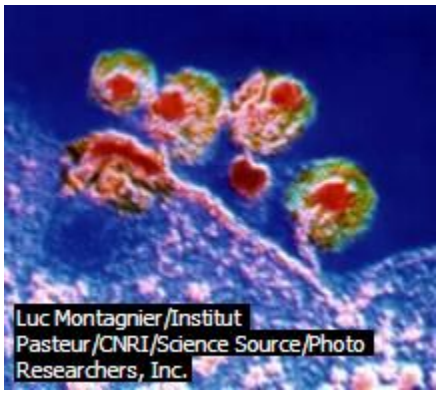
HIV EXAMINER

A Monthly Newsletter of Writers Against Aids and Tobacco Smoking

August Edition

Virus (life science)

I Introduction



AIDS Virus

The human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), principally attacks T-4 lymphocytes, a vital part of the human immune system. As a result, the body's ability to resist opportunistic viral, bacterial, fungal, protozoal, and other infection is greatly weakened. Pneumocystis carinii pneumonia is the leading cause of death among people with HIV infection, but the incidence of certain types of cancers such as B-cell lymphomas and Kaposi's sarcoma is also increased. Neurological complications and dramatic weight loss, or "wasting," are characteristic of endstage HIV disease (AIDS). HIV can be transmitted sexually, through contact with contaminated blood, tissue, or needles, and from mother to child during birth or breast-feeding. Full-blown symptoms of AIDS may not develop for more than 10 years after infection.

Luc Montagnier/Institut Pasteur/CNRI/Science Source/Photo Researchers, Inc.

T4 Bacteriophage

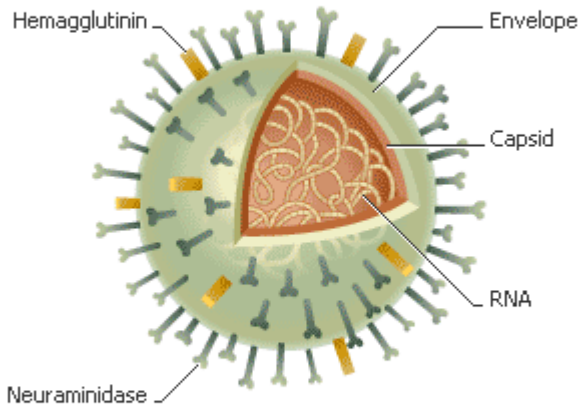
In this image from an electron microscope, a complex virus known as a bacteriophage (“eater of bacteria”) can be seen with its bulging head and tubular tail. Secured to its victim by the stringy fibers visible here, the tail acts like a needle in piercing the bacterium’s cellular wall. The head then passes its reservoir of DNA down the tail and into the host. Within 25 minutes the dying cell is teeming with about 100 fresh copies of the virus, which are created by the rearrangment of the bacterium’s own genetic contents.

M. Wurtz/Univ. of Basel/Science Source/Photo Researchers, Inc.

Virus (life science), infectious agent found in virtually all life forms, including humans, animals, plants, fungi, and bacteria. Viruses consist of genetic material—either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)—surrounded by a protective coating of protein, called a *capsid*, with or without an outer lipid envelope. Viruses are between 20 and 100 times smaller than bacteria and hence are too small to be seen by light microscopy. Viruses vary in size from the largest poxviruses of about 450 nanometers (about 0.000014 in) in length to the smallest polioviruses of about 30 nanometers (about 0.000001 in). Viruses are not considered free-living, since they cannot reproduce outside of a living cell; they have evolved to transmit their genetic information from one cell to another for the purpose of replication.

Viruses often damage or kill the cells that they infect, causing disease in infected organisms. A few viruses stimulate cells to grow uncontrollably and produce cancers. Although many infectious diseases, such as the common cold, are caused by viruses, there are no cures for these illnesses. The difficulty in developing antiviral therapies stems from the large number of variant viruses that can cause the same disease, as well as the inability of drugs to disable a virus without disabling healthy cells. However, the development of antiviral agents is a major focus of current research, and the study of viruses has led to many discoveries important to human health.

II STRUCTURE AND CLASSIFICATION



Viral Structure

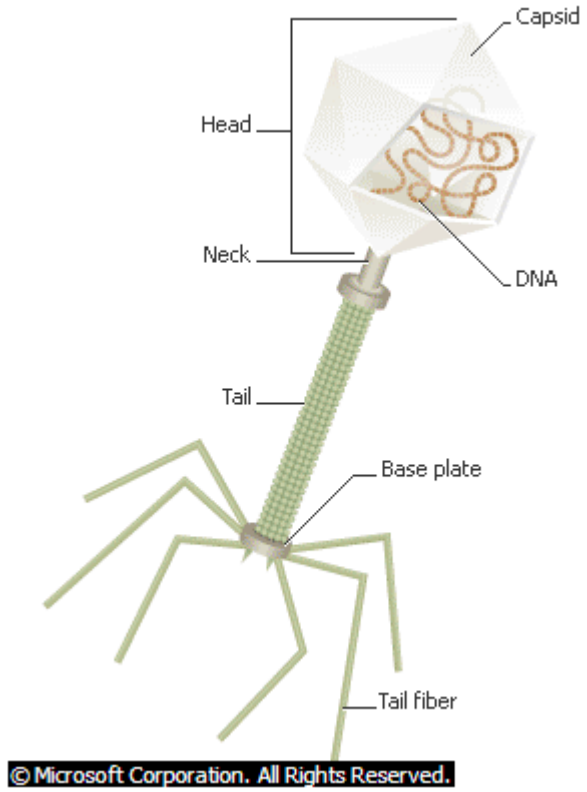
The influenza virus has a relatively simple structure. A lipid (fatty) envelope surrounds the protein shell (capsid), which encloses coiled genetic material (RNA). Projecting from this envelope are two kinds of protein spikes, hemagglutinin and neuraminidase. These proteins act as antigens, eliciting an immune response in the organism that the virus invades. Influenza viruses exhibit the unique quality of periodically mutating these protein spikes. Because the

viruses continually change, they can cause repeated waves of infection, even among people previously infected.

Individual viruses, or virus particles, also called *virions*, contain genetic material, or *genomes*, in one of several forms. Unlike cellular organisms, in which the genes always are made up of DNA, viral genes may consist of either DNA or RNA. Like cell DNA, almost all viral DNA is double-stranded, and it can have either a circular or a linear arrangement. Almost all viral RNA is single-stranded; it is usually linear, and it may be either segmented (with different genes on different RNA molecules) or nonsegmented (with all genes on a single piece of RNA).

The viral protective shell, or capsid, can be either *helical* (spiral-shaped) or *icosahedral* (having 20 triangular sides). Capsids are composed of repeating units of one or a few different proteins. These units are called *protomers* or *capsomers.* The proteins that make up the virus particle are called structural proteins. Viruses also carry genes for making proteins that are never incorporated into the virus particle and are found only in infected cells. These viral proteins are called nonstructural proteins; they include factors required for the replication of the viral genome and the production of the virus particle.

Capsids and the genetic material (DNA or RNA) they contain are together referred to as *nucleocapsids.* Some virus particles consist only of nucleocapsids, while others contain additional structures.



Bacteriophage

A bacteriophage is a type of virus that destroys bacteria. It consists of a head, containing the genetic material, and a tail, which attaches to the exterior of a bacterium. The genetic material of the bacteriophage passes from its head through its tail into the bacterium. The genetic material then directs the bacterium to create new bacteriophages, which eventually burst from their host and, in the process, destroy the bacterium. The released bacteriophages attack nearby bacteria, and the infection process continues.

Some icosahedral and helical animal viruses are enclosed in a lipid envelope acquired when the virus buds through host-cell membranes. Inserted into this envelope are *glycoproteins* that the viral genome directs the cell to make; these molecules bind virus particles to susceptible host cells.

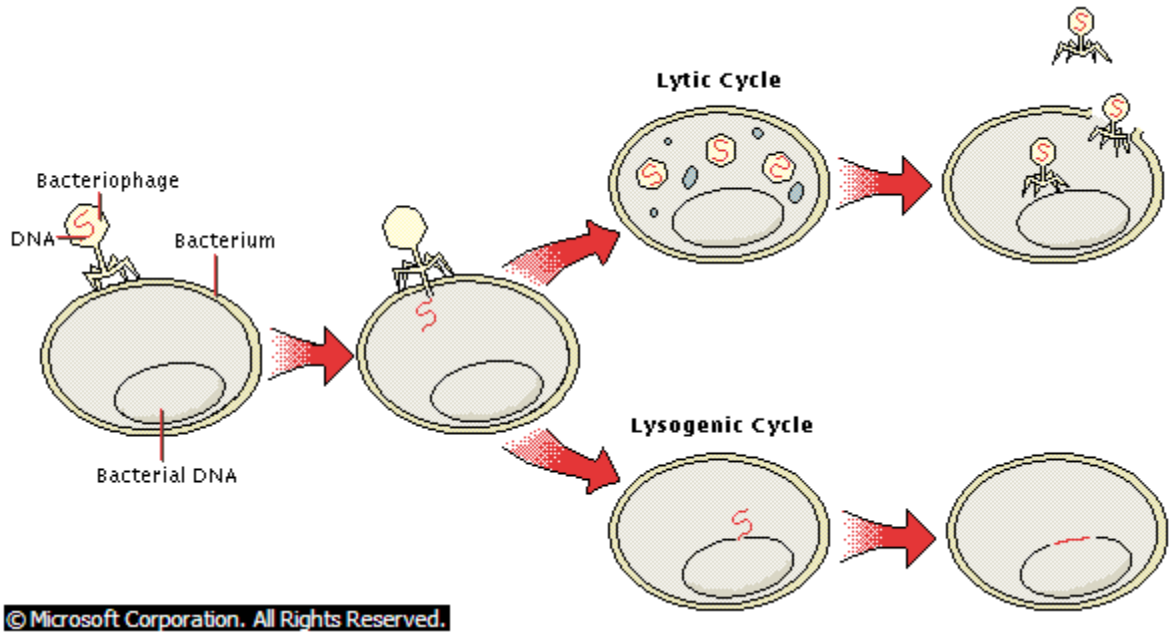
The most elaborate viruses are the bacteriophages, which use bacteria as their hosts. Some bacteriophages resemble an insect with an icosahedral head attached to a tubular sheath. From the base of the sheath extend several long tail fibers that help the virus attach to the bacterium

and inject its DNA to be replicated and to direct capsid production and virus particle assembly inside the cell.

Viroids and *prions* are smaller than viruses, but they are similarly associated with disease. Viroids are plant pathogens that consist only of a circular, independently replicating RNA molecule. The single-stranded RNA circle collapses on itself to form a rodlike structure. The only known mammalian pathogen that resembles plant viroids is the deltavirus (hepatitis D), which requires hepatitis B virus proteins to package its RNA into virus particles. *Co-infection* with hepatitis B and D can produce more severe disease than can infection with hepatitis B alone. Prions are mutated forms of a normal protein found on the surface of certain animal cells. The mutated protein, known as a prion, has been implicated in some neurological diseases such as Creutzfeldt-Jakob disease and Bovine Spongiform Encephalopathy. There is some evidence that prions resemble viruses in their ability to cause infection. Prions, however, lack the nucleic acid found in viruses.

Viruses are classified according to their type of genetic material, their strategy of replication, and their structure. The International Committee on Nomenclature of Viruses (ICNV), established in 1966, devised a scheme to group viruses into families, subfamilies, genera, and species. The ICNV report published in 1995 assigned more than 4000 viruses into 71 virus families. Hundreds of other viruses remain unclassified because of the lack of sufficient information.

III REPLICATION



Lytic and Lysogenic Cycles of a Bacteriophage

All bacteriophages (viruses that parasitize bacteria) have a lytic or infectious cycle, in which the virus, incapable of replicating itself, injects its genetic material into a bacterium. By pirating its host's enzymes and protein-building capacities, the virus can reproduce and repackage, making about 100 new copies before it bursts from and destroys the bacteria. Some bacteriophages, however, behave differently when they infect a bacterium. The injected genetic material instead integrates itself into its host DNA, passively replicating with it to be inherited by bacterial daughter cells. In about 1 in 100,000 of these lysogenic cells, the viral DNA spontaneously activates and starts a new lytic cycle.

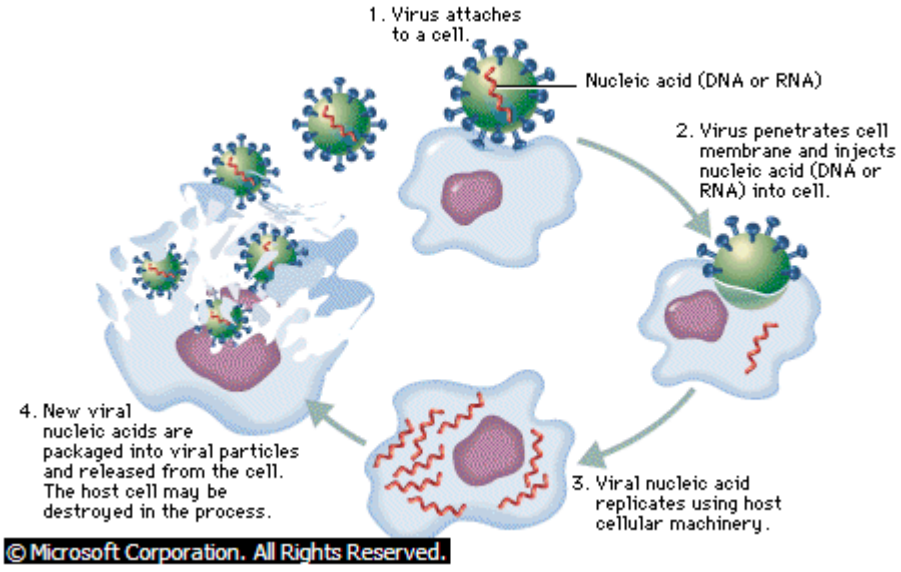
The first contact between a virus particle and its host cell occurs when an outer viral structure docks with a specific molecule on the cell surface. For example, a glycoprotein called gp120 on the surface of the human immunodeficiency virus (HIV, the cause of acquired immunodeficiency syndrome, or AIDS) virion specifically binds to the CD4 molecule found on certain human T lymphocytes (a type of white blood cell). Most cells that do not have surface CD4 molecules generally cannot be infected by HIV.

After binding to an appropriate cell, a virus must cross the cell membrane. Some viruses accomplish this goal by fusing their lipid envelope to the cell membrane, thus releasing the

nucleocapsid into the cytoplasm of the cell. Other viruses must first be *endocytosed* (enveloped by a small section of the cell's plasma membrane that pokes into the cell and pinches off to form a bubblelike vesicle called an endosome) before they can cross the cell membrane. Conditions in the endosome allow many viruses to change the shape of one or more of their proteins. These changes permit the virus either to fuse with the endosomal membrane or to *lyse* the endosome (cause it to break apart), allowing the nucleocapsid to enter the cell cytoplasm.

Once inside the cell, the virus replicates itself through a series of events. Viral genes direct the production of proteins by the host cellular machinery. The first viral proteins synthesized by some viruses are the enzymes required to copy the viral genome. Using a combination of viral and cellular components, the viral genome can be replicated thousands of times. Late in the replication cycle for many viruses, proteins that make up the capsid are synthesized. These proteins package the viral genetic material to make newly formed nucleocapsids.

To complete the virus replication cycle, viruses must exit the cell. Some viruses bud out of the cell's plasma membrane by a process resembling reverse endocytosis. Other viruses cause the cell to lyse, thereby releasing newly formed virus particles ready to infect other cells. Still other viruses pass directly from one cell into an adjacent cell without being exposed to the extracellular environment. The virus replication cycle can be as short as a couple of hours for certain small viruses or as long as several days for some large viruses.



Viral Replication

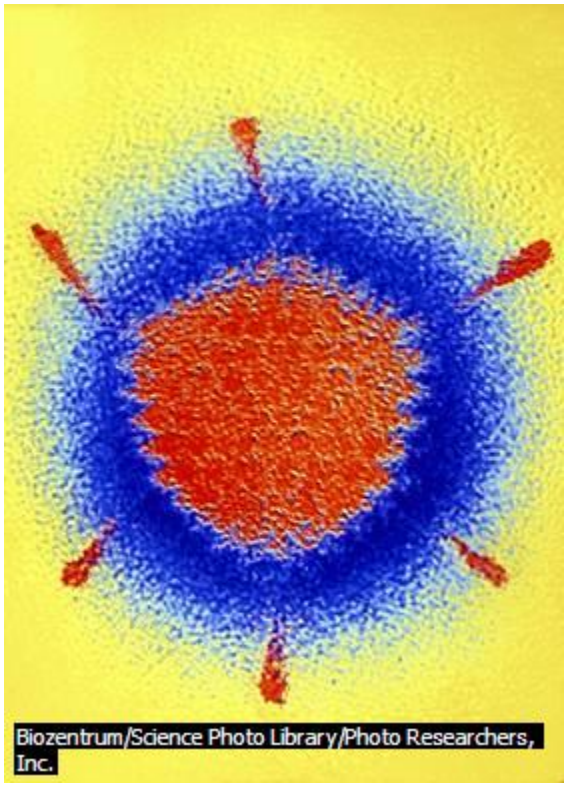
Outside of a host cell, a virus is an inert particle. Once inside a cell, a virus can replicate many times, creating thousands of viruses that leave the cell to find host cells of their own. Viruses that cause disease do so by destroying or damaging cells as they leave them.

Some viruses kill cells by inflicting severe damage resulting in cell lysis; other viruses cause the cell to kill itself in response to virus infection. This programmed cell suicide is thought to be a host defense mechanism to eliminate infected cells before the virus can complete its replication cycle and spread to other cells. Alternatively, cells may survive virus infection, and the virus can persist for the life of its host. Virtually all people harbor harmless viruses.

Retroviruses, such as HIV, have RNA that is transcribed into DNA by the viral enzyme *reverse transcriptase* upon entry into the cell. (The ability of retroviruses to copy RNA into DNA earned them their name because this process is the reverse of the usual transfer of genetic information, from DNA to RNA.) The DNA form of the retrovirus genome is then integrated into the cellular DNA and is referred to as the *provirus.* The viral genome is replicated every time the host cell replicates its DNA and is thus passed on to daughter cells.

Hepatitis B virus can also transcribe RNA to DNA, but this virus packages the DNA version of its genome into virus particles. Unlike retroviruses, hepatitis B virus does not integrate into the host cell DNA.

IV DISEASE



Adenovirus

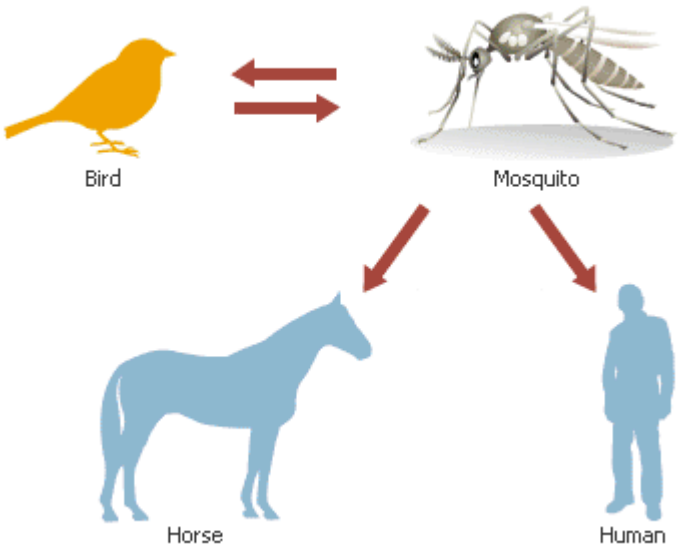
The adenovirus is one of the 100 virus types that causes the common cold. The adenovirus can enter a human host through the respiratory and gastrointestinal tracts or through the eye.

Biozentrum/Science Photo Library/Photo Researchers, Inc.

Most viral infections cause no symptoms and do not result in disease. For example, only a small percentage of individuals who become infected with Epstein-Barr virus or western equine encephalomyelitis virus ever develop disease symptoms. In contrast, most people who are infected with measles, rabies, or influenza viruses develop the disease. A wide variety of viral and host factors determine the outcome of virus infections. A small genetic variation can produce a virus with increased capacity to cause disease. Such a virus is said to have increased virulence.

Viruses can enter the body by several routes. Herpes simplex virus and poxviruses enter through the skin by direct contact with virus-containing skin lesions on infected individuals. Ebola, hepatitis B, and HIV can be contracted from infected blood products. Hypodermic needles and animal and insect bites can transmit a variety of viruses through the skin. Viruses that infect through the respiratory tract are usually transmitted by airborne droplets of mucus or saliva from

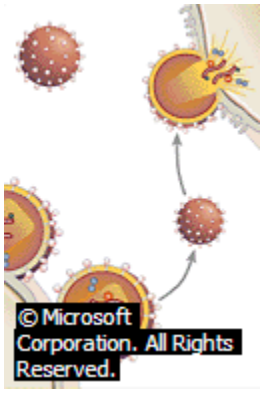
infected individuals who cough or sneeze. Viruses that enter through the respiratory tract include orthomyxovirus (influenza), rhinovirus and adenovirus (common cold), and varicella-zoster virus (chicken pox). Viruses such as rotavirus, coronavirus, poliovirus, hepatitis A, and some adenoviruses enter the host through the gastrointestinal tract. Sexually transmitted viruses, such as herpes simplex, HIV, and human papillomaviruses (HPV), gain entry through the genitourinary route. Other viruses, including some adenoviruses, echoviruses, Coxsackie viruses, and herpesviruses, can infect through the eye.



Life Cycle of West Nile Virus

The West Nile virus is a mosquito-borne virus that can cause encephalitis or meningitis—both potentially fatal conditions—in humans and other vertebrate animals. A mosquito becomes infected when it bites and sucks the blood of a bird that is carrying the virus. Ten days to two weeks later, the virus reaches the mosquito's salivary glands. When the mosquito sucks the blood of other birds, humans, horses, or other vertebrate animals, the virus passes from the mosquito's salivary glands into the bloodstream of the bitten animal. West Nile virus does not spread from person to person and no evidence suggests that the virus can spread directly from birds to humans or other animals.

Virus infections can be either localized or systemic. The path of virus spread through the body in systemic infections differs among different viruses. Following replication at the initial site of entry, many viruses are spread to their target organs by the bloodstream or the nervous system.



Life Cycle of Human Immunodeficiency Virus

The human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS), is genetically programmed to do one thing: highjack the reproductive machinery of a human cell, then trick it into churning out as many copies of the virus as it can before the cell dies. The current best hope for the treatment of AIDS requires that patients take a number of different drugs, each of which interferes with certain steps of the HIV infection process.

The particular cell type can influence the outcome of virus infection. For example, herpes simplex virus undergoes lytic replication in skin cells around the lips but can establish a latent or dormant state in neuron cell bodies (located in ganglia) for extended periods of time. During latency, the viral genome is largely dormant in the cell nucleus until a stimulus such as a sunburn causes the reactivation of latent herpesvirus, leading to the lytic replication cycle. Once reactivated, the virus travels from the ganglia back down the nerve to cause a cold sore on the lip near the original site of infection. The herpesvirus genome does not integrate into the host cell genome.

Virus-induced illnesses can be either acute, in which the patient recovers promptly, or chronic, in which the virus remains with the host or the damage caused by the virus is irreparable. For most acute viruses, the time between infection and the onset of disease can vary from three days to

three weeks. In contrast, onset of AIDS following infection with HIV takes an average of 7 to 11 years.

Several human viruses are likely to be agents of cancer, which can take decades to develop. The precise role of these viruses in human cancers is not well understood, and genetic and environmental factors are likely to contribute to these diseases. But because a number of viruses have been shown to cause tumors in animal models, it is probable that many viruses have a key role in human cancers.

Some viruses—alphaviruses and flaviviruses, for example—must be able to infect more than one species to complete their life cycles. Eastern equine encephalomyelitis virus, an alphavirus, replicates in mosquitoes and is transmitted to wild birds when the mosquitoes feed. Thus, wild birds and perhaps mammals and reptiles serve as the virus *reservoir*, and mosquitoes serve as *vectors* essential to the virus life cycle by ensuring transmission of the virus from one host to another. Horses and people are accidental hosts when they are bitten by an infected mosquito, and they do not play an important role in virus transmission.

V DEFENSE

Although viruses cannot be treated with antibiotics, which are effective only against bacteria, the body's immune system has many natural defenses against virus infections. Infected cells produce *interferons* and other *cytokines* (soluble components that are largely responsible for regulating the immune response), which can signal adjacent uninfected cells to mount their defenses, enabling uninfected cells to impair virus replication. Some cytokines can cause a fever in response to viral infection; elevated body temperature retards the growth of some types of viruses. B lymphocytes produce specific antibodies that can bind and inactivate viruses. Cytotoxic T cells recognize virus-infected cells and target them for destruction. However, many viruses have evolved ways to circumvent some of these host defense mechanisms.

The development of antiviral therapies has been thwarted by the difficulty of generating drugs that can distinguish viral processes from cellular processes. Therefore, most treatments for viral diseases simply alleviate symptoms, such as fever, dehydration, and achiness. Nevertheless,

antiviral drugs for influenza virus, herpesviruses, and HIV are available, and many others are in the experimental and developmental stages.

Prevention has been a more effective method of controlling virus infections. Viruses that are transmitted by insects or rodent excretions can be controlled with pesticides. Successful vaccines are currently available for poliovirus, influenza, rabies, adenovirus, rubella, yellow fever, measles, mumps, and chicken pox. Vaccines are prepared from killed (inactivated) virus, live (attenuated or weakened) virus, or isolated viral proteins (subunits). Each of these types of vaccines elicits an immune response while causing little or no disease, and there are advantages and disadvantages to each. (For a more complete discussion of vaccines, see the Immunization article.)

The principle of vaccination was discovered by British physician Edward Jenner. In 1796 Jenner observed that milkmaids in England who contracted the mild cowpox virus infection from their cows were protected from smallpox, a frequently fatal disease. In 1798 Jenner formally demonstrated that prior infection with cowpox virus protected those that he inoculated with smallpox virus (an experiment that would not meet today's protocol standards because of its use of human subjects). In 1966 the World Health Organization (WHO) initiated a program to eradicate smallpox from the world. Because it was impossible to vaccinate the entire world population, the eradication plan was to identify cases of smallpox and then vaccinate all of the individuals in that vicinity. The last reported case of smallpox was in Somalia in October 1977. An important factor in the success of eradicating smallpox was that humans are the only host and there are no animal reservoirs for smallpox virus. The strain of poxvirus used for immunization against smallpox was called vaccinia. Introduction of the Salk (inactivated) and Sabin (live, attenuated) vaccines for poliovirus, developed in the 1950s by the American physician and epidemiologist Jonas Salk and the American virologist Albert Bruce Sabin, respectively, was responsible for a significant worldwide decline in paralytic poliomyelitis. However, polio has not been eradicated, partly because the virus can mutate and escape the host immune response. Influenza viruses mutate so rapidly that new vaccines are developed for distribution each year.

Viruses undergo very high rates of mutation (genetic alteration) largely because they lack the repair systems that cells have to safeguard against mutations. A high mutation rate enables the

virus to continually adapt to new intracellular environments and to escape from the host immune response. Co-infection of the same cell with different related viruses allows for genetic reassortment (exchange of genome segments) and intramolecular recombination. Genetic alterations can alter virulence or allow viruses to gain access to new cell types or new animal hosts. Many scientists believe that HIV is derived from a closely related monkey virus, SIV (simian immunodeficiency virus), that acquired the ability to infect humans. Many of today's emerging viruses may have similar histories.

VI DISCOVERY

Wendell Stanley

American biochemist Wendell Stanley won the 1946 Nobel Prize in chemistry. Stanley did extensive work on the chemical makeup of viruses, isolating their components and proving that viruses can cause cancer.

By the last half of the 19th century, the microbial world was known to consist of protozoa, fungi, and bacteria, all visible with a light microscope. In the 1840s, the German scientist Jacob Henle suggested that there were infectious agents too small to be seen with a light microscope, but for the lack of direct proof, his hypothesis was not accepted. Although the French scientist Louis Pasteur was working to develop a vaccine for rabies in the 1880s, he did not understand the concept of a virus.

During the last half of the 19th century, several key discoveries were made that set the stage for the discovery of viruses. Pasteur is usually credited for dispelling the notion of spontaneous generation and proving that organisms reproduce new organisms. The German scientist Robert

Koch, a student of Jacob Henle, and the British surgeon Joseph Lister developed techniques for growing cultures of single organisms that allowed the assignment of specific bacteria to specific diseases.

The first experimental transmission of a viral infection was accomplished in about 1880 by the German scientist Adolf Mayer, when he demonstrated that extracts from infected tobacco leaves could transfer tobacco mosaic disease to a new plant, causing spots on the leaves. Because Mayer was unable to isolate a bacterium or fungus from the tobacco leaf extracts, he considered the idea that tobacco mosaic disease might be caused by a soluble agent, but he concluded incorrectly that a new type of bacteria was likely to be the cause. The Russian scientist Dimitri Ivanofsky extended Mayer's observation and reported in 1892 that the tobacco mosaic agent was small enough to pass through a porcelain filter known to block the passage of bacteria. He too failed to isolate bacteria or fungi from the filtered material. But Ivanofsky, like Mayer, was bound by the dogma of his times and concluded in 1903 that the filter might be defective or that the disease agent was a toxin rather than a reproducing organism.

Unaware of Ivanofsky's results, the Dutch scientist Martinus Beijerinck, who collaborated with Mayer, repeated the filter experiment but extended this finding by demonstrating that the filtered material was not a toxin because it could grow and reproduce in the cells of the plant tissues. In his 1898 publication, Beijerinck referred to this new disease agent as a contagious living liquid—*contagium vivum fluid*—initiating a 20-year controversy over whether viruses were liquids or particles.

The conclusion that viruses are particles came from several important observations. In 1917 the French-Canadian scientist Félix H. d'Hérelle discovered that viruses of bacteria, which he named bacteriophage, could make holes in a culture of bacteria. Because each hole, or plaque, developed from a single bacteriophage, this experiment provided the first method for counting infectious viruses (the plaque assay). In 1935 the American biochemist Wendell Meredith Stanley crystallized tobacco mosaic virus to demonstrate that viruses had regular shapes, and in 1939 tobacco mosaic virus was first visualized using the electron microscope.

In 1898 the German bacteriologists Friedrich August Johannes Löffler and Paul F. Frosch (both trained by Robert Koch) described foot-and-mouth disease virus as the first filterable agent of animals, and in 1900, the American bacteriologist Walter Reed and colleagues recognized yellow fever virus as the first human filterable agent. For several decades viruses were referred to as filterable agents, and gradually the term *virus* (Latin for "slimy liquid" or "poison") was employed strictly for this new class of infectious agents. Through the 1940s and 1950s many critical discoveries were made about viruses through the study of bacteriophages because of the ease with which the bacteria they infect could be grown in the laboratory. Between 1948 and 1955, scientists at the National Institutes of Health (NIH) and at Johns Hopkins Medical Institutions revolutionized the study of animal viruses by developing cell culture systems that permitted the growth and study of many animal viruses in laboratory dishes.

VII EVOLUTION

Three theories have been put forth to explain the origin of viruses. One theory suggests that viruses are derived from more complex intracellular parasites that have eliminated all but the essential features required for replication and transmission. A more widely accepted theory is that viruses are derived from normal cellular components that gained the ability to replicate autonomously. A third possibility is that viruses originated from self-replicating RNA molecules. This hypothesis is supported by the observation that RNA can code for proteins as well as carry out enzymatic functions. Thus, viroids may resemble "prehistoric" viruses.

VIII IMPORTANCE OF VIRUSES

Because viral processes so closely resemble normal cellular processes, abundant information about cell biology and genetics has come from studying viruses. Basic scientists and medical researchers at university and hospital laboratories are working to understand viral mechanisms of action and are searching for new and better ways to treat viral illnesses. Many pharmaceutical and biotechnology companies are actively pursuing effective antiviral therapies. Viruses can also serve as tools. Because they are efficient factories for the production of viral proteins, viruses have been harnessed to produce a wide variety of proteins for industrial and research purposes. A new area of endeavor is the use of viruses for gene therapy. Because viruses are programmed to

carry genetic information into cells, they have been used to replace defective cellular genes. Viruses are also being altered by genetic engineering to kill selected cell populations, such as tumor cells. The use of genetically engineered viruses for medical intervention is a relatively new field, and none of these therapies is widely available. However, this is a fast-growing area of research, and many clinical trials are now in progress. The use of genetically engineered viruses extends beyond the medical field. Recombinant insect viruses have agricultural applications and are currently being tested in field trials for their effectiveness as pesticides.

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