MICROBIOLOGY COURSE MATERIAL

Semester - III

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CC5: UNIT 1: NATURE & PROPERTIES OF VIRUSES

B.Sc (HONOURS) MICROBIOLOGY (CBCS STRUCTURE)
SEMESTER – III
CC - 5: UNIT – 1: Part - A
NATURE & PROPERTIES OF VIRUSES

Two scientists contributed to the discovery of the first virus, Tobacco Mosaic Virus. Ivanoski reported in 1892 that extracts from infected leaves were still infectious after filtration through a Chamberland filter-candle. Bacteria are retained by such filters, a new world was discovered: filterable pathogens. However, Ivanovski probably did not grasp the full meaning of his discovery. Beijerinck, in 1898, was the first to call 'virus', the incitant of the tobacco mosaic. He showed that the incitant was able to migrate in an agar gel.

1892	Dimitrii Ivanovsky observed that agent of Tobacco Mosaic disease passes through porcelain filters that retain bacteria
1898	Marcus Beijerinck makes the same observation; concludes that the pathogen must be a distinctive agent
1898	Friedrich Loeffler and Paul Frosch (former students of Koch), find that causative agent of foot-and-mouth disease is filterable (the first animal virus)
1901	Yellow Fever Virus – Walter Reed (the first human virus)
1903	Rabies virus (Remlinger, Riffat-Bay)
1906	Variola virus (Negri)
1908	Poliovirus (Karl Landsteiner and E. Popper); Chicken Leukemia Virus (Ellerman, Bang)
1911	Rous Sarcoma Virus (Peyton Rous)
1915	Bacteriophages -Frederik Twort, Felix D'Herelle
1931	Swine Influenza Virus (Shope)
1933	Human Influenza Virus (Smith)

Therefore being an infectious soluble agent, or a 'contagium vivum fluidum' and definitively not a 'contagium fixum' as would be a bacteria. Ivanovski and Beijerinck brought unequal but decisive and complementary contributions to the discovery of viruses. Since then, discoveries made on Tobacco Mosaic Virus have stood out as milestones of the history of virology.

The name virus was coined from the Latin word meaning *slimy liquid* or *poison*. It was originally used to describe any infectious agent, including the agent of tobacco mosaic disease. In the early years of discovery, viruses were referred to as filterable agents. Only later was the term virus restricted to filterable agents that require a living host for propagation.

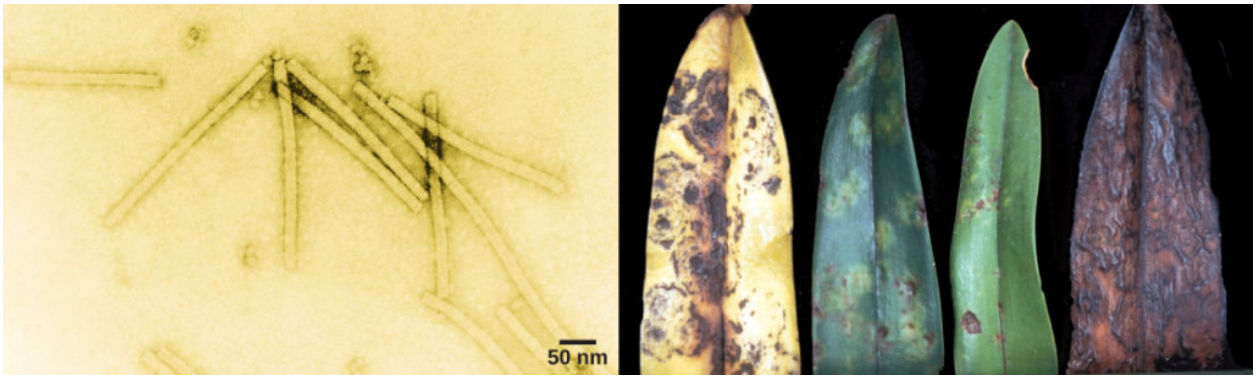

Figure 1: The Tobacco Mosaic Virus (left), seen here by transmission electron microscopy, was the first virus to be discovered. The virus causes disease in tobacco and other plants, such as the orchid (right).

No one knows exactly when viruses emerged or from where they came, since viruses do not leave historical footprints such as fossils. Modern viruses are thought to be a mosaic of bits and pieces of nucleic acids picked up from various sources along their respective evolutionary paths. Viruses are acellular, parasitic entities that are not classified within any kingdom. Unlike most living organisms, viruses are not cells and cannot divide. Instead, they infect a host cell and use the host's replication processes to produce identical progeny virus particles. Viruses infect organisms as diverse as bacteria, plants, and animals. They exist in a netherworld between a living organism and a nonliving entity. Living things grow, metabolize, and reproduce. Viruses

replicate, but to do so, they are entirely dependent on their host cells. They do not metabolize or grow, but are assembled in their mature form.

Virions

Virions, single virus particles, are very small, about 20–250 nanometers in diameter. These individual virus particles are the infectious form of a virus outside the host cell. Unlike bacteria (which are about 100 times larger), we cannot see viruses with a light microscope, with the exception of some large virions of the poxvirus family. It was not until the development of the electron microscope in the late 1930s that scientists got their first good view of the structure of the Tobacco Mosaic Virus (TMV) (Figure 1) and other viruses (Figure 2). The surface structure of virions can be observed by both scanning

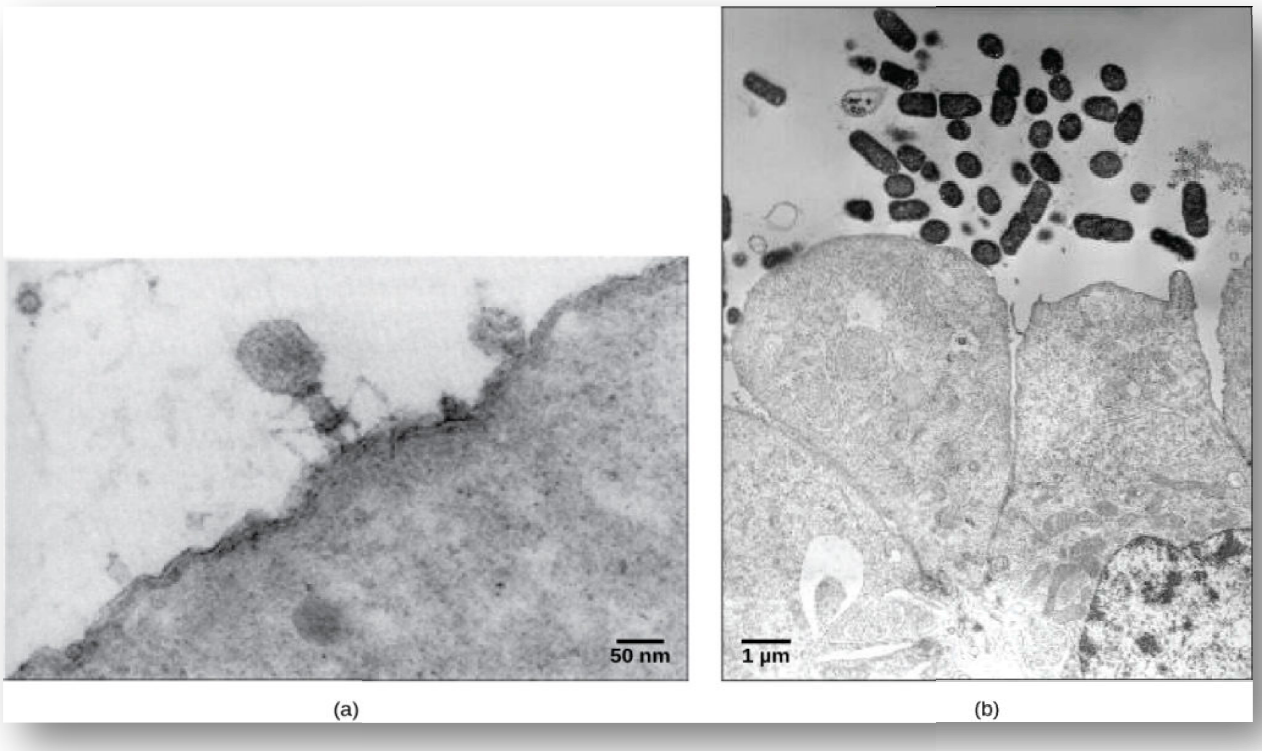

Figure 2. In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these E. coli cells are dwarfed by cultured colon cells.

and transmission electron microscopy, whereas the internal structures of the virus can only be observed in images from a transmission electron microscope. The use of these technologies has allowed for the discovery of many viruses of all types of living organisms. They were initially grouped by shared morphology. Later, groups of viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether their nucleic acid was single- or double-stranded. More recently, molecular analysis of viral replicative cycles has further refined their classification.

❖ Evolution of Viruses

Although biologists have accumulated a significant amount of knowledge about how present-day viruses evolve, much less is known about how viruses originated in the first place. When exploring the evolutionary history of most organisms, scientists can look at fossil records and similar historic evidence. However, viruses do not fossilize, so researchers can only hypothesize about viruses' evolutionary history by investigating how today viruses evolve and by using biochemical and genetic information to create speculative virus histories. While most findings agree that viruses don't have a single common ancestor, scholars have yet to find a single hypothesis about virus origins that is fully accepted in the field—and that fully explains viruses and their characteristics. There are, however, three hypotheses that have risen as the most accepted:

- **Devolution** or **regressive hypothesis**: This hypothesis proposes to explain the origin of viruses by suggesting that viruses evolved from free-living cells. However, many components of how this process might have occurred are a mystery.
- **Escapist** or **progressive hypothesis**: This hypothesis accounts for viruses having either RNA or a DNA genome and suggests that viruses originated from RNA and DNA molecules that escaped from a host cell. However, this hypothesis doesn't explain the complex capsids and other structures on virus particles.

- **Self-replication hypothesis**: This hypothesis posits a system of self-replication similar to that of other self-replicating molecules, likely evolving alongside the cells they rely on as hosts; studies of some plant pathogens support this hypothesis.

Another problem for those studying viral origins and evolution is their high rate of mutation, particularly the case in RNA retroviruses like HIV/AIDS. As technology advances, scientists will develop and refine further hypotheses to explain the origin of viruses—or create new hypotheses. The emerging field called virus molecular systematics attempts to do just that through comparisons of sequenced genetic material. These researchers hope to one day better understand the origin of viruses, a discovery that could lead to advances in the treatments for the ailments they produce.

❖ Viral Morphology

Viruses are acellular, meaning they are biological entities that do not have a cellular structure. Therefore they lack most of the components of cells, such as organelles, ribosomes, and plasma membrane. A virion consists of a nucleic acid core, an outer protein coating or capsid, and sometimes an outer envelope made of protein and phospholipid membranes derived from the host cell. Viruses may also contain additional proteins, such as enzymes. The most obvious difference between members of viral families is their morphology, which is quite diverse. An interesting feature of viral complexity is that the complexity of the host does not correlate with the complexity of the virion. Some of the most complex virion structures are observed in bacteriophages, viruses that infect the simplest living organisms, i.e bacteria.

❖ Types of Nucleic Acid

Unlike nearly all living organisms that use DNA as their genetic material, viruses may use either DNA or RNA as theirs. The virus core contains the

genome or total genetic content of the virus. Viral genomes tend to be small, containing only those genes that encode proteins that the virus cannot get from the host cell. This genetic material may be single or double-stranded. It may also be linear or circular. While most viruses contain a single nucleic acid, others have genomes that have several, which are called segments.

In DNA viruses, the viral DNA directs the host cell's replication proteins to synthesize new copies of the viral genome and to transcribe and translate that genome into viral proteins. DNA viruses cause human diseases, such as chickenpox, hepatitis B, and some venereal diseases, like herpes and genital warts.

RNA viruses contain only RNA as their genetic material. To replicate their genomes in the host cell, the RNA viruses encode enzymes that can replicate RNA into DNA, which cannot be done by the host cell. These RNA polymerase enzymes are more likely to make copying errors than DNA polymerases, and therefore often make mistakes during transcription. For this reason, mutations in RNA viruses occur more frequently than in DNA viruses. This causes them to change and adapt more rapidly to their host. Human diseases caused by RNA viruses include hepatitis C, measles, and rabies.

❖ Morphology

Viruses come in many shapes and sizes, but these are consistent and distinct for each viral family. All virions have a nucleic acid genome covered by a protective layer of proteins, called a capsid. The capsid is made up of protein subunits called capsomeres. Some viral capsids are simple polyhedral "spheres," whereas others are quite complex in structure.

In general, the shapes of viruses are classified into four groups:

1. Filamentous - Filamentous viruses are long and cylindrical. Many plant viruses are filamentous, including TMV.

2. Isometric (or icosahedral) - Isometric viruses have shapes that are roughly spherical, such as poliovirus or herpes viruses.
3. Enveloped- Enveloped viruses have membranes surrounding capsids. Animal viruses, such as HIV, are frequently enveloped.
4. Head and tail- Head and tail viruses infect bacteria and have a head that is similar to icosahedral viruses and a tail shape like filamentous viruses.

Many viruses use some sort of glycoprotein to attach to their host cells via molecules on the cell called viral receptors (Figure 3). For these viruses, attachment is a requirement for later penetration of the cell membrane, so they can complete their replication inside the cell. The receptors that viruses

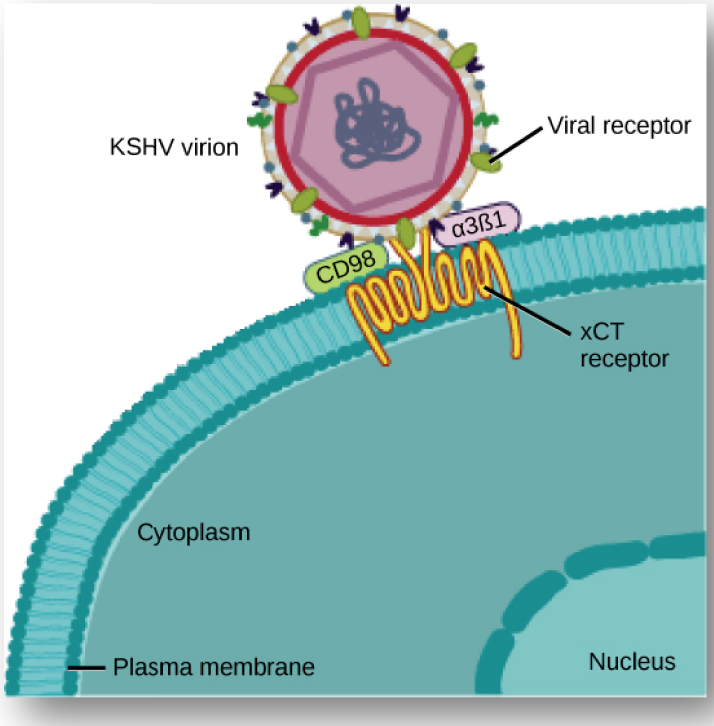

Figure 3: The KSHV virus binds the xCT receptor on the surface of human cells. xCT receptors protect cells against stress. Stressed cells express more xCT receptors than non-stressed cells. The KSHV virion causes cells to become stressed, thereby increasing expression of the receptor to which it binds.

use are molecules that are normally found on cell surfaces and they have their own physiological functions. Viruses have simply evolved to make use of these molecules for their own replication. For example, HIV uses the CD4 molecule on T lymphocytes as one of its receptors. CD4 is a type of molecule called a cell adhesion molecule, which functions to keep different types of immune cells in close proximity to each other during the generation of a T lymphocyte immune response.

Among the most complex virions known, the T4 bacteriophage, which infects the *Escherichia coli* bacterium, has a tail structure that the virus uses to attach to host cells and a head structure that houses its DNA.

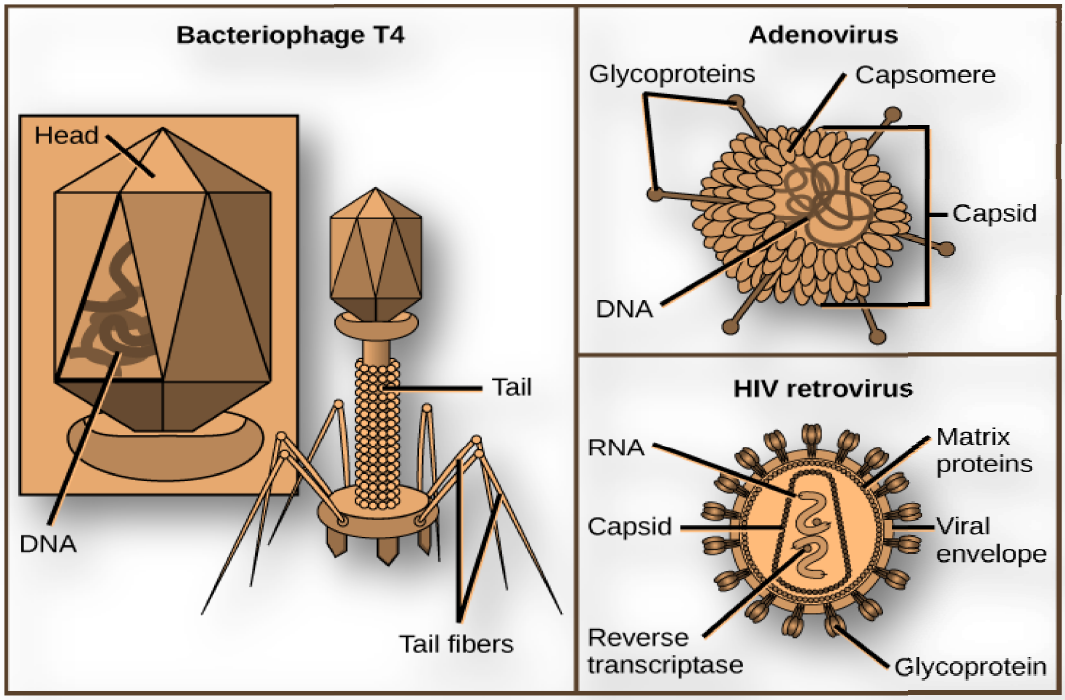

Figure 4: Viruses can be either complex in shape or relatively simple. This figure shows three relatively complex virions: the bacteriophage T4, with its DNA-containing head group and tail fibers that attach to host cells; adenovirus, which uses spikes from its capsid to bind to host cells; and HIV, which uses glycoproteins embedded in its envelope to bind to host cells. Notice that HIV has proteins called matrix proteins, internal to the envelope, which help stabilize virion shape.

Adenovirus, a non-enveloped animal virus that causes respiratory illnesses in humans, uses glycoprotein spikes protruding from its capsomeres to attach to host cells. Non-enveloped viruses also include those that cause polio (poliovirus), plantar warts (papillomavirus), and hepatitis A (hepatitis A virus). Enveloped virions like HIV, the causative agent in AIDS, consist of nucleic acid (RNA in the case of HIV) and capsid proteins surrounded by a phospholipid bilayer envelope and its associated proteins. Glycoproteins embedded in the viral envelope are used to attach to host cells. Other envelope proteins are the matrix proteins that stabilize the envelope and often play a role in the assembly of progeny virions. Chicken pox, influenza, and mumps are examples of diseases caused by viruses with envelopes. Because of the fragility of the envelope, non-enveloped viruses are more resistant to changes in temperature, pH, and some disinfectants than enveloped viruses.

Overall, the shape of the virion and the presence or absence of an envelope tell us little about what disease the virus may cause or what species it might infect, but they are still useful means to begin viral classification (Figure 4).

❖ Virus Classification

To understand the features shared among different groups of viruses, a classification scheme is necessary. As most viruses are not thought to have evolved from a common ancestor, however, the methods that scientists use to classify living things are not very useful. Biologists have used several classification systems in the past, based on the morphology and genetics of the different viruses. However, these earlier classification methods grouped viruses differently, based on which features of the virus they were using to classify them. The most commonly used classification method today is called the Baltimore Classification scheme and is based on how messenger RNA (mRNA) is generated in each particular type of virus.

Past Systems of Classification

Viruses are classified in several ways: by factors such as their core content (Table 1), the structure of their capsids, and whether they have an outer envelope. The type of genetic material (DNA or RNA) and its structure (single or double-stranded, linear or circular, and segmented or non-segmented) are used to classify the virus core structures.

Viruses can also be classified by the design of their capsids. Capsids are classified as naked icosahedral, enveloped icosahedral, enveloped helical, naked helical, and complex. The type of genetic material (DNA or RNA) and its structure (single or double-stranded, linear or circular, and segmented or non-segmented) are used to classify the virus core structures (Table 2).

Table 1: Virus Classification by Genome Structure and Core

Core Classifications	Examples
RNA	Rabies virus, retroviruses
DNA	Herpesviruses, smallpox virus
Single-stranded	Rabies virus, retroviruses
Double-stranded	Herpesviruses, smallpox virus
Linear	Rabies virus, retroviruses, herpesviruses, smallpox virus
Circular	Papillomaviruses, many bacteriophages
Non-segmented: genome consists of a single segment of genetic material	Parainfluenza viruses
Segmented: genome is divided into multiple segments	Influenza viruses

Table 2. Virus Classification by Capsid Structure

Capsid Classification	Examples
Naked icosahedral	Hepatitis A virus, polioviruses
Enveloped icosahedral	Epstein-Barr virus, herpes simplex virus, rubella virus, yellow fever virus, HIV-1
Enveloped helical	Influenza viruses, mumps virus, measles virus, rabies virus
Naked helical	Tobacco mosaic virus
Complex with many proteins; some have combinations of icosahedral and helical capsid structures	Herpesviruses, smallpox virus, hepatitis B virus, T4 bacteriophage

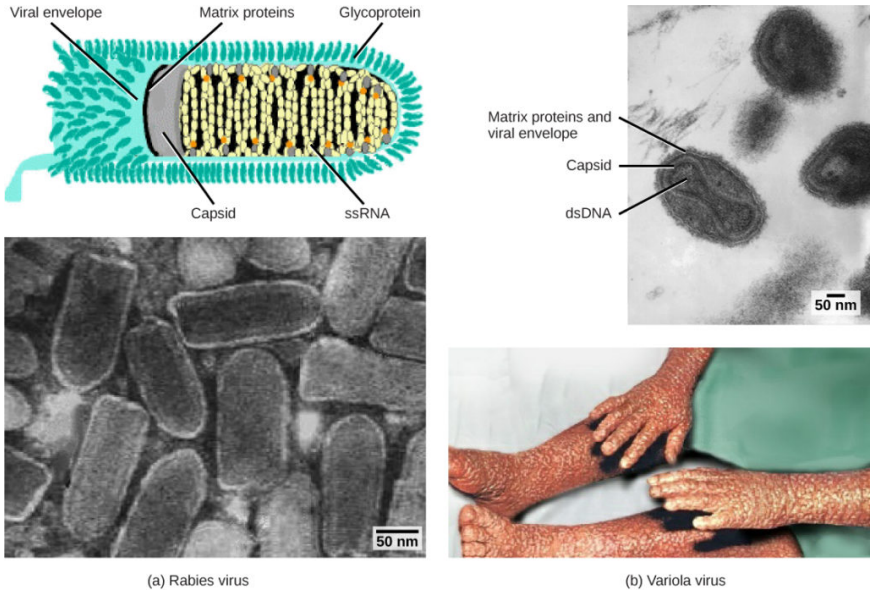

Figure 5. Viruses are classified based on their core genetic material and capsid design. (a) Rabies virus has a single-stranded RNA (ssRNA) core and an enveloped helical capsid, whereas (b) variola virus, the causative agent of smallpox, has a double-stranded DNA (dsDNA) core and a complex capsid.

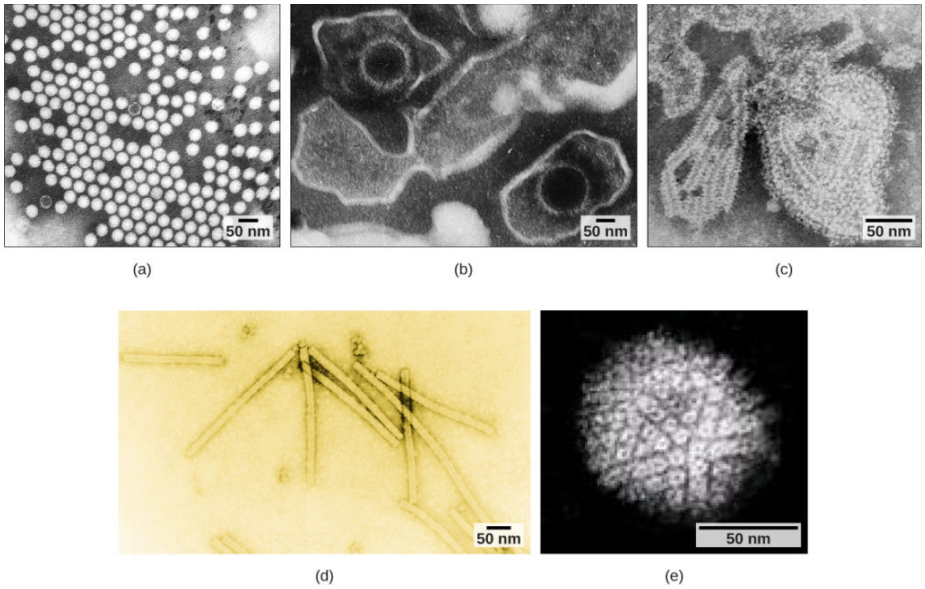

Figure 6: Transmission electron micrographs of various viruses show their structures. The capsid of the (a) polio virus is naked icosahedral; (b) the Epstein-Barr virus capsid is enveloped icosahedral; (c) the mumps virus capsid is an enveloped helix; (d) the tobacco mosaic virus capsid is naked helical; and (e) the herpesvirus capsid is complex.

❖ Baltimore Classification

The most commonly used system of virus classification was developed by Nobel Prize-winning biologist David Baltimore in the early 1970s. In addition to the differences in morphology and genetics mentioned above, the Baltimore classification scheme groups viruses according to how the mRNA is produced during the replicative cycle of the virus.

- **Group I** viruses contain double-stranded DNA (dsDNA) as their genome. Their mRNA is produced by transcription in much the same way as with cellular DNA.

- **Group II** viruses have single-stranded DNA (ssDNA) as their genome. They convert their single-stranded genomes into a dsDNA intermediate before transcription to mRNA can occur.

- **Group III** viruses use dsRNA as their genome. The strands separate, and one of them is used as a template for the generation of mRNA using the RNA-dependent RNA polymerase encoded by the virus.

- **Group IV** viruses have ssRNA as their genome with a positive polarity. Positive polarity means that the genomic RNA can serve directly as mRNA. Intermediates of dsRNA, called replicative intermediates, are made in the process of copying the genomic RNA. Multiple, full-length RNA strands of negative polarity (complimentary to the positive-stranded genomic RNA) are formed from these intermediates, which may then serve as templates for the production of RNA with positive polarity, including both full length genomic RNA and shorter viral mRNAs.

- **Group V** viruses contain ssRNA genomes with a negative polarity, meaning that their sequence is complementary to the mRNA. As with Group IV viruses, dsRNA intermediates are used to make copies of the genome and produce mRNA. In this case, the negative-stranded genome can be converted directly to mRNA. Additionally, full length positive RNA strands are made to serve as templates for the production of the negative-stranded genome.

- **Group VI** viruses have diploid (two copies) ssRNA genomes that must be converted, using the enzyme reverse transcriptase, to dsDNA; the dsDNA is then transported to the nucleus of the host cell and inserted into the host genome. Then, mRNA can be produced by transcription of the viral DNA that was integrated into the host genome.

- **Group VII** viruses have partial dsDNA genomes and make ssRNA intermediates that act as mRNA, but are also converted back into dsDNA genomes by reverse transcriptase, necessary for genome replication. The characteristics of each group in the Baltimore classification are summarized in Table 3 with examples of each group.

Table 3. Baltimore Classification

Group	Characteristics	Mode of mRNA Production	Example
I	Double-stranded DNA	mRNA is transcribed directly from the DNA template	Herpes simplex (herpesvirus)
II	Single-stranded DNA	DNA is converted to double-stranded form before RNA is transcribed	Canine parvovirus (parvovirus)
III	Double-stranded RNA	mRNA is transcribed from the RNA genome	Childhood gastroenteritis (rotavirus)
IV	Single stranded RNA (+)	Genome functions as mRNA	Common cold (pircornavirus)
V	Single stranded RNA (−)	mRNA is transcribed from the RNA genome	Rabies (rhabdovirus)
VI	Single stranded RNA viruses with reverse transcriptase	Reverse transcriptase makes DNA from the RNA genome; DNA is then incorporated in the host genome; mRNA is transcribed from the incorporated DNA	Human immunodeficiency virus (HIV)
VII	Double stranded DNA viruses with reverse transcriptase	The viral genome is double-stranded DNA, but viral DNA is replicated through an RNA intermediate; the RNA may serve directly as mRNA or as a template to make mRNA	Hepatitis B virus (hepadnavirus)

❖ Introduction to Virus Infections and Hosts

Viruses can be seen as obligate, intracellular parasites. A virus must attach to a living cell, be taken inside, manufacture its proteins and copy its genome, and find a way to escape the cell so that the virus can infect other cells. Viruses can infect only certain species of hosts and only certain cells within that host. Cells that a virus may use to replicate are called permissive. For most viruses, the molecular basis for this specificity is that a particular surface molecule known as the viral receptor must be found on the host cell surface for the virus to attach. Also, metabolic and host cell immune response differences seen in different cell types based on differential gene expression are a likely factor in which cell a virus may target for replication. The permissive cell must make the substances that the virus needs or the virus will not be able to replicate there.

Steps of Virus Infections

A virus must use cell processes to replicate. The viral replication cycle can produce dramatic biochemical and structural changes in the host cell, which may cause cell damage. These changes are called cytopathic (causing cell damage) effects, can change cell functions or even destroy the cell. Some infected cells, such as those infected by the common cold virus known as rhinovirus, die through lysis (bursting) or apoptosis (programmed cell death or "cell suicide"), releasing all progeny virions at once. The symptoms of viral diseases result from the immune response to the virus, which attempts to control and eliminate the virus from the body, and from cell damage caused by the virus.

Many animal viruses, such as HIV (human immunodeficiency virus), leave the infected cells of the immune system by a process known as budding, where virions leave the cell individually. During the budding process, the cell does not undergo lysis and is not immediately killed. However, the damage to the

cells that the virus infects may make it impossible for the cells to function normally, even though the cells remain alive for a period of time. Most productive viral infections follow similar steps in the virus replication cycle: attachment, penetration, uncoating, replication, assembly, and release. In Figure 7, the host cell is destroyed at the end of the replication cycle, it is important to remember that this doesn't always happen; sometimes the host cell lives on and continues to replicate the virus.

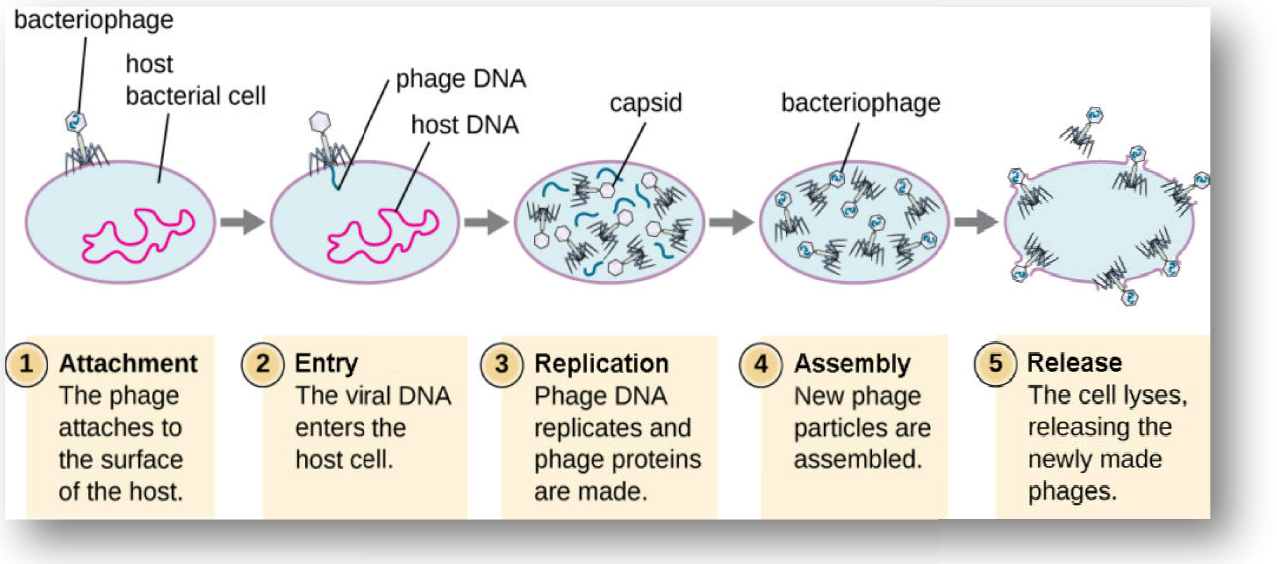

Figure 7. A bacteriophage replicates and lyses (bursts) the host cell

Attachment

A virus attaches to a specific receptor site on the host cell membrane through attachment proteins in the capsid or via glycoproteins embedded in the viral envelope. The specificity of this interaction determines the host and the cells within the host that can be infected by a particular virus. This can be illustrated by thinking of several keys and several locks, where each key will fit only in one specific lock.

Entry (Penetration and Uncoating)

The nucleic acid of bacteriophages enters the host cell naked, leaving the capsid outside the cell. Plant and animal viruses can enter through endocytosis, in which the cell membrane surrounds and engulfs the entire virus. Some enveloped viruses enter the cell when the viral envelope fuses directly with the cell membrane. Once inside the cell, the viral capsid is degraded, and the viral nucleic acid is released, which then becomes available for replication and transcription.

Replication and Assembly

The replication mechanism depends on the viral genome. DNA viruses usually use host cell proteins and enzymes to make additional DNA that is transcribed to messenger RNA (mRNA), which is then used to direct protein synthesis. RNA viruses usually use the RNA core as a template for synthesis of viral genomic RNA and mRNA. The viral mRNA directs the host cell to synthesize viral enzymes and capsid proteins, and assemble new virions. Of course, there are exceptions to this pattern. If a host cell does not provide the enzymes necessary for viral replication, viral genes supply the information to direct synthesis of the missing proteins. Retroviruses, such as HIV, have an RNA genome that must be reverse transcribed into DNA, which then is incorporated into the host cell genome. They are within group VI of the Baltimore classification scheme. To convert RNA into DNA, retroviruses must contain genes that encode the virus-specific enzyme reverse transcriptase that transcribes an RNA template to DNA. Reverse transcription never occurs in uninfected host cells while the needed enzyme reverse transcriptase is only derived from the expression of viral genes within the infected host cells.

The fact that HIV produces some of its own enzymes not found in the host has allowed researchers to develop drugs that inhibit these enzymes. These drugs, including the reverse transcriptase inhibitor AZT, inhibit HIV replication by reducing the activity of the enzyme without affecting the host's metabolism.

This approach has led to the development of a variety of drugs used to treat HIV and has been effective at reducing the number of infectious virions (copies of viral RNA) in the blood to non-detectable levels in many HIV-infected individuals.

- **Egress (Release)**

The last stage of viral replication is the release of the new virions produced in the host organism, where they are able to infect adjacent cells and repeat the replication cycle. As we know, some viruses are released when the host cell dies, and other viruses can leave infected cells by budding through the membrane without directly killing the cell.

❖ Steps of Virus Infections

The flu virus is probably the first thing that comes to your mind when you hear the word virus. We've all probably had the flu at one point or another in our lives. So just how does the flu invade our bodies? As we've seen, viruses go through as specific cycle as they replicate—and they target and infect cells in order to do so. Let's look at the process of a flu virus replicating. Each of the steps in viral replication has a name:

- Step 1: Attachment: The virus attaches itself to the target cell.
- Step 2: Penetration: The virus is brought into the target cell.
- Step 3: Uncoating and Replication: The enveloped virus loses its envelope, and viral RNA is released into the nucleus, where it is replicated.
- Step 4: Assembly: Viral proteins are assembled.
- Step 5: Egress (Release): New viral particles are released.

In the case of the flu, the target cell is not killed; however, other viruses, like the T4 bacteriophage, cause cell death to release the newly created copies of itself.

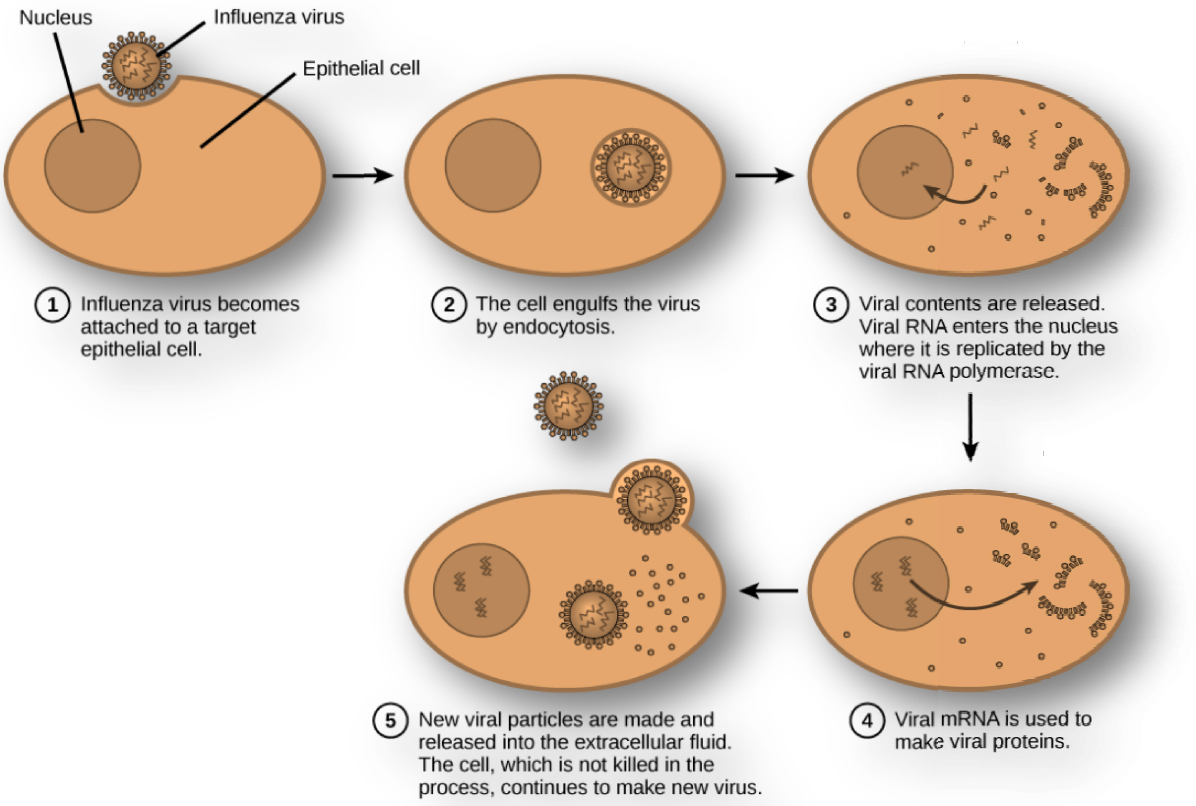

Figure 8. Steps in Viral Replication (Example: Influenza)

As mentioned earlier, some viruses kill the cells they infect. The influenza virus is packaged in a viral envelope that fuses with the plasma membrane. This way, the virus can exit the host cell without killing it. What advantage does the virus gain by keeping the host cell alive? The host cell can continue to make new virus particles.

❖ Different Hosts and their Viruses

Viruses are often very specific as to which hosts and which cells within the host they will infect. This feature of a virus makes it specific to one or a few species of life on Earth. On the other hand, so many different types of viruses exist on Earth that nearly every living organism has its own set of viruses that tries to infect its cells. Even the smallest and simplest of cells, prokaryotic bacteria, may be attacked by specific types of viruses. Viruses that target bacteria are known as bacteriophages.

When a temperate bacteriophage infects a bacterial cell, it replicates by means of a lysogenic cycle (Figure 9), and the viral genome is incorporated into the genome of the host cell. When the phage DNA is incorporated into the host cell genome, it is called a prophage. An example of a lysogenic bacteriophage is the λ (lambda) virus, which infects the *E. coli* bacterium. Viruses that infect plant or animal cells may also undergo infections where they are not producing

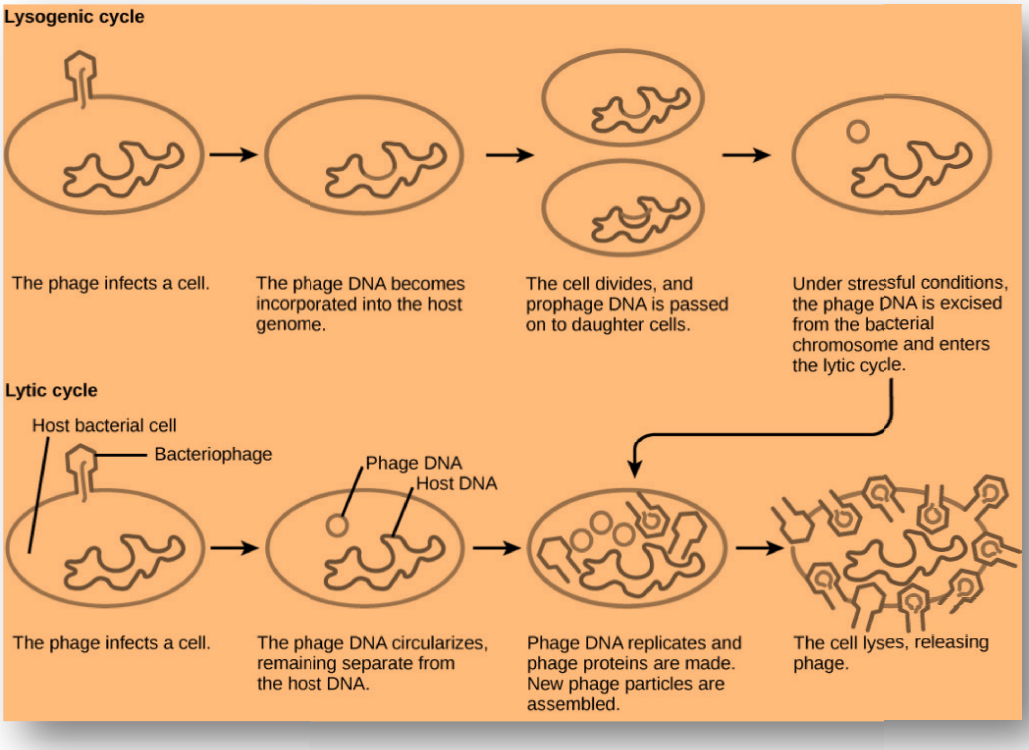

Figure 9: A temperate bacteriophage has both lytic and lysogenic cycles. In the lytic cycle, the phage replicates and lyses the host cell. In the lysogenic cycle, phage DNA is incorporated into the host genome, where it is passed on to subsequent generations. Environmental stressors such as starvation or exposure to toxic chemicals may cause the prophage to excise and enter the lytic cycle.

virions for long periods. An example is the animal herpesviruses, including herpes simplex viruses, the cause of oral and genital herpes in humans. In a process called latency, these viruses can exist in nervous tissue for long periods of time without producing new virions, only to leave latency periodically and cause lesions in the skin where the virus replicates. Even

though there are similarities between lysogeny and latency, the term lysogenic cycle is usually reserved to describe bacteriophages.

❖ Animal Viruses

Animal viruses, unlike the viruses of plants and bacteria, do not have to penetrate a cell wall to gain access to the host cell. Non-enveloped or "naked" animal viruses may enter cells in two different ways. As a protein in the viral capsid binds to its receptor on the host cell, the virus may be taken inside the cell via a vesicle during the normal cell process of receptor-mediated endocytosis. An alternative method of cell penetration used by non-enveloped viruses is for capsid proteins to undergo shape changes after binding to the receptor, creating channels in the host cell membrane. The viral genome is then "injected" into the host cell through these channels in a manner analogous to that used by many bacteriophages. Enveloped viruses also have two ways of entering cells after binding to their receptors: receptor-mediated endocytosis, or fusion. Many enveloped viruses enter the cell by receptor-mediated endocytosis in a fashion similar to some non-enveloped viruses. On the other hand, fusion only occurs with enveloped virions. These viruses, which include HIV among others, use special fusion proteins in their envelopes to cause the envelope to fuse with the plasma membrane of the cell, thus releasing the genome and capsid of the virus into the cell cytoplasm.

After making their proteins and copying their genomes, animal viruses complete the assembly of new virions and exit the cell. Considering the example of HIV, enveloped animal viruses may bud from the cell membrane as they assemble themselves, taking a piece of the cell's plasma membrane in the process. On the other hand, non-enveloped viral progeny, such as rhinoviruses, accumulate in infected cells until there is a signal for lysis or apoptosis, and all virions are released together.

Animal viruses are associated with a variety of human diseases. Some of them follow the classic pattern of acute disease, where symptoms get increasingly worse for a short period followed by the elimination of the virus from the body by the immune system and eventual recovery from the infection. Examples of acute viral diseases are the common cold and influenza. Other viruses cause long-term chronic infections, such as the virus causing hepatitis C, whereas others, like herpes simplex virus, only cause intermittent symptoms. Still other viruses, such as human herpes viruses 6 and 7, which in some cases can cause the minor childhood disease roseola, often successfully cause productive infections without causing any symptoms at all in the host, and thus we say these patients have an asymptomatic infection.

In hepatitis C infections, the virus grows and reproduces in liver cells, causing low levels of liver damage. The damage is so low that infected individuals are often unaware that they are infected, and many infections are detected only by routine blood work on patients with risk factors such as intravenous drug use. On the other hand, since many of the symptoms of viral diseases are caused by immune responses, a lack of symptoms is an indication of a weak immune response to the virus. This allows for the virus to escape elimination by the immune system and persist in individuals for years, all the while producing low levels of progeny virions in what is known as a chronic viral disease. Chronic infection of the liver by this virus leads to a much greater chance of developing liver cancer, sometimes as much as 30 years after the initial infection.

As already discussed, herpes simplex virus can remain in a state of latency in nervous tissue for months, even years. As the virus “hides” in the tissue and makes few if any viral proteins, there is nothing for the immune response to act against, and immunity to the virus slowly declines. Under certain conditions, including various types of physical and psychological stress, the latent herpes simplex virus may be reactivated and undergo a lytic replication cycle in the skin, causing the lesions associated with the disease. Once virions

are produced in the skin and viral proteins are synthesized, the immune response is again stimulated and resolves the skin lesions in a few days by destroying viruses in the skin. As a result of this type of replicative cycle, appearances of cold sores and genital herpes outbreaks only occur intermittently, even though the viruses remain in the nervous tissue for life. Latent infections are common with other herpes viruses as well, including the varicella-zoster virus that causes chickenpox. After having a chickenpox infection in childhood, the varicella-zoster virus can remain latent for many years and reactivate in adults to cause the painful condition known as "shingles" (Figure 10).

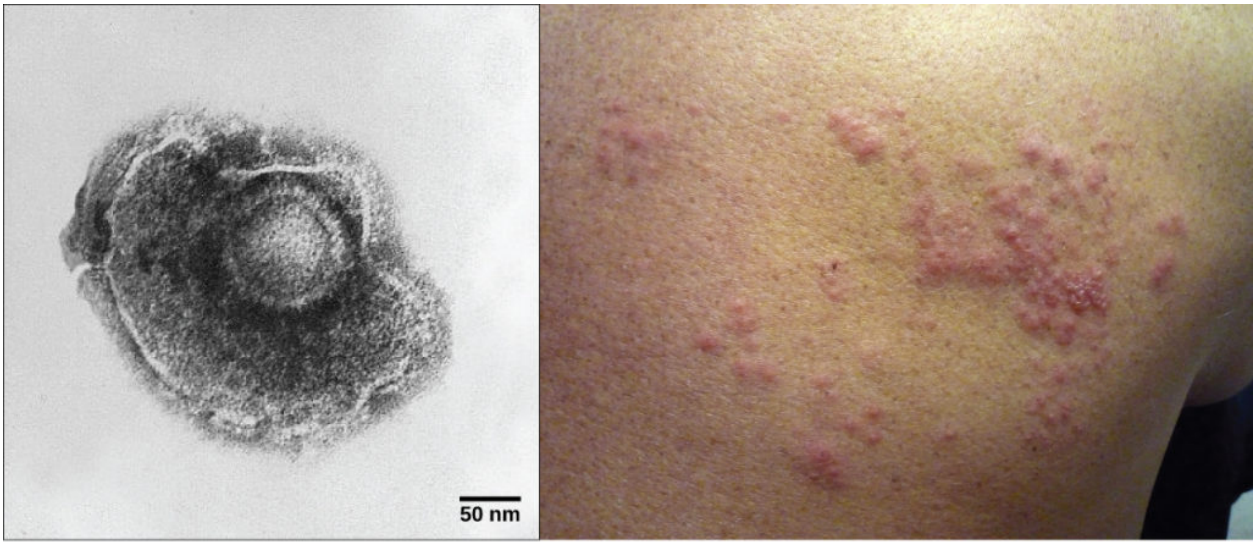

Figure 10: (a) Varicella-zoster, the virus that causes chickenpox, has an enveloped icosahedral capsid visible in this transmission electron micrograph. Its double-stranded DNA genome becomes incorporated in the host DNA and can reactivate after latency in the form of (b) shingles, often exhibiting a rash.

Some animal infecting viruses, including the hepatitis C virus discussed above, are known as oncogenic viruses. They have the ability to cause cancer. These viruses interfere with the normal regulation of the host cell cycle either by introducing genes that stimulate unregulated cell growth (oncogenes) or by interfering with the expression of genes that inhibit cell growth. Oncogenic viruses can be either DNA or RNA viruses. Cancers known to be associated with viral infections include cervical cancer caused by human papillomavirus

(HPV), liver cancer caused by hepatitis B virus, T-cell leukemia, and several types of lymphoma. HPV, or human papillomavirus (Figure 11), has a naked icosahedral capsid visible in this transmission electron micrograph and a double-stranded DNA genome that is incorporated into the host DNA. The virus, which is sexually transmitted, is oncogenic and can lead to cervical cancer.

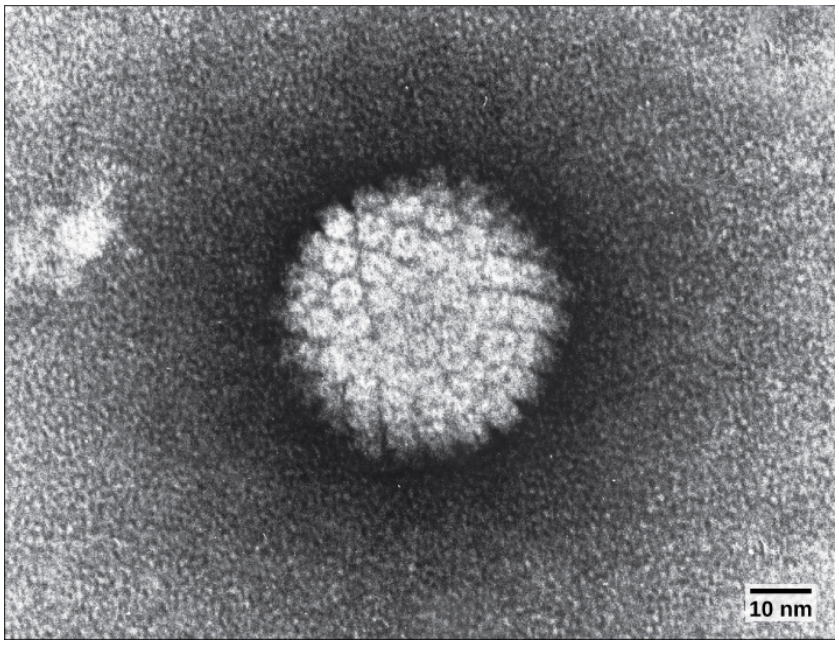

Figure 11: HPV, or human papillomavirus

❖ Plant Viruses

Plant viruses, like other viruses, contain a core of either DNA or RNA. As plants have a cell wall to protect their cells, these viruses do not use receptor-mediated endocytosis to enter host cells as it is seen with animal viruses. For many plant viruses to be transferred from plant to plant, damage to some of the plants' cells must occur to allow the virus to enter a new host. This damage is often caused by weather, insects, animals, fire, or human activities like farming or landscaping. Additionally, plant offspring may inherit viral diseases from parent plants. Plant viruses can be transmitted by a variety of vectors, through contact with an infected plant's sap, by living organisms such as insects and nematodes, and through pollen. When plant viruses are

transferred between different plants, this is known as horizontal transmission, and when they are inherited from a parent, this is called vertical transmission. Symptoms of viral diseases vary according to the virus and its host (shown in the table below). One common symptom is hyperplasia, the abnormal proliferation of cells that causes the appearance of plant tumors known as galls. Other viruses induce hypoplasia, or decreased cell growth, in the leaves of plants, causing thin, yellow areas to appear. Still other viruses affect the plant by directly killing plant cells, a process known as cell necrosis. Other symptoms of plant viruses include malformed leaves, black streaks on the stems of the plants, altered growth of stems, leaves, or fruits, and ring spots, which are circular or linear areas of discoloration found in a leaf.

Table 1. Some Common Symptoms of Plant Viral Diseases

Symptom	Appears as
Hyperplasia	Galls (tumors)
Hypoplasia	Thinned, yellow splotches on leaves
Cell necrosis	Dead, blackened stems, leaves, or fruit
Abnormal growth patterns	Malformed stems, leaves, or fruit
Discoloration	Yellow, red, or black lines, or rings in stems, leaves, or fruit

Plant viruses can seriously disrupt crop growth and development, significantly affecting our food supply. They are responsible for poor crop quality and quantity globally, and can bring about huge economic losses annually. Others viruses may damage plants used in landscaping. Some viruses that infect

agricultural food plants include the name of the plant they infect, such as tomato spotted wilt virus, bean common mosaic virus, and cucumber mosaic virus. In plants used for landscaping, two of the most common viruses are peony ring spot and rose mosaic virus. There are far too many plant viruses to discuss each in detail, but symptoms of bean common mosaic virus result in lowered bean production and stunted, unproductive plants. In the ornamental rose, the rose mosaic disease causes wavy yellow lines and colored splotches on the leaves of the plant.

❖ Introduction to Prevention and Treatment of Viral Infections

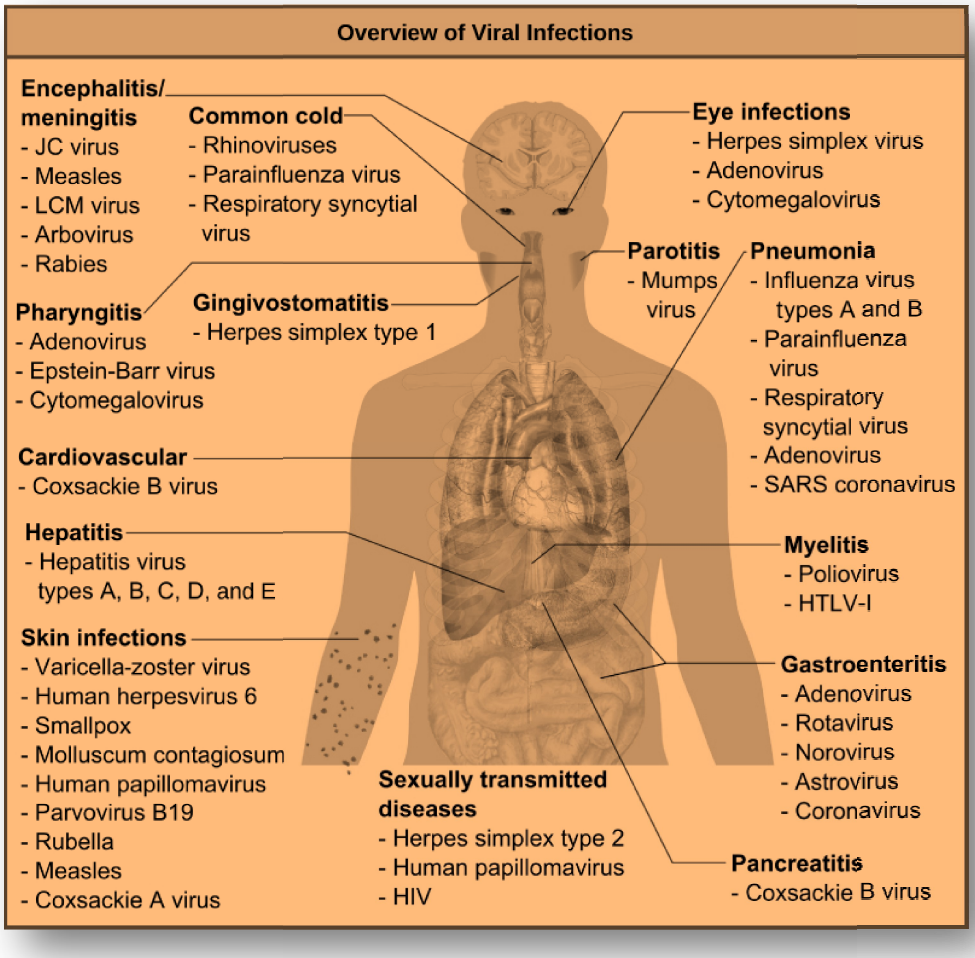

Figure 12: Viruses can cause dozens of ailments in humans, ranging from mild illnesses to serious diseases.

Viruses cause a variety of diseases in animals, including humans, ranging from the common cold to potentially fatal illnesses like meningitis. These diseases can be treated by antiviral drugs or by vaccines, but some viruses, such as HIV, are capable of both avoiding the immune response and mutating to become resistant to antiviral drugs.

- **Vaccines for Prevention**

While we do have limited numbers of effective antiviral drugs, such as those used to treat HIV and influenza, the primary method of controlling viral disease is by vaccination, which is intended to prevent outbreaks by building immunity to a virus or virus family. Vaccines may be prepared using live viruses, killed viruses, or molecular subunits of the virus. The killed viral vaccines and subunit viruses are both incapable of causing disease. Live viral vaccines are designed in the laboratory to cause few symptoms in recipients while giving them protective immunity against future infections. Polio was one disease that represented a milestone in the use of vaccines. Mass immunization campaigns in the 1950s (killed vaccine) and 1960s (live vaccine) significantly reduced the incidence of the disease, which caused muscle paralysis in children and generated a great amount of fear in the general population when regional epidemics occurred. The success of the polio vaccine paved the way for the routine dispensation of childhood vaccines against measles, mumps, rubella, chickenpox, and other diseases.

The danger of using live vaccines, which are usually more effective than killed vaccines, is the low but significant danger that these viruses will revert to their disease-causing form by back mutations. Live vaccines are usually made by attenuating (weakening) the “wild-type” (disease-causing) virus by growing it in the laboratory in tissues or at temperatures different from what the virus is accustomed to in the host. Adaptations to these new cells or temperatures induce mutations in the genomes of the virus, allowing it to grow better in the

laboratory while inhibiting its ability to cause disease when reintroduced into conditions found in the host. This attenuated virus thus still cause infection, but they do not grow very well, allowing the immune response to develop in time to prevent major disease. Back mutations occur when the vaccine undergoes mutations in the host such that it readapts to the host and can again cause disease, which can then be spread to other humans in an epidemic.

Some vaccines are in continuous development because certain viruses, such as influenza and HIV, have a high mutation rate compared to other viruses and normal host cells. With influenza, mutations in the surface molecules of the virus help the organism evade the protective immunity that may have been obtained in a previous influenza season, making it necessary for individuals to get vaccinated every year. Other viruses, such as those that cause the childhood diseases measles, mumps, and rubella, mutate so infrequently that the same vaccine is used year after year.

- **Vaccines and Anti-Viral Drugs for Treatment**

In some cases, vaccines can be used to treat an active viral infection. The concept behind this is that by giving the vaccine, immunity is boosted without adding more disease-causing virus. In the case of rabies, a fatal neurological disease transmitted via the saliva of rabies virus-infected animals, the progression of the disease from the time of the animal bite to the time it enters the central nervous system may be 2 weeks or longer. This is enough time to vaccinate an individual who suspects that they have been bitten by a rabid animal, and their boosted immune response is sufficient to prevent the virus from entering nervous tissue. Thus, the potentially fatal neurological consequences of the disease are averted, and the individual only has to recover from the infected bite. This approach is also being used for the treatment of Ebola, one of the fastest and most deadly viruses on earth. Transmitted by bats and great apes, this disease can cause death in 70–90

percent of infected humans within 2 weeks. Using newly developed vaccines that boost the immune response in this way, there is hope that affected individuals will be better able to control the virus, potentially saving a greater percentage of infected persons from a rapid and very painful death.

Another way of treating viral infections is the use of antiviral drugs. These drugs often have limited success in curing viral disease, but in many cases, they have been used to control and reduce symptoms for a wide variety of viral diseases. For most viruses, these drugs can inhibit the virus by blocking the actions of one or more of its proteins. It is important that the targeted proteins be encoded by viral genes and that these molecules are not present in a healthy host cell. In this way, viral growth is inhibited without damaging the host. There are large numbers of antiviral drugs available to treat infections, some specific for a particular virus and others that can affect multiple viruses.

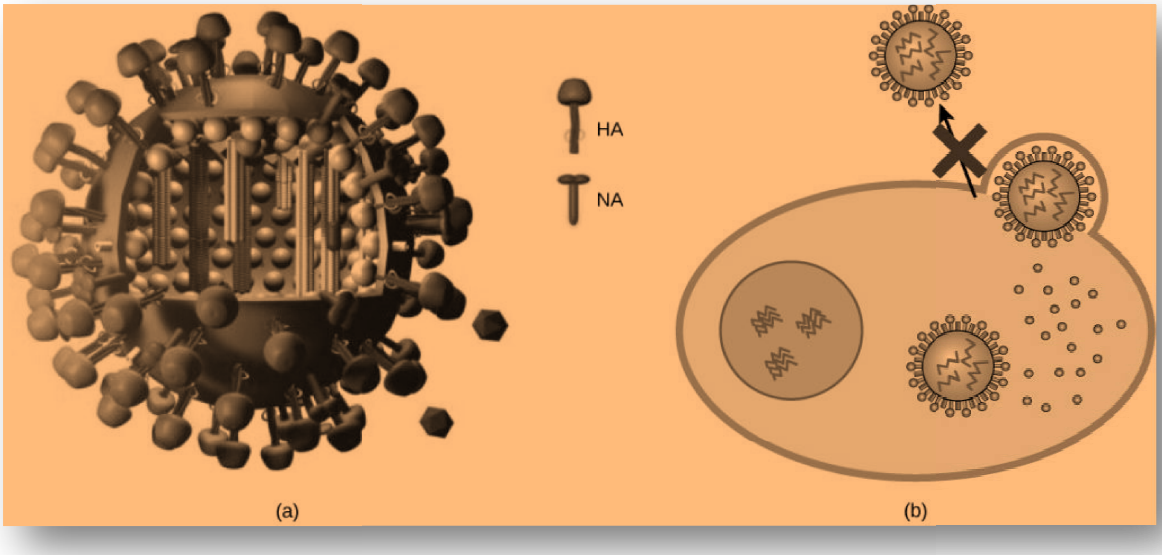

Figure 13: (a) Tamiflu inhibits a viral enzyme called neuraminidase (NA) found in the influenza viral envelope. (b) Neuraminidase cleaves the connection between viral hemagglutinin (HA), also found in the viral envelope, and glycoproteins on the host cell surface. Inhibition of neuraminidase prevents the virus from detaching from the host cell, thereby blocking further infection.

Anti-viral drugs have been developed to treat genital herpes (herpes simplex II) and influenza. For genital herpes, drugs such as acyclovir can reduce the number and duration of episodes of active viral disease, during which patients

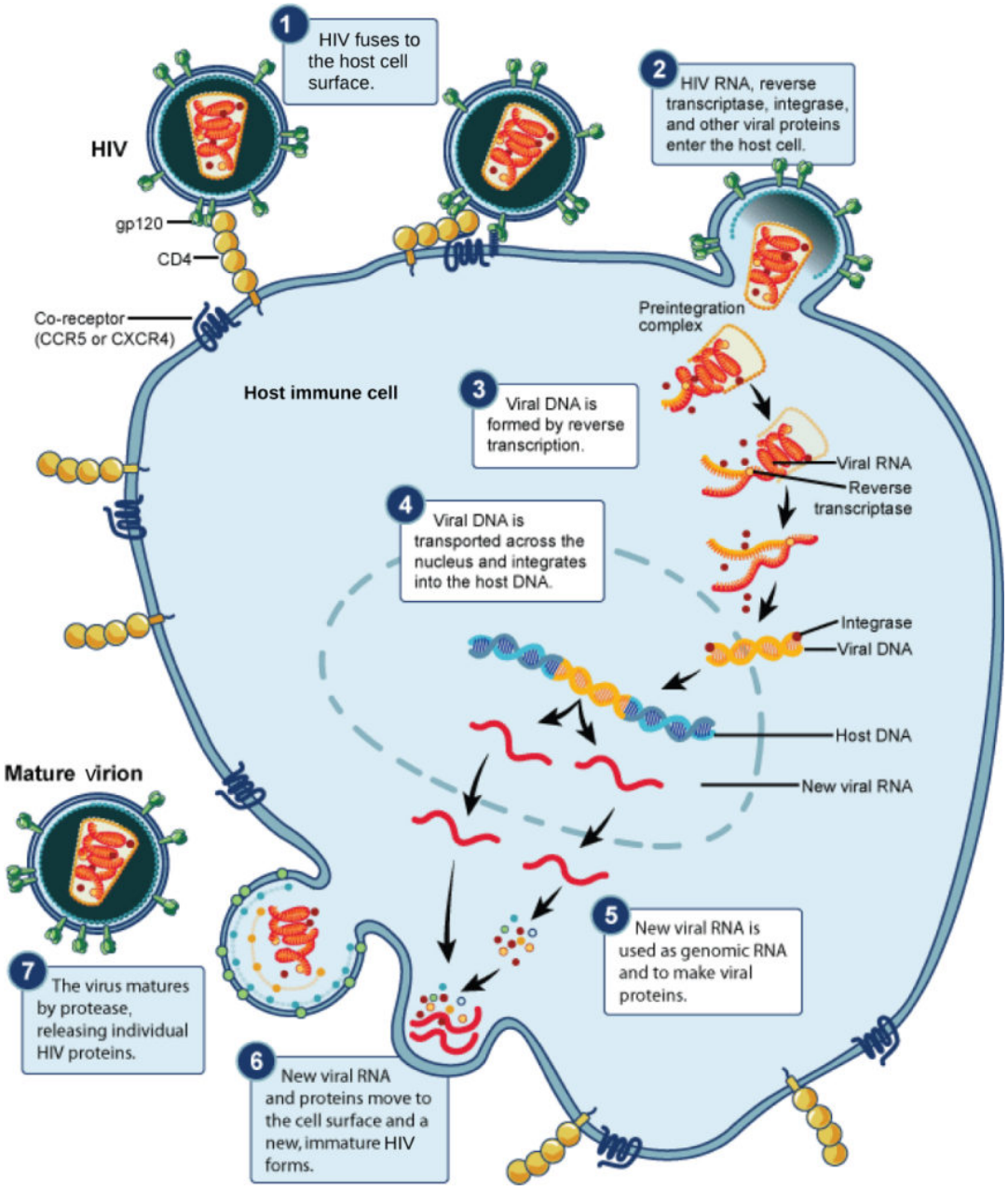

Figure 14: HIV, an enveloped, icosahedral virus, attaches to the CD4 receptor of an immune cell and fuses with the cell membrane. Viral contents are released into the cell, where viral enzymes convert the single-stranded RNA genome into DNA and incorporate it into the host genome.

develop viral lesions in their skin cells. As the virus remains latent in nervous tissue of the body for life, this drug is not curative but can make the symptoms of the disease more manageable. For influenza, drugs like Tamiflu (oseltamivir) (Figure 13) can reduce the duration of "flu" symptoms by 1 or 2 days, but the drug does not prevent symptoms entirely. Tamiflu works by inhibiting an enzyme (viral neuraminidase) that allows new virions to leave their infected cells. Thus, Tamiflu inhibits the spread of virus from infected to uninfected cells. Other antiviral drugs, such as Ribavirin, have been used to treat a variety of viral infections, although its mechanism of action against certain viruses remains unclear.

By far, the most successful use of antiviral drugs has been in the treatment of the retrovirus HIV, which causes a disease that, if untreated, is usually fatal within 10–12 years after infection. Anti-HIV drugs have been able to control viral replication to the point that individuals receiving these drugs survive for a significantly longer time than the untreated. Anti-HIV drugs inhibit viral replication at many different phases of the HIV replicative cycle (Figure 14). Drugs have been developed that inhibit the fusion of the HIV viral envelope with the plasma membrane of the host cell (fusion inhibitors), the conversion of its RNA genome into double-stranded DNA (reverse transcriptase inhibitors), the integration of the viral DNA into the host genome (integrase inhibitors), and the processing of viral proteins (protease inhibitors).

When any of these drugs are used individually, the high mutation rate of the virus allows it to easily and rapidly develop resistance to the drug, limiting the drug's effectiveness. The breakthrough in the treatment of HIV was the development of HAART, highly active anti-retroviral therapy, which involves a mixture of different drugs, sometimes called a drug "cocktail." By attacking the virus at different stages of its replicative cycle, it is much more difficult for the virus to develop resistance to multiple drugs at the same time. Still, even with the use of combination HAART therapy, there is concern that, over time, the virus will develop resistance to this therapy. Thus, new anti-HIV drugs are

constantly being developed with the hope of continuing the battle against this highly fatal virus.

❖ Applied Virology

The study of viruses has led to the development of a variety of new ways to treat non-viral diseases. Viruses have been used in gene therapy. Gene therapy is used to treat genetic diseases such as severe combined immunodeficiency (SCID), a heritable, recessive disease in which children are born with severely compromised immune systems. One common type of SCID is due to the lack of an enzyme, adenosine deaminase (ADA), which breaks down purine bases. To treat this disease by gene therapy, bone marrow cells are taken from a SCID patient and the ADA gene is inserted. This is where viruses come in, and their use relies on their ability to penetrate living cells and bring genes in with them. Viruses such as adenovirus, an upper respiratory human virus, are modified by the addition of the ADA gene, and the virus then transports this gene into the cell. The modified cells, now capable of making ADA, are then given back to the patients in the hope of curing them. Gene therapy using viruses as carrier of genes (viral vectors), although still experimental, holds promise for the treatment of many genetic diseases. Still, many technological problems need to be solved for this approach to be a viable method for treating genetic disease.

Another medical use for viruses relies on their specificity and ability to kill the cells they infect. Oncolytic viruses are engineered in the laboratory specifically to attack and kill cancer cells. A genetically modified adenovirus known as H101 has been used since 2005 in clinical trials in China to treat head and neck cancers. The results have been promising, with a greater short-term response rate to the combination of chemotherapy and viral therapy than to chemotherapy treatment alone. This ongoing research may herald the beginning of a new age of cancer therapy, where viruses are engineered to find

and specifically kill cancer cells, regardless of where in the body they may have spread.

A third use of viruses in medicine relies on their specificity and involves using bacteriophages in the treatment of bacterial infections. Bacterial diseases have been treated with antibiotics since the 1940s. Therefore, over time, many bacteria have developed resistance to antibiotics. A good example is methicillin-resistant *Staphylococcus aureus* (MRSA, pronounced "mersa"), an infection commonly acquired in hospitals. This bacterium is resistant to a variety of antibiotics, making it difficult to treat. The use of bacteriophages specific for such bacteria would bypass their resistance to antibiotics and specifically kill them. Although phage therapy is in use in the Republic of Georgia to treat antibiotic-resistant bacteria, its use to treat human diseases has not been approved in most countries. However, the safety of the treatment was confirmed in the United States when the U.S. Food and Drug Administration approved spraying meats with bacteriophages to destroy the food pathogen *Listeria.* As more and more antibiotic-resistant strains of bacteria evolve, the use of bacteriophages might be a potential solution to the problem, and the development of phage therapy is of much interest to researchers worldwide.

❖ Prions and Viroids

Prions

Prions are proteinaceous, infectious particle, smaller than viruses that contain no nucleic acids (neither DNA nor RNA). Historically, the idea of an infectious agent that did not use nucleic acids was considered impossible, but pioneering work by Nobel Prize-winning biologist Stanley Prusiner has convinced the majority of biologists that such agents do indeed exist.

Fatal neurodegenerative diseases, such as kuru in humans and bovine spongiform encephalopathy (BSE) in cattle (commonly known as "mad cow

disease"), were shown to be transmitted by prions. The disease was spread by the consumption of meat, nervous tissue, or internal organs between members of the same species. Kuru, native to humans in Papua New Guinea, was spread from human to human via ritualistic cannibalism. BSE, originally detected in the United Kingdom, was spread between cattle by the practice of including cattle nervous tissue in feed for other cattle. Individuals with kuru and BSE show symptoms of loss of motor control and unusual behaviors, such as uncontrolled bursts of laughter with kuru, followed by death. Kuru was controlled by inducing the population to abandon its ritualistic cannibalism.

On the other hand, BSE was initially thought to only affect cattle. Cattle dying of the disease were shown to have developed lesions or "holes" in the brain, causing the brain tissue to resemble a sponge. Later on in the outbreak,

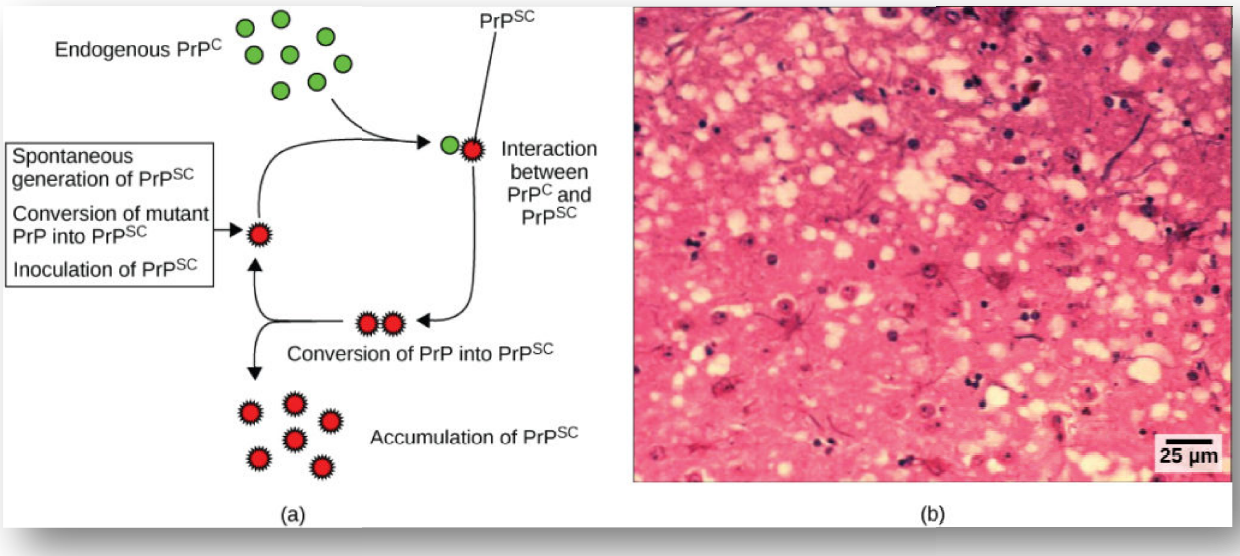

Figure 15: (PrPsc) when it encounters this variant form of the protein. PrPsc may arise spontaneously in brain tissue, especially if a mutant form of the protein is present, or it may occur via the spread of misfolded prions consumed in food into brain tissue. (b) This prion-infected brain tissue, visualized using light microscopy, shows the vacuoles that give it a spongy texture, typical of transmissible spongiform encephalopathies.

however, it was shown that a similar encephalopathy in humans known as variant Creutzfeldt-Jakob disease (CJD) could be acquired from eating beef from animals with BSE, sparking bans by various countries on the importation of British beef and causing considerable economic damage to the British beef industry (Figure 15). BSE still exists in various areas, and although a rare disease, CJD is difficult to treat. The disease can be spread from human to human by blood, so many countries have banned blood donation from regions associated with BSE.

The cause of spongiform encephalopathies, such as kuru and BSE, is an infectious structural variant of a normal cellular protein called PrP (prion protein). It is this variant that constitutes the prion particle. PrP exists in two forms, PrP^{c}, the normal form of the protein, and PrP^{sc}, the infectious form. Once introduced into the body, the PrP^{sc} contained within the prion binds to PrP^{c} and converts it to PrP^{sc}. This leads to an exponential increase of the PrP^{sc} protein, which aggregates. PrP^{sc} is folded abnormally, and the resulting conformation (shape) is directly responsible for the lesions seen in the brains of infected cattle. Thus, although not fully accepted among scientists, the prion seems likely to be an entirely new form of infectious agent; the first one found whose transmission is not reliant upon genes made of DNA or RNA.

❖ Viroids

Viroids are plant pathogens, small, single-stranded, circular RNA particles that are much simpler than a virus. They do not have a capsid or outer envelope, but like viruses can reproduce only within a host cell. Viroids do not, however, manufacture any proteins, and they only produce a single, specific RNA molecule. Human diseases caused by viroids have yet to be identified. Viroids are known to infect plants and are responsible for crop failures and the loss of millions of dollars in agricultural revenue each year. Some of the plants they infect include potatoes, cucumbers, tomatoes, chrysanthemums, avocados, and coconut palms. For example, the potato

spindle tuber viroid (PSTVd), which typically spreads when infected knives cut healthy potatoes in preparation for planting, can affect potatoes and tomatoes. The symptoms of PSTVd can be seen in Figure 16.

Figure 16: These potatoes have been infected by the potato spindle tuber viroid.

❖ Virusoids

A second type of pathogenic RNA that can infect commercially important agricultural crops are the virusoids, which are subviral particles best described as non–self-replicating ssRNAs. RNA replication of virusoids is similar to that of viroids but, unlike viroids, virusoids require that the cell also be infected with a specific "helper" virus. There are currently only five described types of virusoids and their associated helper viruses. The helper viruses are all from the family of Sobemoviruses. An example of a helper virus is the subterranean clover mottle virus, which has an associated virusoid packaged inside the viral capsid. Once the helper virus enters the host cell, the virusoids are released and can be found free in plant cell cytoplasm, where they possess ribozyme activity. The helper virus undergoes typical viral replication independent of the activity of the virusoid. The virusoid genomes

are small, only 220 to 388 nucleotides long. A virusoid genome does not code for any proteins, but instead serves only to replicate virusoid RNA.

Virusoids belong to a larger group of infectious agents called satellite RNAs, which are similar pathogenic RNAs found in animals. Unlike the plant virusoids, satellite RNAs may encode for proteins; however, like plant virusoids, satellite RNAs must coinfect with a helper virus to replicate. One satellite RNA that infects humans and that has been described by some scientists as a virusoid is the hepatitis delta virus (HDV), which is also called hepatitis delta virusoid. Much larger than a plant virusoid, HDV has a circular, ssRNA genome of 1,700 nucleotides and can direct the biosynthesis of HDV-associated proteins. The HDV helper virus is the hepatitis B virus (HBV). Coinfection with HBV and HDV results in more severe pathological changes in the liver during infection, which is how HDV was first discovered.

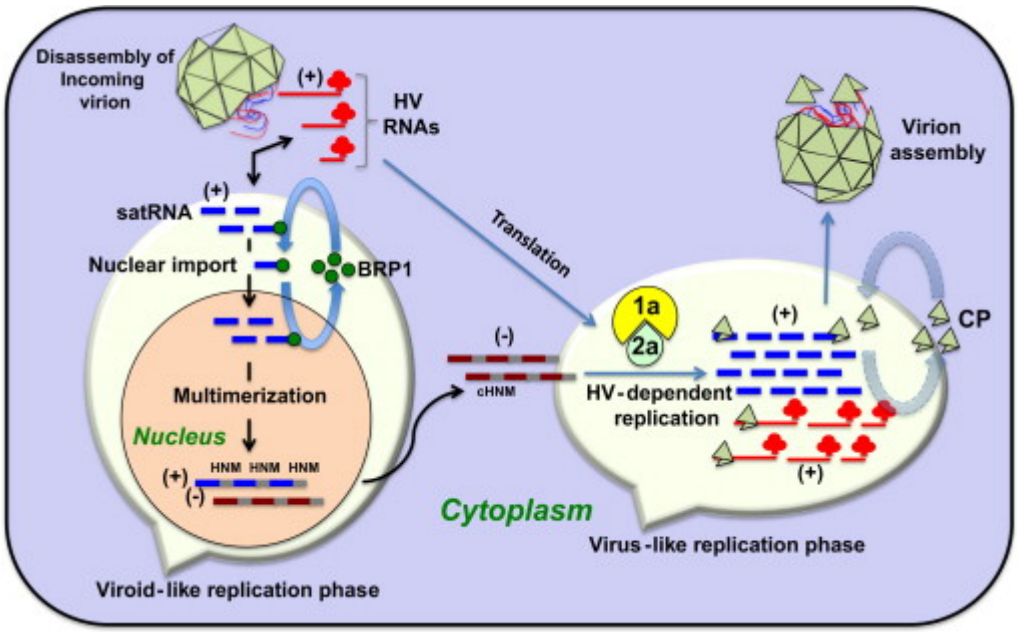

Figure 17. Showing Satellite RNA and its involvement in replication of Viroids

❖ Satellite viruses

Satellites are subviral agents that differ from viroids because they depend on the presence of a helper virus for their propagation. Satellite

viruses are particles that contain nucleic acid genomes encoding a structural protein that encapsidates the satellite genome. Satellite RNAs do not encode capsid protein, but are packaged by a protein encoded in the helper virus genome. Satellite genomes may be single-stranded RNA or DNA or circular RNA, and are replicated by enzymes provided by the helper virus. The origin of satellites remains obscure, but they are not derived from the helper virus.

Satellite viruses may infect plants, animals, or bacteria. An example of a satellite virus is satellite tobacco necrosis virus, which encodes a capsid protein that forms an icosahedral capsid that packages only the 1,260 nucleotide satellite RNA. The helper virus, tobacco necrosis virus, encodes an RNA polymerase that replicates its genome and that of the satellite.

Satellite RNAs do not encode a capsid protein and therefore require helper virus proteins for both genome encapsidation and replication. Satellite RNA genomes range in length from 220-1500 nucleotides, and have been placed into one of the three classes.

1. Class 1 satellite RNAs are 800-1500 nucleotide linear molecules with a single open reading frame encoding at least one non-structural protein.
2. Class 2 satellite RNAs are linear, less than 700 nucleotides long and do not encode protein.
3. Class 3 satellite RNAs are 350-400 nucleotide long circles without an open reading frame.

In plants, satellites and satellite viruses may attenuate or exacerbate disease caused by the helper virus. Examples of disease include necrosis and systemic chlorosis, or reduced chlorophyll production leading to leaves that are pale, yellow, or yellow-white. The symptoms induced by satellite RNAs are thought to be a consequence of silencing of host genes like the Y-satellite RNA of cucumber mosaic virus causes systemic chlorosis in tobacco. This syndrome is caused by production of a small RNA from the Y-satellite RNA that has homology to a gene needed for chlorophyll biosynthesis. Production of this

small RNA leads to degradation of the corresponding mRNA, causing the bright yellow leaves.

The giant DNA viruses including *Acanthamoeba polyophaga* mimivirus, *Cafeteria roenbergensis* virus, and others are associated with much smaller viruses (sputnik and mavirus, respectively) that depend upon the larger viruses for reproduction. For example, sputnik virus can only replicate in cells infected with mimivirus, and does so within viral factories. Whether these are satellite viruses or something new (they have been called virophages) has been a matter of controversy.

Most known satellites are associated with plant viruses, but hepatitis delta satellite virus is associated with a human helper virus, hepatitis B virus. The genome is 1.7 kb, smallest of any known animal virus, circular single-stranded RNA that is 70% base paired and folds upon itself in a tight rod-like structure. The RNA molecule is replicated by cellular RNA polymerase II. These properties resemble those of viroid genomes. On the other hand, the genome encodes a protein (delta) that encapsidates the RNA, a property shared with satellite nucleic acids. The hepatitis delta satellite virus particle comprises the satellite nucleocapsid packaged within an envelope that contains the surface protein of the helper, hepatitis B virus.

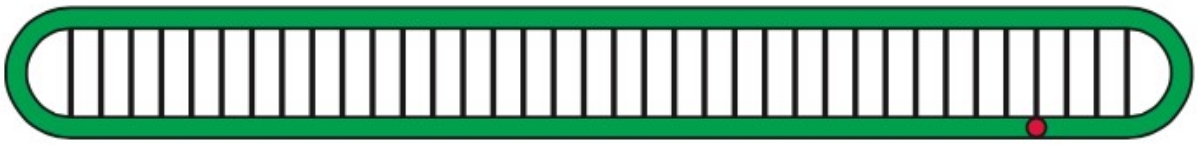

Figure 18. Structure of a Satellite Virus

Infection with hepatitis delta satellite virus only occurs in individuals infected with hepatitis B virus: it is globally distributed, present in about 5% of the 350 million carriers of hepatitis B virus. Acute co-infections of the two viruses can be more severe than infection with hepatitis B virus alone, leading to more cases of liver failure. In chronic hepatitis B virus infections, hepatitis delta

satellite virus aggravates pre-existing liver disease, and may lead to more rapid progression to cirrhosis and death than monoinfections. Why co-infection with both viruses leads to more serious outcomes is not known.

Viruses cause a variety of diseases in humans. Many of these diseases can be prevented by the use of viral vaccines, which stimulate protective immunity against the virus without causing major disease. Viral vaccines may also be used in active viral infections, boosting the ability of the immune system to control or destroy the virus. A series of antiviral drugs that target enzymes and other protein products of viral genes have been developed and used with mixed success. Combinations of anti-HIV drugs have been used to effectively control the virus, extending the lifespans of infected individuals. Viruses have many uses in medicines, such as in the treatment of genetic disorders, cancer, and bacterial infections.

❖ VIROLOGY

Virology is the study of viruses, and a virologist is an individual trained in this discipline. Training in virology can lead to many different career paths. Virologists are actively involved in academic research and teaching in colleges and medical schools. Some virologists treat patients or are involved in the generation and production of vaccines. They might participate in epidemiologic studies or become science writers, to name just a few possible careers. If you think you may be interested in a career in virology, find a mentor in the field. Many large medical centers have departments of virology, and smaller hospitals usually have virology labs within their microbiology departments. Volunteer in a virology lab for a semester or work in one over the summer. Discussing the profession and getting a first-hand look at the work will help you decide whether a career in virology is right for you. The American Society of Virology's **website** is a good resource for information regarding training and careers in virology.