-stranded. Viruses are frequently classified by the nature of their genomes. RNA-based viruses are known as **retroviruses.**

Nearly all viruses form a protein sheath, or **capsid,** around their nucleic acid core. The capsid is composed of one to a few different protein molecules repeated many times (figure 33.3) In some viruses, specialized enzymes are stored within the capsid. Many animal viruses form an **envelope** around the capsid rich in proteins, lipids, and glycoprotein molecules. While some of the material of the envelope is derived from the host cell's membrane, the envelope does contain proteins derived from viral genes as well.

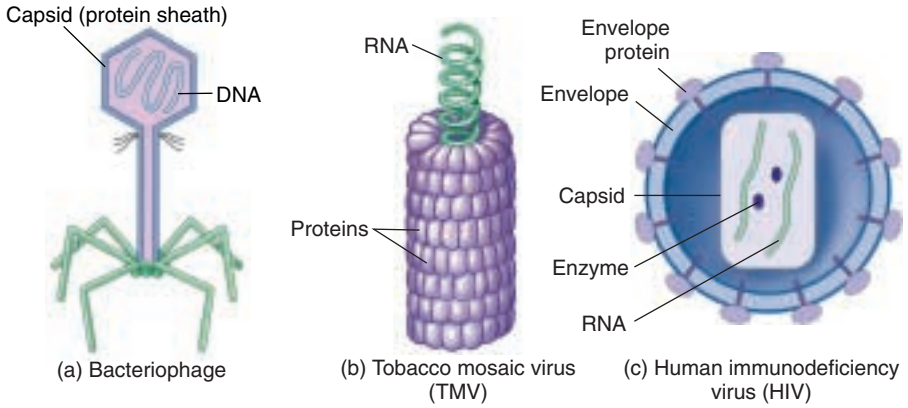


FIGURE 33.3
The structure of a bacterial, plant, and animal virus. (*a*) Bacterial viruses, called bacteriophages, often have a complex structure. (*b*) TMV infects plants and consists of 2130 identical protein molecules (*purple*) that form a cylindrical coat around the single strand of RNA (*green*). The RNA backbone determines the shape of the virus and is protected by the identical protein molecules packed tightly around it. (*c*) In the human immunodeficiency virus (HIV), the RNA core is held within a capsid that is encased by a protein envelope.

Viruses occur in virtually every kind of organism that has been investigated for their presence. However, each type of virus can replicate in only a very limited number of cell types. The suitable cells for a particular virus are collectively referred to as its **host range.** The size of the host range reflects the coevolved histories of the virus and its potential hosts. A recently discovered herpesvirus turned lethal when it expanded its host range from the African elephant to the Indian elephant, a situation made possible through cross-species contacts between elephants in zoos. Some viruses wreak havoc on the cells they infect; many others produce no disease or other outward sign of their infection. Still other viruses remain dormant for years until a specific signal triggers their expression. A given organism often has more than one kind of virus. This suggests that there may be many more kinds of viruses than there are kinds of organisms—perhaps millions of them. Only a few thousand viruses have been described at this point.

Viral Replication

An infecting virus can be thought of as a set of instructions, not unlike a computer program. A computer's operation is directed by the instructions in its operating program, just as a cell is directed by DNA-encoded instructions. A new program can be introduced into the computer that will cause the computer to cease what it is doing and devote all of its energies to another activity, such as making copies of the introduced program. The new program is not itself a computer and cannot make copies of itself when it is outside the computer, lying on the desk. The introduced program, like a virus, is simply a set of instructions.

Viruses can reproduce only when they enter cells and utilize the cellular machinery of their hosts. Viruses code their genes on a single type of nucleic acid, either DNA or RNA, but viruses lack ribosomes and the enzymes necessary for protein synthesis. Viruses are able to reproduce because their genes are translated into proteins by the cell's genetic machinery. These proteins lead to the production of more viruses.

Viral Shape

Most viruses have an overall structure that is either **helical** or **isometric.** Helical viruses, such as the tobacco mosaic virus, have a rodlike or threadlike appearance. Isometric viruses have a roughly spherical shape whose geometry is revealed only under the highest magnification.

The only structural pattern found so far among isometric viruses is the **icosahedron,** a structure with 20 equilateral triangular facets, like the adenovirus shown in figure 33.2. Most viruses are icosahedral in basic structure. The icosahedron is the basic design of the geodesic dome. It is the most efficient symmetrical arrangement that linear subunits can take to form a shell with maximum internal capacity.

Viruses occur in all organisms and can only reproduce within living cells. Most are icosahedral in structure.

33.2 Bacterial viruses exhibit two sorts of reproductive cycles.

Bacteriophages

Bacteriophages are viruses that infect bacteria. They are diverse both structurally and functionally, and are united solely by their occurrence in bacterial hosts. Many of these bacteriophages, called *phages* for short, are large and complex, with relatively large amounts of DNA and proteins. Some of them have been named as members of a "T" series (T1, T2, and so forth); others have been given different kinds of names. To illustrate the diversity of these viruses, T3 and T7 phages are icosahedral and have short tails. In contrast, the so-called T-even phages (T2, T4, and T6) have an icosahedral head, a capsid that consists primarily of three proteins, a connecting neck with a collar and long "whiskers," a long tail, and a complex base plate (figure 33.4).

The Lytic Cycle

During the process of bacterial infection by T4 phage, at least one of the tail fibers of the phage—they are normally held near the phage head by the "whiskers"—contacts the lipoproteins of the host bacterial cell wall. The other tail fibers set the phage perpendicular to the surface of the bacterium and bring the base plate into contact with the cell surface. The tail contracts, and the tail tube passes through an opening that appears in the base plate, piercing the bacterial cell wall. The contents of the head, mostly DNA, are then injected into the host cytoplasm.

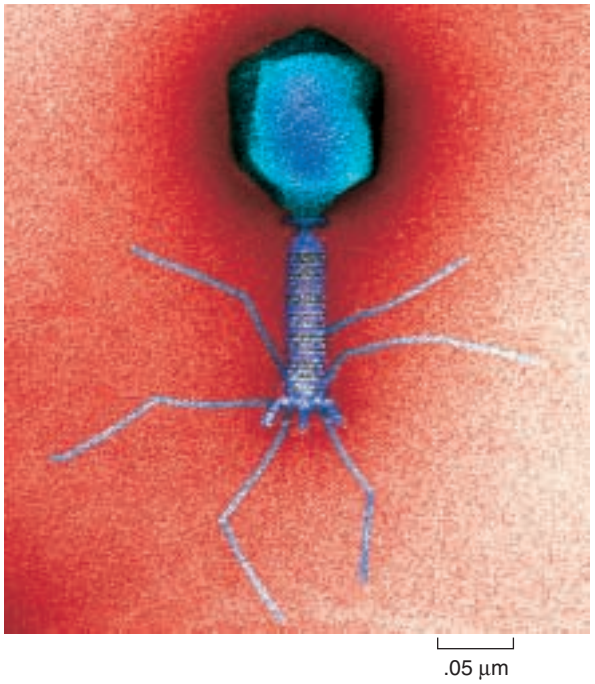
When a virus kills the infected host cell in which it is replicating, the reproductive cycle is referred to as a **lytic cycle** (figure 33.5). The T-series bacteriophages are all **virulent viruses,** multiplying within infected cells and eventually lysing (rupturing) them. However, they vary considerably as to when they become virulent within their host cells.

The Lysogenic Cycle

Many bacteriophages do not immediately kill the cells they infect, instead integrating their nucleic acid into the genome of the infected host cell. While residing there, it is called a **prophage.** Among the bacteriophages that do this is the lambda (λ) phage of *Escherichia coli.* We know as much about this bacteriophage as we do about virtually any other biological particle; the complete sequence of its 48,502 bases has been determined. At least 23 proteins are associated with the development and maturation of lambda phage, and many other enzymes are involved in the integration of these viruses into the host genome.

The integration of a virus into a cellular genome is called **lysogeny.** At a later time, the prophage may exit the genome and initiate virus replication. This sort of reproductive cycle, involving a period of genome integration, is called a **lysogenic cycle.** Viruses that become stably integrated within the genome of their host cells are called **lysogenic viruses** or **temperate viruses.**

Bacteriophages are a diverse group of viruses that attack bacteria. Some kill their host in a lytic cycle; others integrate into the host's genome, initiating a lysogenic cycle.



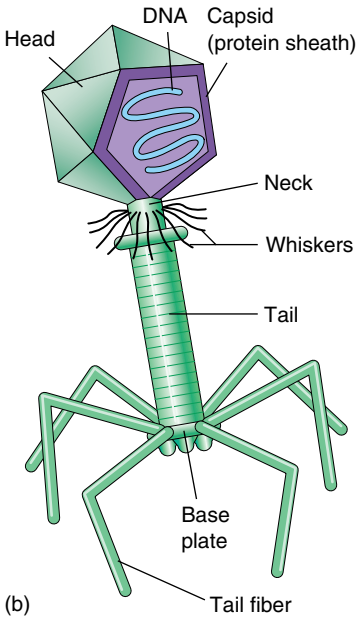


FIGURE 33.4
A bacterial virus. Bacteriophages exhibit a complex structure. (*a*) Electron micrograph and (*b*) diagram of the structure of a T4 bacteriophage.

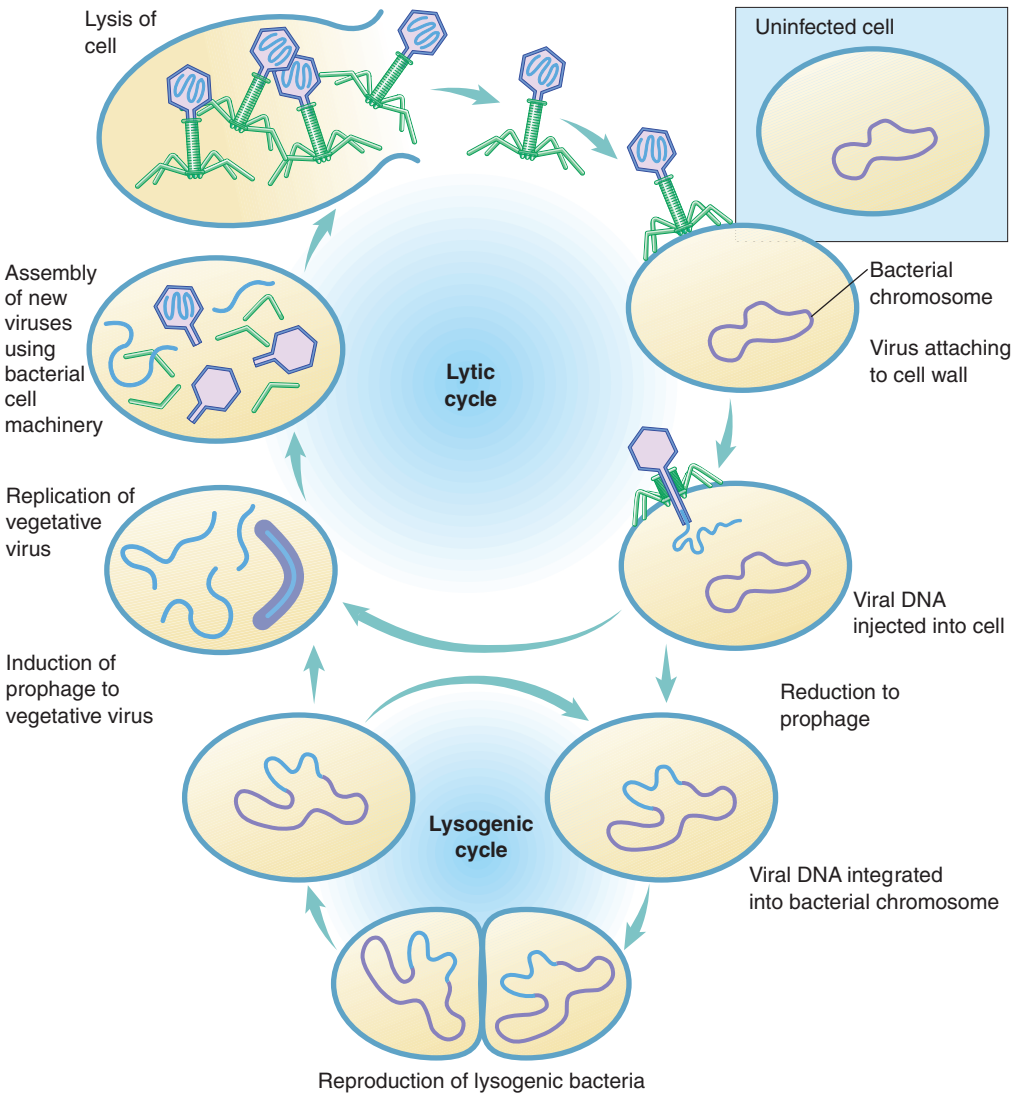


FIGURE 33.5
Lytic and lysogenic cycles of a bacteriophage. In the lytic cycle, the bacteriophage exists as viral DNA free in the bacterial host cell's cytoplasm; the viral DNA directs the production of new viral particles by the host cell until the virus kills the cell by lysis. In the lysogenic cycle, the bacteriophage DNA is integrated into the large, circular DNA molecule of the host bacterium and is reproduced along with the host DNA as the bacterium replicates. It may continue to replicate and produce lysogenic bacteria or enter the lytic cycle and kill the cell. Bacteriophages are much smaller relative to their hosts than illustrated in this diagram.

Cell Transformation and Phage Conversion

During the integrated portion of a lysogenic reproductive cycle, virus genes are often expressed. The RNA polymerase of the host cell reads the viral genes just as if they were host genes. Sometimes, expression of these genes has an important effect on the host cell, altering it in novel ways. The genetic alteration of a cell's genome by the introduction of foreign DNA is called **transformation.** When the foreign DNA is contributed by a bacterial virus, the alteration is called phage conversion.

Phage Conversion of the Cholera-Causing Bacterium

An important example of this sort of phage conversion directed by viral genes is provided by the bacterium responsible for an often-fatal human disease. The disease-causing bacteria *Vibrio cholerae* usually exists in a harmless form, but a second disease-causing, virulent form also occurs. In this latter form, the bacterium causes the deadly disease cholera, but how the bacteria changed from harmless to deadly was not known until recently. Research now shows that a bacteriophage that infects *V. cholerae* introduces into the host bacterial cell a gene that codes for the cholera toxin. This gene becomes incorporated into the bacterial chromosome, where it is translated along with the other host genes, thereby converting the benign bacterium to a disease-causing agent. The transfer occurs through bacterial pili (see chapter 34); in further experiments, mutant bacteria that did not have pili were resistant to infection by the bacteriophage. This discovery has important implications in efforts to develop vaccines against cholera, which have been unsuccessful up to this point.

Bacteriophages convert *Vibrio cholerae* bacteria from harmless gut residents into disease-causing agents.

33.3 HIV is a complex animal virus.

AIDS

A diverse array of viruses occur among animals. A good way to gain a general idea of what they are like is to look at one animal virus in detail. Here we will look at the virus responsible for a comparatively new and fatal viral disease, acquired immunodeficiency syndrome (AIDS). AIDS was first reported in the United States in 1981. It was not long before the infectious agent, a retrovirus called human immunodeficiency virus (HIV), was identified by laboratories in France and the United States. Study of HIV revealed it to be closely related to a chimpanzee virus, suggesting a recent host expansion to humans in central Africa from chimpanzees.

Infected humans have little resistance to infection, and nearly all of them eventually die of diseases that noninfected individuals easily ward off. Few who contract AIDS survive more than a few years untreated. The risk of HIV transmission from an infected individual to a healthy one in the course of day-to-day contact is essentially nonexistent. However, the transfer of body fluids, such as blood, semen, or vaginal fluid, or the use of nonsterile needles, between infected and healthy individuals poses a severe risk. In addition, HIV-infected mothers can pass the virus on to their unborn children during fetal development.

The incidence of AIDS is growing very rapidly in the United States. It is estimated that over 33 million people worldwide are infected with HIV. Many—perhaps all of them—will eventually come down with AIDS. Over 16 million people have died already since the outbreak of the epidemic. AIDS incidence is already very high in many African countries and is growing at 20% worldwide. The AIDS epidemic is discussed further in chapter 57.

How HIV Compromises the Immune System

In normal individuals, an army of specialized cells patrols the bloodstream, attacking and destroying any invading bacteria or viruses. In AIDS patients, this army of defenders is vanquished. One special kind of white blood cell, called a $CD4^+$ T cell (discussed further in chapter 57) is required to rouse the defending cells to action. In AIDS patients, the virus homes in on $CD4^+$ T cells, infecting and killing them until none are left (figure 33.6). Without these crucial immune system cells, the body cannot mount a defense against invading bacteria or viruses. AIDS patients die of infections that a healthy person could fight off.

Clinical symptoms typically do not begin to develop until after a long latency period, generally 8 to 10 years after the initial infection with HIV. During this long interval, carriers of HIV have no clinical symptoms but are apparently fully infectious, which makes the spread of HIV very difficult to control. The reason why HIV remains hidden for so long seems to be that its infection cycle continues throughout the 8- to 10-year latent period without doing serious harm to the infected person. Eventually, however, a random mutational event in the virus allows it to quickly overcome the immune defense, starting AIDS.

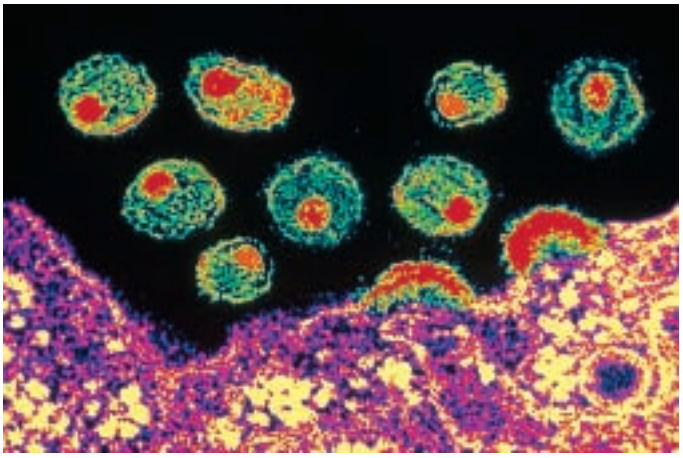


FIGURE 33.6
The AIDS virus. HIV particles exit an infected $CD4^+$ T cell (both shown in false color). The free virus particles are able to infect neighboring $CD4^+$ T cells.

The HIV Infection Cycle

The HIV virus infects and eliminates key cells of the immune system, destroying the body's ability to defend itself from cancer and infection. The way HIV infects humans (figure 33.7) provides a good example of how animal viruses replicate. Most other viral infections follow a similar course, although the details of entry and replication differ in individual cases.

Attachment. When HIV is introduced into the human bloodstream, the virus particle circulates throughout the entire body but will only infect $CD4^+$ cells. Most other animal viruses are similarly narrow in their requirements; hepatitis goes only to the liver, and rabies to the brain.

How does a virus such as HIV recognize a specific kind of target cell? Recall from chapter 7 that every kind of cell in the human body has a specific array of cell-surface glycoprotein markers that serve to identify them to other, similar cells. Each HIV particle possesses a glycoprotein (called **gp120**) on its surface that precisely fits a cell-surface marker protein called **CD4** on the surfaces of immune system cells called macrophages and T cells. Macrophages are infected first.

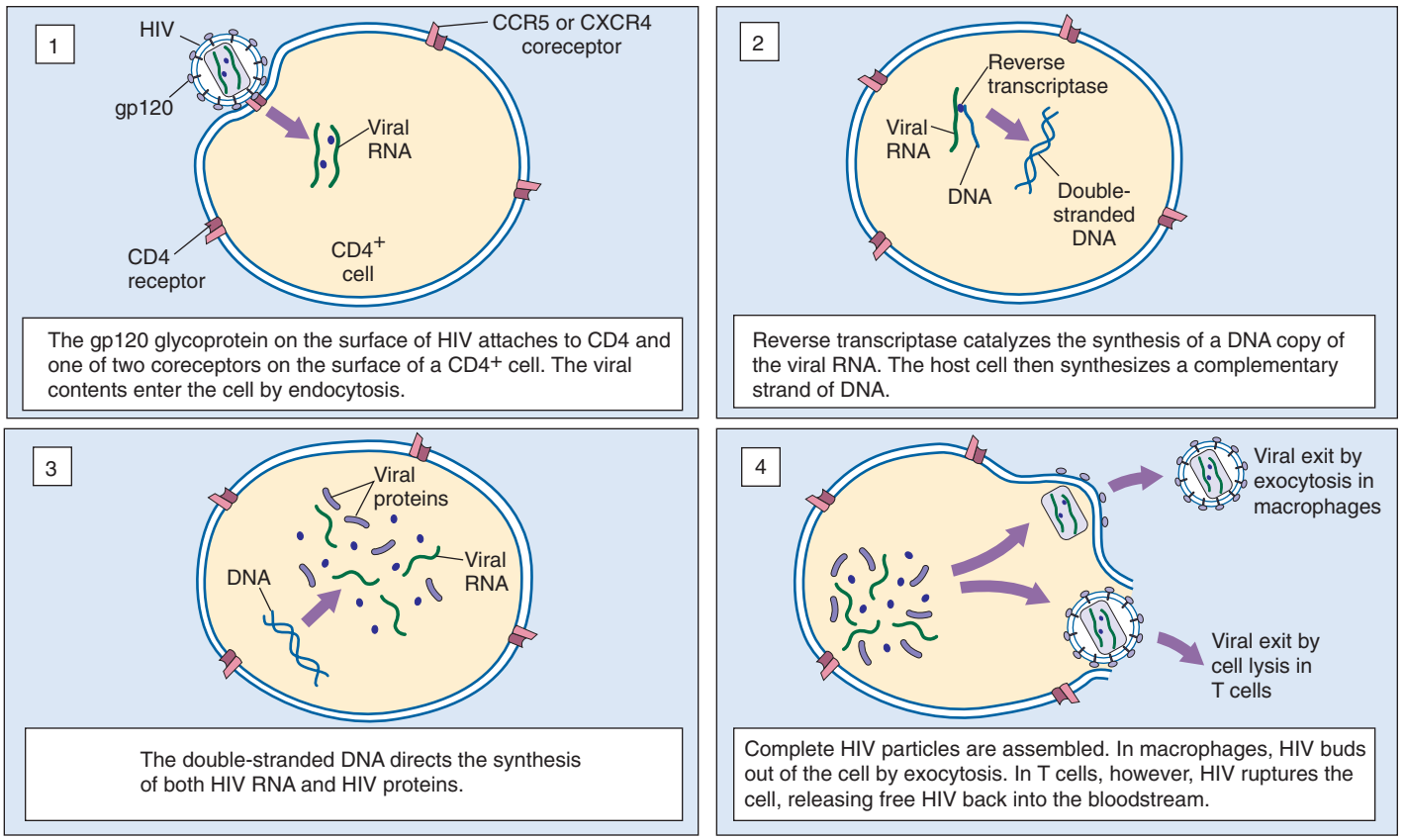


FIGURE 33.7
The HIV infection cycle. The cycle begins and ends with free HIV particles present in the bloodstream of its human host. These free viruses infect white blood cells called $CD4^+$ T cells.

Entry into Macrophages. After docking onto the CD4 receptor of a macrophage, HIV requires a second macrophage receptor, called CCR5, to pull itself across the cell membrane. After gp120 binds to CD4, it goes through a conformational change that allows it to bind to CCR5. The current model suggests that after the conformational change, the second receptor passes the gp120-CD4 complex through the cell membrane, triggering passage of the contents of the HIV virus into the cell by endocytosis, with the cell membrane folding inward to form a deep cavity around the virus.

Replication. Once inside the macrophage, the HIV particle sheds its protective coat. This leaves virus RNA floating in the cytoplasm, along with a virus enzyme that was also within the virus shell. This enzyme, called **reverse transcriptase,** synthesizes a double strand of DNA complementary to the virus RNA, often making mistakes and so introducing new mutations. This double-stranded DNA directs the host cell machinery to produce many copies of the virus. HIV does not rupture and kill the macrophage cells it infects. Instead, the new viruses are released from the cell by exocytosis. HIV synthesizes large numbers of viruses in this way, challenging the immune system over a period of years.

Entry into T Cells. During this time, HIV is constantly replicating and mutating. Eventually, by chance, HIV alters the gene for gp120 in a way that causes the gp120 protein to change its second-receptor allegiance. This new form of gp120 protein prefers to bind instead to a different second receptor, CXCR4, a receptor that occurs on the surface of T lymphocyte $CD4^+$ cells. Soon the body's T lymphocytes become infected with HIV. This has deadly consequences, as new viruses exit the cell by rupturing the cell membrane, effectively killing the infected T cell. Thus, the shift to the CXCR4 second receptor is followed swiftly by a steep drop in the number of T cells. This destruction of the body's T cells blocks the immune response and leads directly to the onset of AIDS, with cancers and opportunistic infections free to invade the defenseless body.

HIV, the virus that causes AIDS, is an RNA virus that replicates inside human cells by first making a DNA copy of itself. It is only able to gain entrance to those cells possessing a particular cell surface marker recognized by a glycoprotein on its own surface.

The Future of HIV Treatment

New discoveries of how HIV works continue to fuel research on devising ways to counter HIV. For example, scientists are testing drugs and vaccines that act on HIV receptors, researching the possibility of blocking CCR5, and looking for defects in the structures of HIV receptors in individuals that are infected with HIV but have not developed AIDS. Figure 33.8 summarizes some of the recent developments and discoveries.

Combination Drug Therapy

A variety of drugs inhibit HIV in the test tube. These include AZT and its analogs (which inhibit virus nucleic acid replication) and protease inhibitors (which inhibit the cleavage of the large polyproteins encoded by *gag*, *poll*, and *env* genes into functional capsid, enzyme, and envelope segments). When combinations of these drugs were administered to people with HIV in controlled studies, their condition improved. A combination of a protease inhibitor and two AZT analog drugs entirely eliminated the HIV virus from many of the patients' bloodstreams. Importantly, all of these patients began to receive the drug therapy within three months of contracting the virus, before their bodies had an opportunity to develop tolerance to any one of them. Widespread use of this **combination therapy** has cut the U.S. AIDS death rate by three-fourths since its introduction in the mid-1990s, from 49,000 AIDS deaths in 1995 to 36,000 in 1996, and just over 10,000 in 1999.

Unfortunately, this sort of combination therapy does not appear to actually succeed in eliminating HIV from the body. While the virus disappears from the bloodstream, traces of it can still be detected in lymph tissue of the patients. When combination therapy is discontinued, virus levels in the bloodstream once again rise. Because of demanding therapy schedules and many side effects, long-term combination therapy does not seem a promising approach.

Using a Defective HIV Gene to Combat AIDS

Recently, five people in Australia who are HIV-positive but have not developed AIDS in 14 years were found to have all received a blood transfusion from the same HIV-positive person, who also has not developed AIDS. This led scientists to believe that the strain of virus transmitted to these people has some sort of genetic defect that prevents it from effectively disabling the human immune system. In subsequent research, a defect was found in one of the nine genes present in this strain of HIV. This gene is called ***nef***, named for "negative factor," and the defective version of *nef* in the HIV strain that infected the six Australians seems to be missing some pieces. Viruses with the defective gene may have reduced reproductive capability, allowing the immune system to keep the virus in check.

This finding has exciting implications for developing a vaccine against AIDS. Before this, scientists have been unsuccessful in trying to produce a harmless strain of AIDS that can elicit an effective immune response. The Australian strain with the defective *nef* gene has the potential to be used in a vaccine that would arm the immune system against this and other strains of HIV.

Another potential application of this discovery is its use in developing drugs that inhibit HIV proteins that speed virus replication. It seems that the protein produced from the *nef* gene is one of these critical HIV proteins, because viruses with defective forms of *nef* do not reproduce, as seen in the cases of the six Australians. Research is currently underway to develop a drug that targets the *nef* protein.

Chemokines and CAF

In the laboratory, chemicals called **chemokines** appear to inhibit HIV infection by binding to and blocking the CCR5 and CXCR4 coreceptors. As you might expect, people long infected with the HIV virus who have not developed AIDS prove to have high levels of chemokines in their blood.

The search for HIV-inhibiting chemokines is intense. Not all results are promising. Researchers report that in their tests, the levels of chemokines were not different between patients in which the disease was not progressing and those in which it was rapidly progressing. More promising, levels of another factor called **CAF** ($CD8^+$ cell antiviral factor) *are* different between these two groups. Researchers have not yet succeeded in isolating CAF, which seems not to block receptors that HIV uses to gain entry to cells, but, instead, to prevent replication of the virus once it has infected the cells. Research continues on the use of chemokines in treatments for HIV infection, either increasing the amount of chemokines or disabling the CCR5 receptor. However, promising research on CAF suggests that it may be an even better target for treatment and prevention of AIDS.

One problem with using chemokines as drugs is that they are also involved in the inflammatory response of the immune system. The function of chemokines is to attract white blood cells to areas of infection. Chemokines work beautifully in small amounts and in local areas, but chemokines in mass numbers can cause an inflammatory response that is worse than the original infection. Injections of chemokines may hinder the immune system's ability to respond to local chemokines, or they may even trigger an out-of-control inflammatory response. Thus, scientists caution that injection of chemokines could make patients *more* susceptible to infections, and they continue to research other methods of using chemokines to treat AIDS.

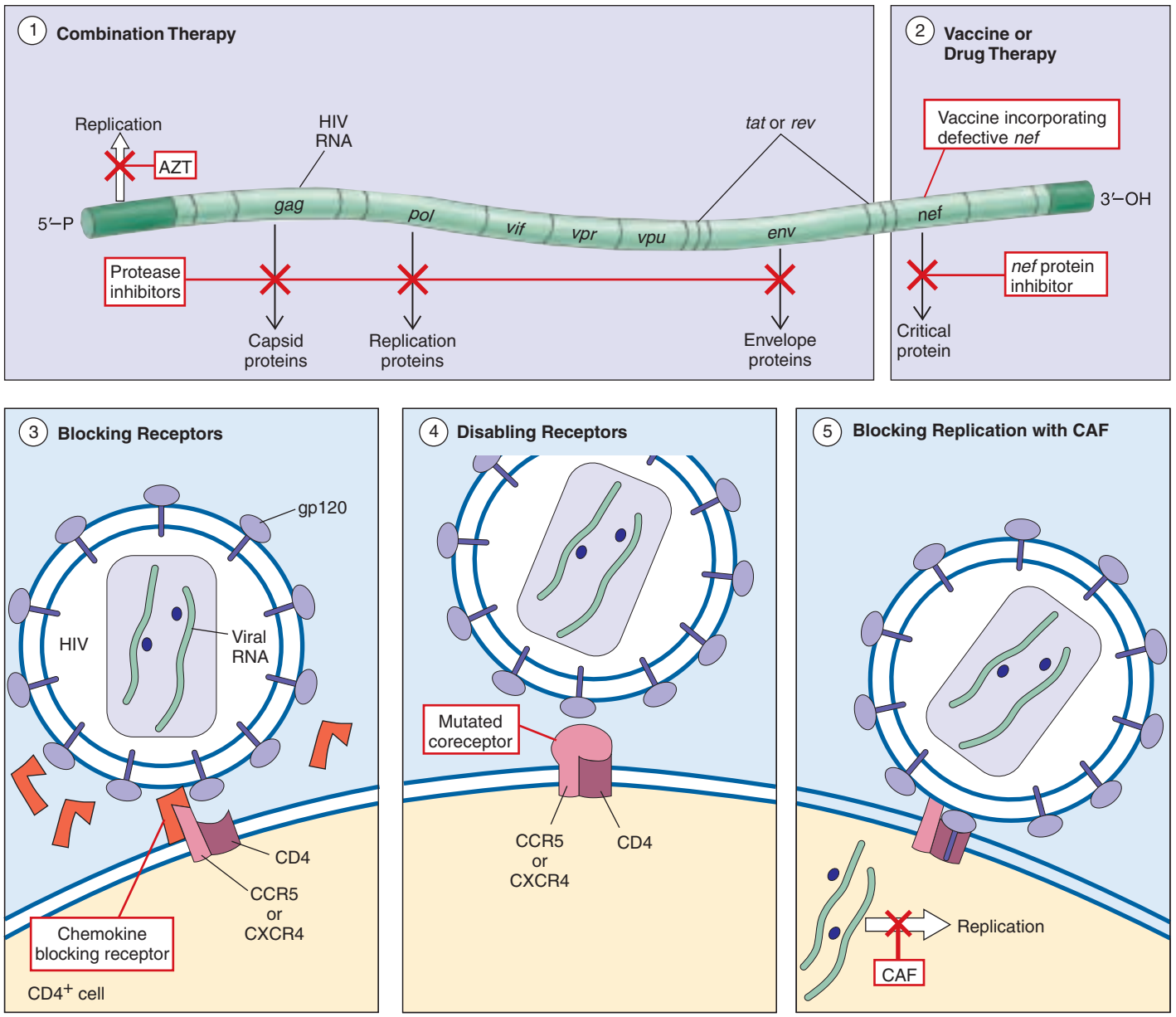


FIGURE 33.8
Research is currently underway to develop new treatments for HIV. Among them are these five: (*1*) *Combination therapy* involves using two drugs, AZT to block replication of the virus and protease inhibitors to block the production of critical viral proteins. (*2*) Using a defective form of the viral gene *nef*, scientists may be able to construct an HIV *vaccine*. Also, *drug therapy* that inhibits *nef's* protein product is being tested. (*3*) Other research focuses on the use of chemokine chemicals to *block receptors* (CXCR4 and CCR5), thereby disabling the mechanism HIV uses to enter $CD4^+$ T cells. (*4*) Producing mutations that will *disable receptors* may also be possible. (*5*) Lastly, CAF, an antiviral factor which acts inside the $CD4^+$ T cell, may be able to *block replication* of HIV.

Disabling Receptors

A 32-base-pair deletion in the gene that codes for the CCR5 receptor appears to block HIV infection. Individuals at high risk of HIV infection who are homozygous for this mutation do not seem to develop AIDS. In one study of 1955 people, scientists found no individuals who were infected and homozygous for the mutated allele. The allele seems to be more common in Caucasian populations (10 to 11%) than in African-American populations (2%), and absent in African and Asian populations. Treatment for AIDS involving disruption of CCR5 looks promising, as research indicates that people live perfectly well without CCR5. Attempts to block or disable CCR5 are being sought in numerous laboratories.

A cure for AIDS is not yet in hand, but many new approaches look promising.

33.4 Nonliving infectious agents are responsible for many human diseases.

Disease Viruses

Humans have known and feared diseases caused by viruses for thousands of years. Among the diseases that viruses cause (table 33.1) are influenza, smallpox, infectious hepatitis, yellow fever, polio, rabies, and AIDS, as well as many other diseases not as well known. In addition, viruses have been implicated in some cancers and leukemias. For many autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, and for diabetes, specific viruses have been found associated with certain cases. In view of their effects, it is easy to see why the late Sir Peter Medawar, Nobel laureate in Physiology or Medicine, wrote, "A virus is a piece of bad news wrapped in protein." Viruses not only cause many human diseases, but also cause major losses in agriculture, forestry, and in the productivity of natural ecosystems.

Influenza

Perhaps the most lethal virus in human history has been the influenza virus. Some 22 million Americans and Europeans died of flu within 18 months in 1918 and 1919, an astonishing number.

Types. Flu viruses are animal retroviruses. An individual flu virus resembles a rod studded with spikes composed of two kinds of protein (figure 33.9). There are three general "types" of flu virus, distinguished by their capsid (inner membrane) protein, which is different for each type: Type A flu virus causes most of the serious flu epidemics in humans, and also occurs in mammals and birds. Type B and Type C viruses, with narrower host ranges, are restricted to humans and rarely cause serious health problems.

Subtypes. Different strains of flu virus, called subtypes, differ in their protein spikes. One of these proteins, hemagglutinin (H) aids the virus in gaining access to the cell interior. The other, neuraminidase (N) helps the daughter virus break free of the host cell once virus replication has been completed. Parts of the H molecule contain "hot spots" that display an unusual tendency to change as a result of mutation of the virus RNA during imprecise replication. Point mutations cause changes in these spike proteins in 1 of 100,000 viruses during the course of each generation. These highly variable segments of the H molecule are targets against which the body's antibodies are directed. The high variability of these targets improves the reproductive capacity of the virus and hinders our ability to make perfect vaccines. Because of accumulating changes in the H and N molecules, different flu vaccines are required to protect against different subtypes. Type A flu viruses are currently classified into 13 distinct H subtypes and 9 distinct N subtypes, each of which requires a different vaccine to protect against infection. Thus, the type A virus that caused the Hong Kong flu epidemic of 1968 has type 3 H molecules and type 2 N molecules, and is called A(H3N2).

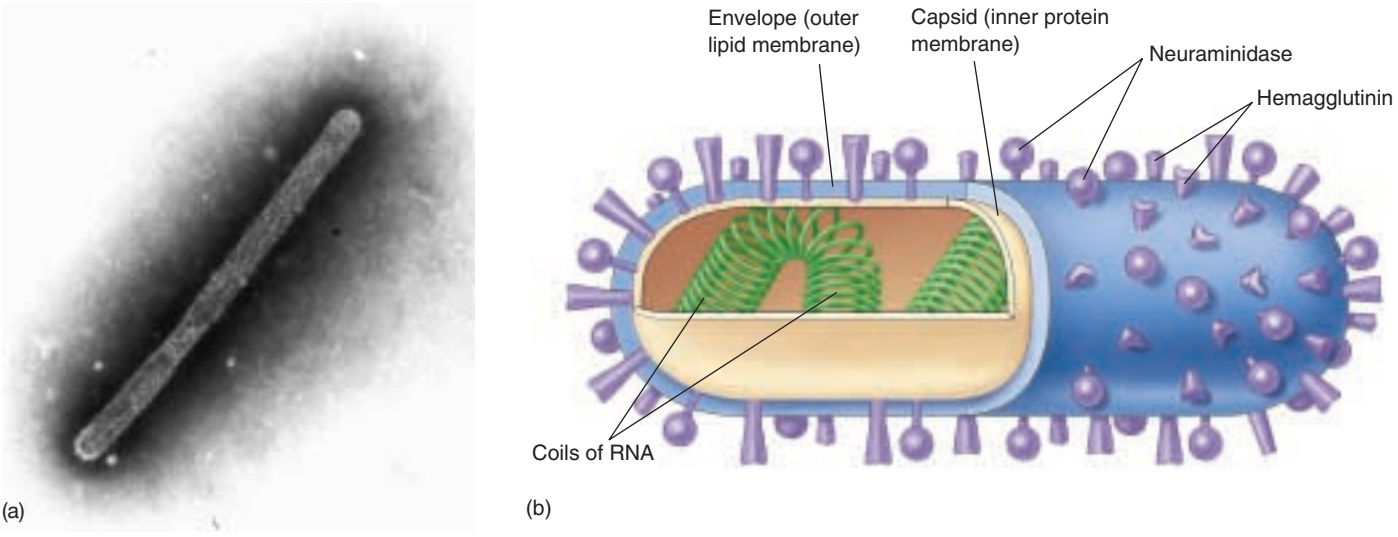


FIGURE 33.9
The influenza virus. (*a*) TEM of the so-called "bird flu" influenza virus, A(H5N1), which first infected humans in Hong Kong in 1997. (*b*) Diagram of an influenza virus. The coiled RNA has been revealed by cutting through the outer lipid-rich envelope, with its two kinds of projecting spikes, and the inner protein capsid.

Table 33.1 Important Human Viral Diseases

Disease	Pathogen	Reservoir	Vector/Epidemiology
AIDS	HIV	STD	Destroys immune defenses, resulting in death by infection or cancer. Over 33 million cases worldwide by 1998.
Chicken pox	Human herpesvirus 3 (varicella-zoster)	Humans	Spread through contact with infected individuals. No cure. Rarely fatal. Vaccine approved in U.S. in early 1995.
Ebola	Filoviruses	Unknown	Acute hemorrhagic fever; virus attacks connective tissue, leading to massive hemorrhaging and death. Peak mortality is 50–90% if the disease goes untreated. Outbreaks confined to local regions of central Africa.
Hepatitus B (viral)	Hepatitis B virus (HBV)	Humans	Highly infectious through contact with infected body fluids. Approximately 1% of U.S. population infected. Vaccine available, no cure. Can be fatal.
Herpes	Herpes simplex virus (HSV)	Humans	Fever blisters; spread primarily through contact with infected saliva. Very prevalent worldwide. No cure. Exhibits latency—the disease can be dormant for several years.
Influenza	Influenza viruses	Humans, ducks	Historically a major killer (22 million died in 18 months in 1918–19); wild Asian ducks, chickens, and pigs are major reservoirs. The ducks are not affected by the flu virus, which shuffles its antigen genes while multiplying within them, leading to new flu strains.
Measles	Paramyxoviruses	Humans	Extremely contagious through contact with infected individuals. Vaccine available. Usually contracted in childhood, when it is not serious; more dangerous to adults.
Mononucleosis	Epstein-Barr virus (EBV)	Humans	Spread through contact with infected saliva. May last several weeks; common in young adults. No cure. Rarely fatal.
Mumps	Paramyxovirus	Humans	Spread through contact with infected saliva. Vaccine available; rarely fatal. No cure.
Pneumonia	Influenza virus	Humans	Acute infection of the lungs, often fatal without treatment.
Polio	Poliovirus	Humans	Acute viral infection of the CNS that can lead to paralysis and is often fatal. Prior to the development of Salk's vaccine in 1954, 60,000 people a year contracted the disease in the U.S. alone.
Rabies	Rhabdovirus	Wild and domestic Canidae (dogs, foxes, wolves, coyotes), bats, and raccoons	An acute viral encephalomyelitis transmitted by the bite of an infected animal. Fatal if untreated.
Smallpox	Variola virus	Formerly humans, now only exists in two research labs—may be eliminated	Historically a major killer; the last recorded case of smallpox was in 1977. A worldwide vaccination campaign wiped out the disease completely.
Yellow fever	Flavivirus	Humans, mosquitoes	Spread from individual to individual by mosquito bites; a notable cause of death during the construction of the Panama Canal. If untreated, this disease has a peak mortality rate of 60%.

Importance of Recombination. The greatest problem in combating flu viruses arises not through mutation, but through recombination. Viral genes are readily reassorted by genetic recombination, sometimes putting together novel combinations of H and N spikes unrecognizable by human antibodies specific for the old configuration. Viral recombination of this kind seems to have been responsible for the three major flu pandemics (that is, worldwide epidemics) that occurred in the last century, by producing drastic shifts in H N combinations. The "killer flu" of 1918, A(H1N1), killed 40 million people. The Asian flu of 1957, A(H2N2), killed over 100,000 Americans. The Hong Kong flu of 1968, A(H3N2), infected 50 million people in the United States alone, of which 70,000 died.

It is no accident that new strains of flu usually originate in the far east. The most common hosts of influenza virus are ducks, chickens, and pigs, which in Asia often live in close proximity to each other and to humans. Pigs are subject to infection by both bird and human strains of the virus, and individual animals are often simultaneously infected with multiple strains. This creates conditions favoring genetic recombination between strains, producing new combinations of H and N subtypes. The Hong Kong flu, for example, arose from recombination between A(H3N8) [from ducks] and A(H2N2) [from humans]. The new strain of influenza, in this case A(H3N2), then passed back to humans, creating an epidemic because the human population has never experienced that H N combination before.

A potentially deadly new strain of flu virus emerged in Hong Kong in 1997, A(H5N1). Unlike all previous instances of new flu strains, A(H5N1) passed to humans directly from birds, in this case chickens. A(H5N1) was first identified in chickens in 1961, and in the spring of 1997 devastated flocks of chickens in Hong Kong. Fortunately, this strain of flu virus does not appear to spread easily from person to person, and the number of human infections by A(H5N1) remains small. Public health officials remain concerned that the genes of A(H5N1) could yet mix with those of a human strain to create a new strain that could spread widely in the human population, and to prevent this ordered the killing of all 1.2 million chickens in Hong Kong in 1997.

Emerging Viruses

Sometimes viruses that originate in one organism pass to another, thus expanding their host range. Often, this expansion is deadly to the new host. HIV, for example, arose in chimpanzees and relatively recently passed to humans. Influenza is fundamentally a bird virus. Viruses that originate in one organism and then pass to another and cause disease are called **emerging viruses** and represent a considerable threat in an age when airplane travel potentially allows infected individuals to move about the world quickly, spreading an infection.

Among the most lethal of emerging viruses are a collection of filamentous viruses arising in central Africa that cause severe hemorrhagic fever. With lethality rates in excess of 50%, these so-called filoviruses are among the most lethal infectious diseases known. One, Ebola virus (figure 33.10), has exhibited lethality rates in excess of 90% in isolated outbreaks in central Africa. The outbreak of Ebola virus in the summer of 1995 in Zaire killed 245 people out of 316 infected—a mortality rate of 78%. The latest outbreak occurred in Gabon, West Africa, in February 1996. The natural host of Ebola is unknown.

Another type of emerging virus caused a sudden outbreak of a hemorrhagic-type infection in the southwestern United States in 1993. This highly fatal disease was soon attributed to the hantavirus, a single-stranded RNA virus associated with rodents. The hantavirus is transmitted to humans through rodent fecal contamination in areas of human habitation. Although hantavirus has been known for some period of time, this particular outbreak was attributed to the presence of an unusually large rodent population in the area following a higher than normal amount of rainfall the previous winter.

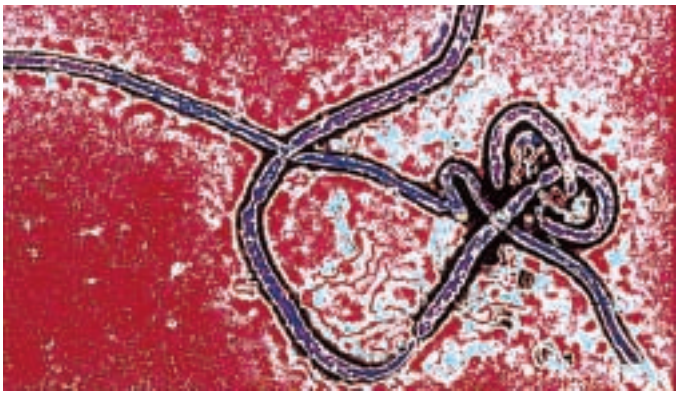


FIGURE 33.10
The Ebola virus. This virus, with a fatality rate that can exceed 90%, appears sporadically in West Africa. Health professionals are scrambling to identify the natural host of the virus, which is unknown, so they can devise strategies to combat transmission of the disease.

Viruses and Cancer

Through epidemiological studies and research, scientists have established a link between some viral infections and the subsequent development of cancer. Examples include the association between chronic hepatitis B infections and the development of liver cancer and the development of cervical carcinoma following infections with certain strains of papillomaviruses. It has been suggested that viruses contribute to about 15% of all human cancer cases worldwide. Viruses are capable of altering the growth properties of human cells they infect by triggering the expression of oncogenes (cancer-causing genes). Certain viruses can either activate host proto-oncogenes (see chapter 18) or bring in viral oncogenes that become incorporated into the host genome. Virus-induced cancer is not simply a matter of infection. The disease involves complex interactions with cellular genes and requires a series of events in order to develop.

Viruses are responsible for some of the most lethal diseases of humans. Some of the most serious examples are viruses that have transferred to humans from some other host. Influenza, a bird virus, has been responsible for the most devastating epidemics in human history. Newly emerging viruses such as Ebola have received considerable public attention.

Prions and Viroids

For decades scientists have been fascinated by a peculiar group of fatal brain diseases. These diseases have the unusual property that it is years and often decades after infection before the disease is detected in infected individuals. The brains of infected individuals develop numerous small cavities as neurons die, producing a marked spongy appearance. Called **transmissible spongiform encephalopathies** (**TSE**s), these diseases include scrapie in sheep, "mad cow" disease in cattle, and kuru and Creutzfeldt-Jakob disease in humans.

TSEs can be transmitted by injecting infected brain tissue into a recipient animal's brain. TSEs can also spread via tissue transplants and, apparently, food. Kuru was common in the Fore people of Papua New Guinea, when they practiced ritual cannibalism, literally eating the brains of infected individuals. Mad cow disease spread widely among the cattle herds of England in the 1990s because cows were fed bone meal prepared from cattle carcasses to increase the protein content of their diet. Like the Fore, the British cattle were literally eating the tissue of cattle that had died of the disease.

A Heretical Suggestion

In the 1960s, British researchers T. Alper and J. Griffith noted that infectious TSE preparations remained infectious even after exposed to radiation that would destroy DNA or RNA. They suggested that the infectious agent was a protein. Perhaps, they speculated, the protein usually preferred one folding pattern, but could sometimes misfold, and then catalyze other proteins to do the same, the misfolding spreading like a chain reaction. This heretical suggestion was not accepted by the scientific community, as it violates a key tenant of molecular biology: only DNA or RNA act as hereditary material, transmitting information from one generation to the next.

Prusiner's Prions

In the early 1970s, physician Stanley Prusiner, moved by the death of a patient from Creutzfeldt-Jakob disease, began to study TSEs. Prusiner became fascinated with Alper and Griffith's hypothesis. Try as he might, Prusiner could find no evidence of nucleic acids or viruses in the infectious TSE preparations, and concluded, as Alper and Griffith had, that the infectious agent was a *protein*, which in a 1982 paper he named a **prion**, for "proteinaceous infectious particle."

Prusiner went on to isolate a distinctive prion protein, and for two decades continued to amass evidence that prions play a key role in triggering TSEs. The scientific community resisted Prusiner's renegade conclusions, but eventually experiments done in Prusiner's and other laboratories began to convince many. For example, when

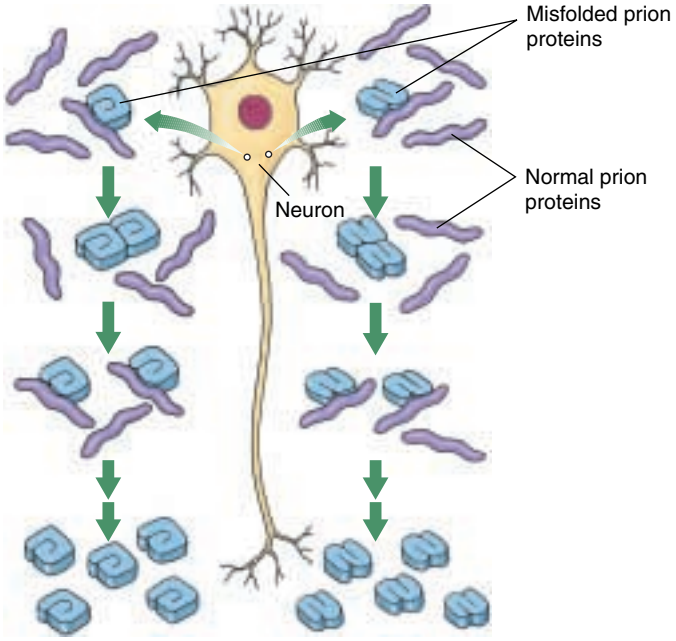


FIGURE 33.11
How prions arise. Misfolded prions seem to cause normal prion protein to misfold simply by contacting them. When prions misfolded in different ways (*blue*) contact normal prion protein (*purple*), the normal prion protein misfolds in the same way.

Prusiner injected prions of a different abnormal conformation into several different hosts, these hosts developed prions with the same abnormal conformations as the parent prions (figure 33.11). In another important experiment, Charles Weissmann showed that mice genetically engineered to lack Prusiner's prion protein are immune to TSE infection. However, if brain tissue with the prion protein is grafted into the mice, the grafted tissue—but not the rest of the brain—can then be infected with TSE. In 1997, Prusiner was awarded the Nobel Prize in Physiology or Medicine for his work on prions.

Viroids

Viroids are tiny, naked molecules of RNA, only a few hundred nucleotides long, that are important infectious disease agents in plants. A recent viroid outbreak killed over ten million coconut palms in the Philippines. It is not clear how viroids cause disease. One clue is that viroid nucleotide sequences resemble the sequences of introns within ribosomal RNA genes. These sequences are capable of catalyzing excision from DNA—perhaps the viroids are catalyzing the destruction of chromosomal integrity.

Prions are infectious proteins that some scientists believe are responsible for serious brain diseases. In plants, naked RNA molecules called viroids can also transmit disease.

Chapter 33

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Summary

Questions

Media Resources

33.1 Viruses are strands of nucleic acid encased within a protein coat.

- Viruses are fragments of DNA or RNA surrounded by protein that are able to replicate within cells by using the genetic machinery of those cells.
- The simplest viruses use the enzymes of the host cell for both protein synthesis and gene replication; the more complex ones contain up to 200 genes and are capable of synthesizing many structural proteins and enzymes.
- Viruses are basically either helical or isometric. Most isometric viruses are icosahedral in shape.

1. Why are viruses not considered to be living organisms?

2. How did early scientists come to the conclusion that the infectious agents associated with hoof-and-mouth disease in cattle were not bacteria?

3. What is the approximate size range of viruses and type of microscope is generally required to visualize viruses?

- Characteristics of Viruses

33.2 Bacterial viruses exhibit two sorts of reproductive cycles.

- Virulent bacteriophages infect bacterial cells by injecting their viral DNA or RNA into the cell, where it directs the production of new virus particles, ultimately lysing the cell.
- Temperate bacteriophages, upon entering a bacterial cell, insert their DNA into the cell genome, where they may remain integrated into the bacterial genome as a prophage for many generations.

4. What is a bacteriophage? How does a T4 phage infect a host cell?

- Life Cycle of Viruses

33.3 HIV is a complex animal virus.

- AIDS, a viral infection that destroys the immune system, is caused by HIV (human immunodeficiency virus). After docking on a specific protein called CD4, HIV enters the cell and replicates, destroying the cell.
- Considerable progress has been made in the treatment of AIDS, particularly with drugs such as protease inhibitors that block cleavage of HIV polyproteins into functional segments.

5. What specific type of human cell does the AIDS virus infect? How does it recognize this specific kind of cell?

6. How do many animal viruses penetrate the host cell? How does a plant virus infect its host? How does a bacterial virus infect its host?

- Bioethics Case Study: AIDS Vaccine

On Science Articles:

- HIV's Waiting Game
- Drug Therapy for AIDS
- Curing AIDS Just Got Harder
- HIV Delivery Protein

33.4 Nonliving infectious agents are responsible for many human diseases.

- Viruses are responsible for many serious human diseases. Some of the most serious, like AIDS and Ebola, have only recently transferred to humans from some other animal host.
- Proteins called prions may transmit serious brain diseases from one individual to another.

7. Why is it so much more difficult to treat a viral infection than a bacterial one? Is this different from treating bacterial infections?

8. What is a prion? How does it integrate into living systems?

- Scientists on Science: Prions
- Book Review: *The Coming Plague* by Garrett

On Science Articles:

- Smallpox: Tomorrow's Nightmare?
- Smallpox Questions
- Mad Cows and Prions
- Prions and Blood Supply
- Hepatitis C
- Increasing Mad Cow Diseases