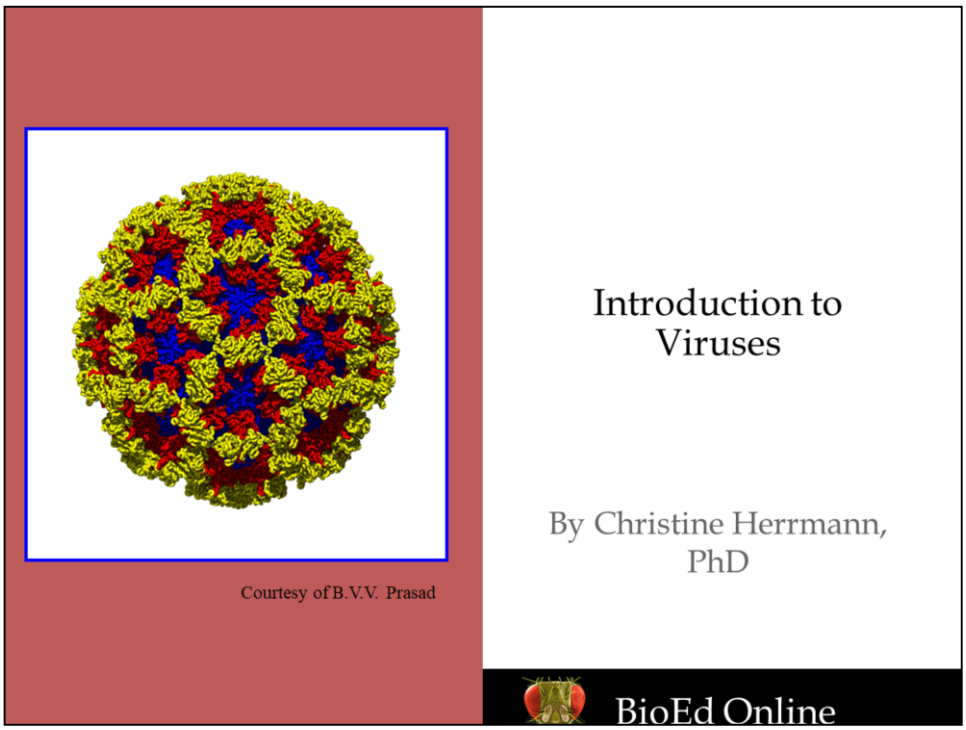

Image References:

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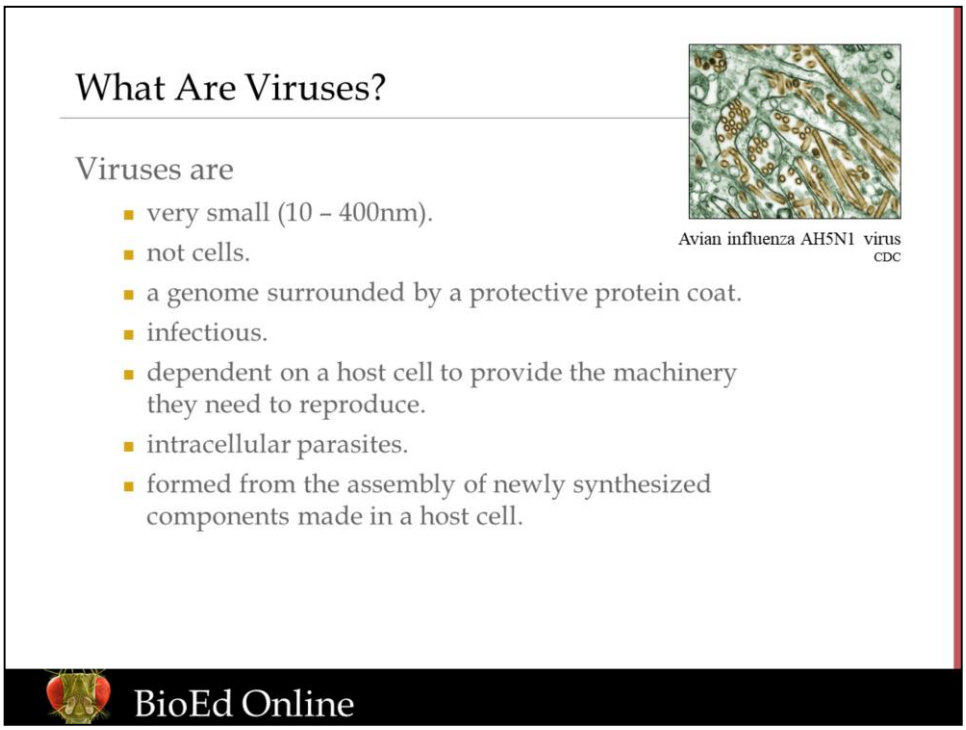

What Are Viruses?

Viruses are submicroscopic particles that can be seen only with a powerful electron microscope. They are not cells, but consist of genetic material, either DNA or RNA, that is enclosed in a protective layer of protein. Viruses are able to enter certain host cells and, in fact, must invade a host cell to reproduce. Once inside living cells, viruses hijack cellular apparatuses necessary to make copies of themselves. For this reason, they are considered intracellular parasites. Viruses use the instructions contained in their genomes to produce virus components, both nucleic acid and proteins, which are then assembled to produce new virus particles. The new virus particles then can go on to infect other cells and continue the cycle of virus reproduction.

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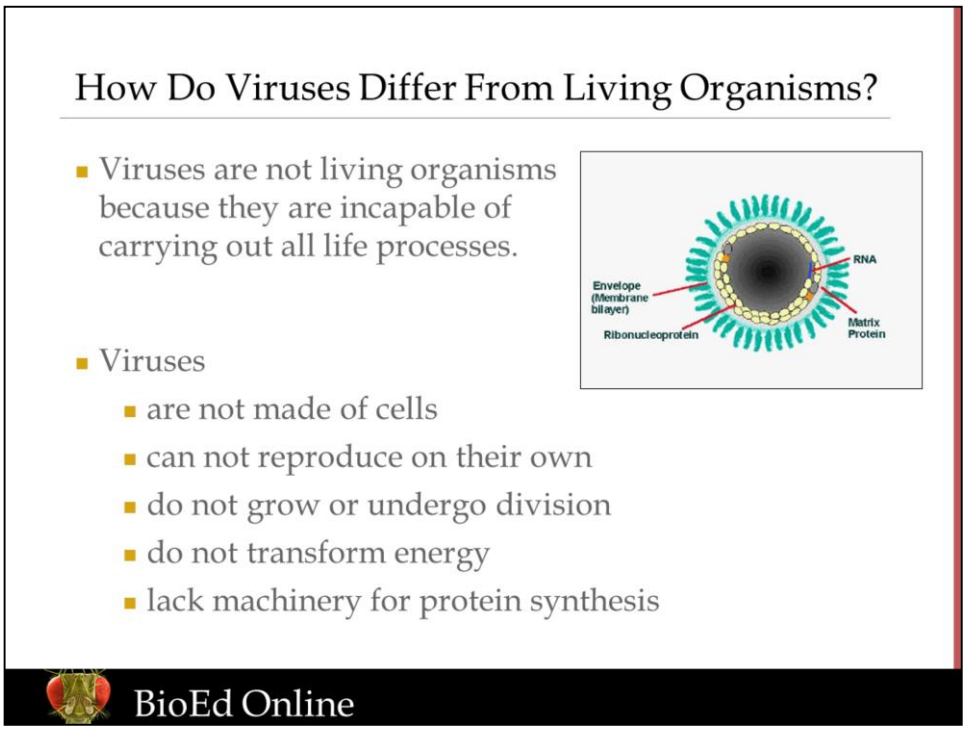

How Do Viruses Differ From Other Organisms?

Viruses are distinct from living organisms. They are not alive. Because of their small size, they do not encode enough genetic information to perform all the functions of life. They can reproduce only within a living host cell, where they usurp the cellular components they need to reproduce. Because viruses are not cells, they do not undergo normal cellular processes, such as cell growth and division. They are incapable of transforming energy on their own or of producing and assembling the complex machinery needed for protein synthesis. Viruses carry only the minimal information (four to several hundred genes) needed to take over a host cell and create more viruses.

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Cann, A.J. (2005). *Principles of Molecular Virology* (4th Ed.). Elsevier, Inc.

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Image Reference:

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How Were Viruses First Discovered I?

In the late 1800s, filter apparatuses were devised that could remove bacteria (the smallest known organisms), from a liquid. It was not known at that time that smaller infectious agents existed that could pass through the filter. The Russian scientist, Dimitri Ivanowsky, studying the plant tobacco mosaic disease (TMV*), which affect plants, discovered that when he applied sap from infected tobacco leaves to the filter, the liquid that passed through still was infectious. However, he did not recognize that he had discovered a new type of infectious agent.

This insight was obtained six years later by the Dutch scientist, Martinus Beijerinck, who discovered that the infectious agent which passed through the filter could reproduce but would not grow on Petri dishes used to cultivate bacteria. He further realized that these agents required the presence of a host cell to reproduce. He named the agent responsible for tobacco mosaic disease a virus, after the Latin term for poison. He thought that this agent must be much smaller and simpler than bacteria. The subsequent crystallization and electron microscope images obtained by the American scientist, Wendell Stanley, in 1935 confirmed this, and the agent was named tobacco mosaic virus.

*Tobacco mosaic virus causes stunted plant growth and mottled, discolored plant leaves, especially in tobacco and other members of the tomato family (Solanceae).

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How Were Viruses First Discovered II?

In the same year that Beijerinck discovered the tobacco mosaic agent, the German scientists, Friedrich Loeffler and Paul Frosch, observed that the agent which causes foot-and-mouth illness in livestock also was small enough to pass through a filter and required the host organism to reproduce. The first human virus, the agent that causes yellow fever, was discovered in 1901 by a team of researchers led by Walter Reed. Dr. Reed's team was sent to Cuba to control an outbreak of yellow fever that occurred during the Spanish-American War.

Bacterial viruses (viruses that infect bacterial cells) were first described in the early 1900s and were named bacteriophages. Many other viruses have since been discovered. Identification of agents that cause disease sometimes is difficult because of the dangers involved in working with infectious agents. In addition, researchers must find a suitable host in which to grow and study certain viruses, but new technologies are facilitating this work.

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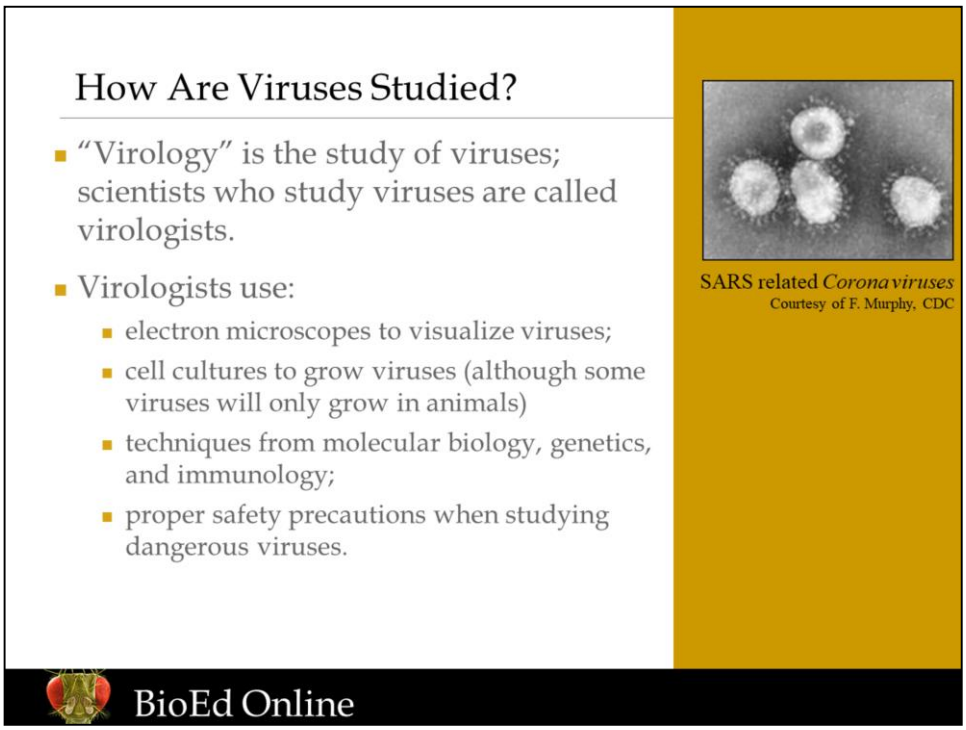

How Are Viruses Studied?

With a few exceptions, viruses are too small (in the range of 10 to 200 nm) to be seen with a light microscope, so virologists use the more powerful electron transmission microscope to study them. The higher resolutions, facilitate identification of the type of virus and its structure. When there is a new outbreak of disease, such as during the 2003 SARS outbreak scientists can examine the unknown agent under an electron microscope and obtain clues about the virus with which they are dealing. Knowing the structure of a virus also is very helpful when designing drugs and vaccines to combat the agent.

Scientists prefer to be able to grow viruses in cell culture (cells derived from another organism and grown in controlled conditions), where it is much easier to study the virus. Some viruses, however, will not grow in cell culture using existing techniques (the techniques may work, but sometimes it takes awhile to find the right cell culture system). To study these viruses, virologists must infect susceptible animals to obtain enough of the agent to conduct their research.

Virologists study the genetics of viruses, how viruses cause disease, and how they interact with components within the host cell and the host's immune system. Wherever possible, scientists also mutate viral genes to determine their functions in the virus life cycle. Using all these lines of research, virologists work to understand viruses, especially those which cause disease, and to gain information that can be applied to the design of antiviral drugs and vaccines. Particularly when working with potentially deadly viruses, virologists must adhere to strict safety procedures and perform manipulations in laboratories specially designed to contain the viruses.

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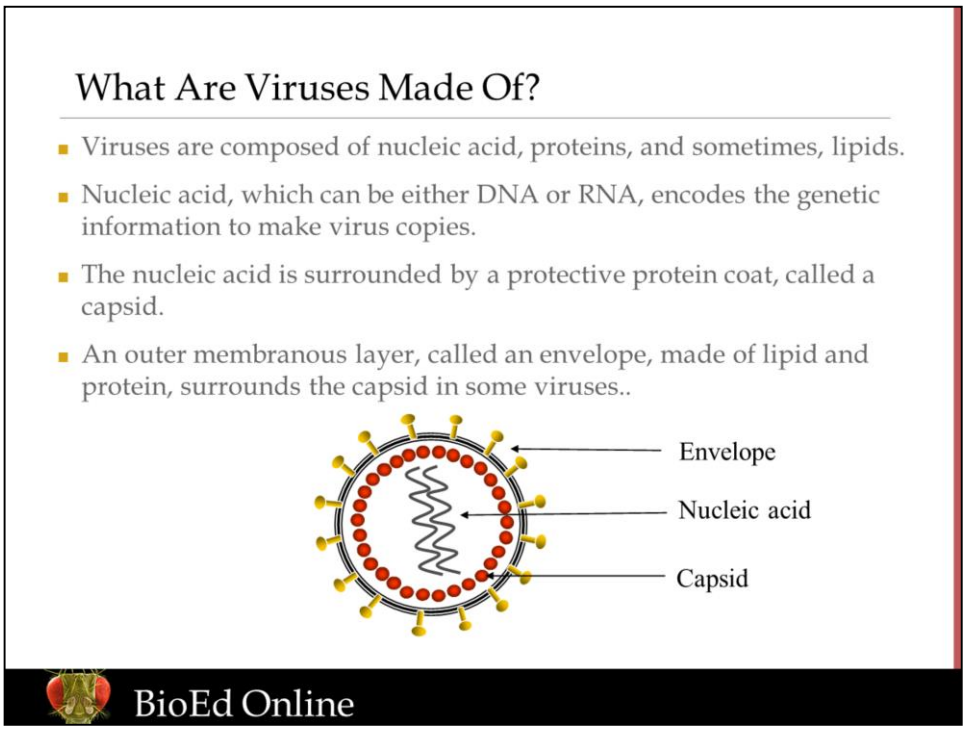

What are Viruses Made Of?

Viruses are particles of nucleic acid surrounded by a protective protein coat; some viruses also have a membranous outer layer containing lipids. Genetic material consisting of the nucleic acid DNA or RNA makes up the core of a virus. The nucleic acid contains the genetic code that holds the instructions to make more copies of the virus. The nucleic acid core is surrounded by a shell made of protein, called a capsid, surrounds the genome and protects the genetic information. In addition to capsid proteins, other proteins may be included in a virus particle to facilitate its entry into cells and aid the early steps of replication.

Certain viruses have an outer membranous layer, called an envelope, that is derived from the lipid bilayer of the host cell and into which viral glycoproteins (proteins that are covalently linked to carbohydrates) are inserted. Key proteins on the envelope surface help these viruses recognize and invade their hosts. Examples of viruses with envelopes are HIV and influenza.

The diagram illustrates the structure of an enveloped virus particle (in cross-section). The genetic material is shown in the center in black. The capsid, composed of multiple copies of the same protein, is shown in red. And an envelope studded with viral glycoproteins (yellow) is present at the outer surface.

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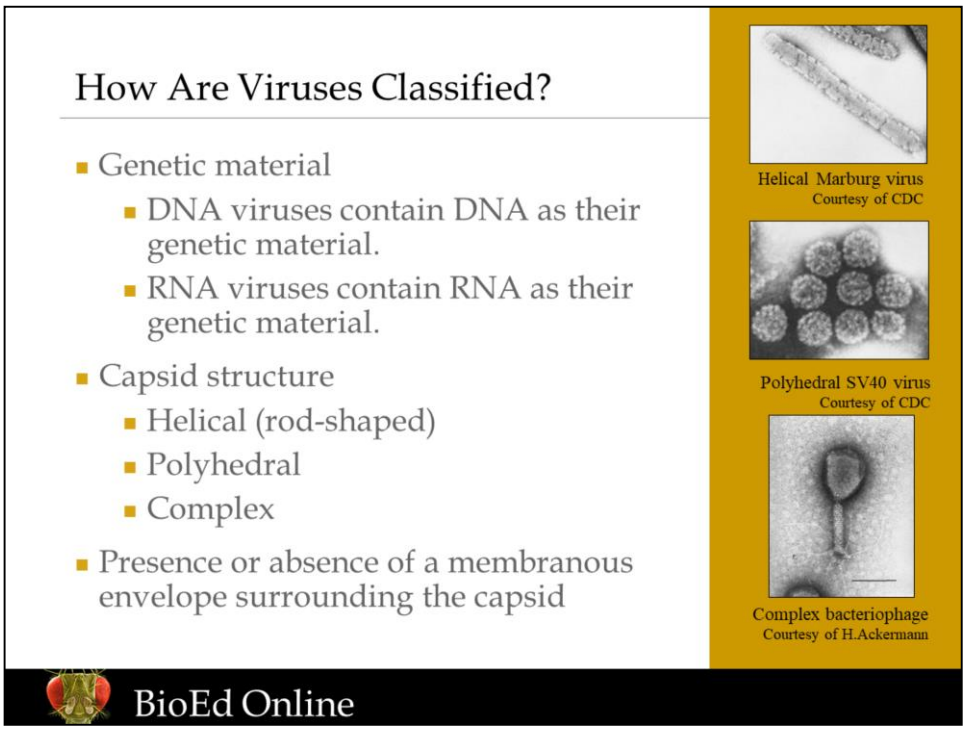

How Are Viruses Classified?

Viruses are extremely diverse. The International Committee on Taxonomy of Viruses (ICTV) has organized them into over 70 different families. Criteria used in classifying viruses include the type of nucleic acid that serves as the genetic material, the shape of the capsid, and whether or not the virus has a membranous envelope.

The genetic material of viruses can be made up of either DNA or RNA. Almost all DNA viruses contain double-stranded DNA as their genome. The DNA can be arranged as linear or circular molecules. Most RNA viruses have single-stranded genomes, which can be found on one or more segments, depending on the virus. When the single RNA strand contains information that is immediately translatable (analogous to mRNA), the virus is categorized as a positive (+) strand RNA virus. RNA viruses that contain the complement of a (+) strand are referred to as negative (-) strand RNA viruses.

Capsids are made up of many copies of protein subunits, often consisting of only a single type of protein. The arrangements of subunits determines the symmetry and shape of the capsid. There are three main types of capsid structure: helical, polyhedral, and complex. For helical viruses, the subunits are assembled in a helix, and the viruses are rod-shaped. The subunits of polyhedral viruses are arranged into an icosahedron (a structure with 20 equilateral triangular faces). These viruses generally have a spherical structure. Complex viruses have capsid structures that do not fit into either of the other categories and are not well understood. Bacteriophages are an example of such a virus.

Some viruses contain an envelope consisting of a lipid bilayer that surrounds the capsid. Viruses acquire an envelope when they bud out through the membrane of a host cell. Virus proteins become inserted into the lipid bilayer and play an important role when viruses infect another host cell. Viruses that lack an envelope are known as naked viruses.

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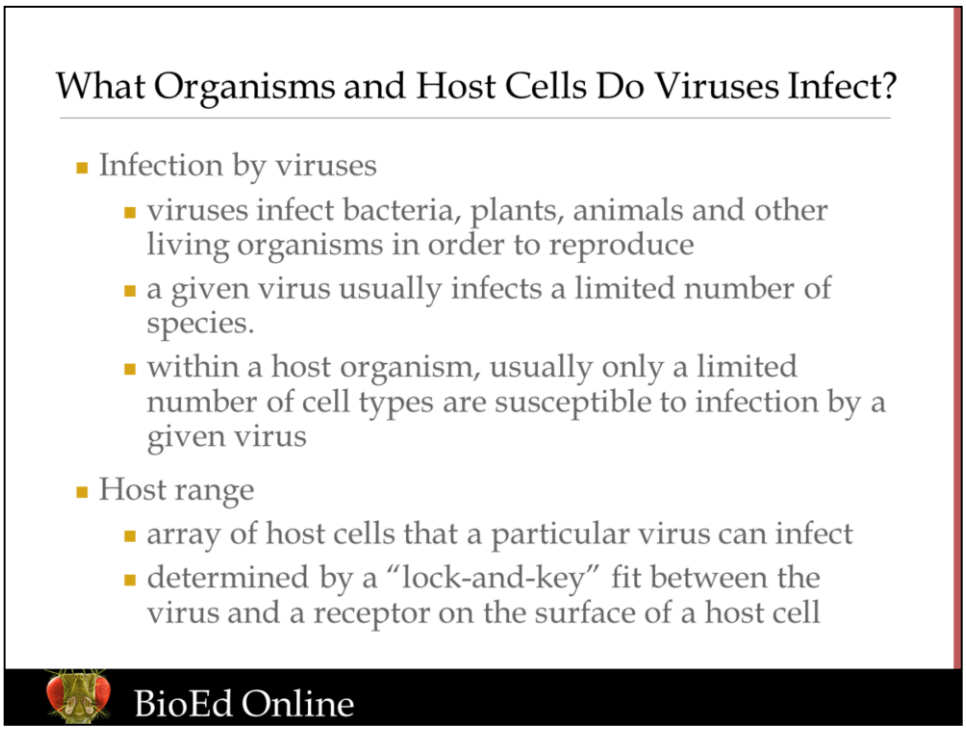
Polyhedral-shaped SV40 virus. Courtesy: CDC. Retrieved 08-15-2006, from http://phil.cdc.gov/phil/ Image #5629.



What Organisms and Host Cells Do Viruses Infect?

A virus must infect (invade cells of) a living organism in order to reproduce. The organism that a virus infects is said to be the "host," and the variety of organisms that a virus can infect is termed the "host range." Although viruses infect many kinds of living organisms, each particular virus usually can infect only a narrow range of organisms, and sometimes only a single species. In such cases, the virus is said to have a "narrow host range". Smallpox, for example, only is capable of infecting humans and no other species. This property of smallpox facilitated its eradication.

In addition, within a specific organism, viruses usually infect only a particular cell type or a limited number of cell types. Therefore, viruses that cause respiratory disease usually infect cells only in the respiratory tract. Viruses infect only certain cell types because a virus must bind to a certain receptor on the surface of the host cell, which allows the virus to enter into the cell. Using a "lock-and-key" analogy, the virus has a specially-shaped "key" that will fit only into a particular "lock"—the receptor. Different cell types express different genes, so the proteins present on the outsides of their cells will be different. A lung cell, therefore, will have different proteins on its surface than a blood cell. HIV, for example, only will enter cells that have a surface protein molecule called CD4. These molecules are found only on white blood cells. Thus, HIV will only infect white blood cells and not lung cells or other cell types.

Sometimes, a virus can mutate and change its host range. This appears to be happening with the avian flu virus (influenza A/H5N1) currently circulating. At first, the flu virus could infect only birds, but changes in the virus genome have allowed it to infect humans. So now, its host range has expanded. The change in host range of a virus can be one factor in the emergence of a new disease.

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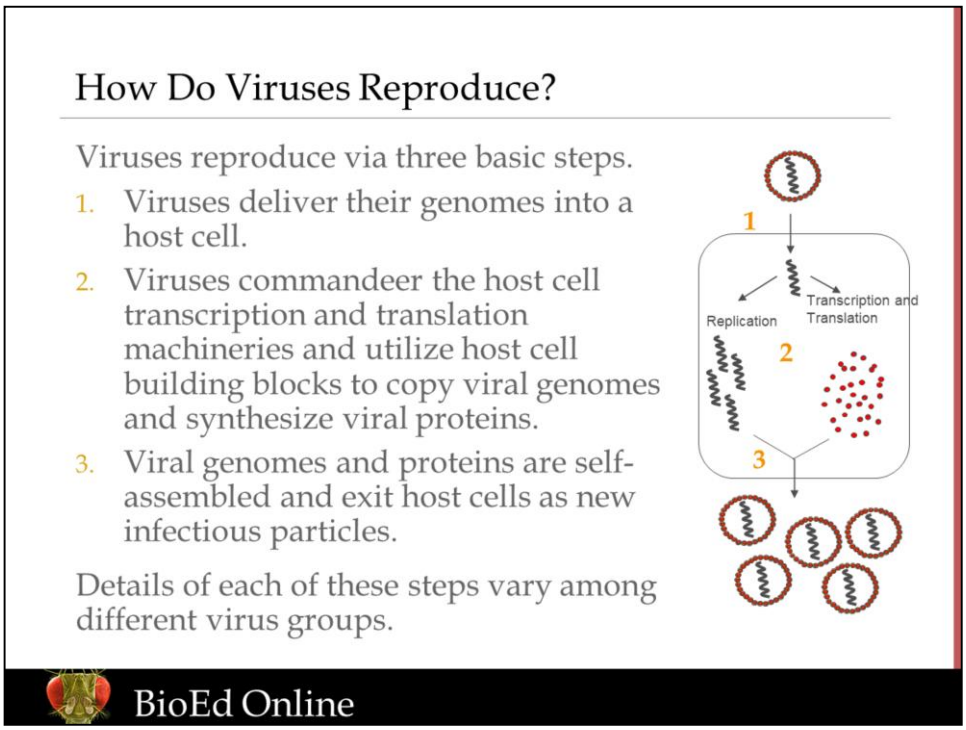

How Do Viruses Reproduce?

Although details of the mechanisms vary widely among different virus groups, all viruses must follow three basic steps to reproduce. First, they must gain entrance and deliver their genomes into cells. Bacteriophages attach to cells and inject their DNA into the host bacteria cell. Other viruses bind to specific receptors (protein molecules) on the surface of host cells. Binding of the virus can trigger the cellular process of endocytosis, essentially tricking the cell into letting the virus inside. Enveloped viruses (viruses surrounded by a lipid bilayer) use the glycoproteins, contained in the envelope, to bind to a cellular receptor. Next, the envelope fuses with the plasma membrane of the cell and the viral contents are released inside the cell. If the viral genome is still surrounded by a layer of protein after it enters the cell, the virus undergoes an "uncoating" step to make the genetic material accessible.

Second, the virus commandeers the machinery of the host cell so that it can make copies of its viral genome and synthesize viral proteins. In addition to the manufacturing machinery, the virus needs building blocks for its nucleic acid and proteins. It utilizes the host cell's nucleotides to make copies of its genetic material and the cell's amino acids to make proteins. At the most basic level, all viruses need to replicate their genome and produce capsid proteins. Many viruses encode additional proteins, that enhance their abilities to take over a cell, replicate to higher levels, or to evade host immune responses. RNA viruses often provide their own enzyme, a polymerase, to replicate their genome, because the host cell does not provide some the necessary enzymes. Virus-encoded polymerases are especially important for RNA viruses that need to make a DNA copy of their genome or for (-) strand RNA viruses to synthesize a (+) strand that can be translated. DNA viruses usually use the host cell DNA polymerase, which normally copies cellular DNA. Viruses use the transcription and translation machinery of the cell to manufacture virus proteins. Some viruses produce proteins that modify the cellular transcription and translation apparatus to ensure preferential synthesis of viral proteins over cellular ones, and some viruses even can completely shut down the

synthesis of host cell proteins or destroy the host cell's DNA.

Finally, the nucleic acid and protein components are synthesized, the virus particle is assembled with the protein capsid surrounding the genome. There are various mechanisms by which a virus can exit a cell. Some viruses lyse, or burst open cells to release the virus particles. This process immediately destroys the host cell. Other viruses will bud out of the cell through the plasma membrane and acquire an envelope. In any case, hundreds or thousands of infectious virus particles are released from an infected cell. These newly made virus particles then go on to infect new host cells and continue the cycle of virus reproduction.

It is constructive to keep in mind that unlike a cell, which duplicates its DNA and reproduces from a preexisting cell by dividing to form two daughter cells, a virus can use a single nucleic acid template to make hundreds or more copies of its genome. A useful analogy is that a virus genome can be reproduced multiple times from a single copy, much like a piece of paper can be reproduced numerous times in a copy machine.

Note: The relative sizes of the virus particles and the cell in the diagram are not to scale. The viruses actually are much smaller, relative to cells, than indicated.

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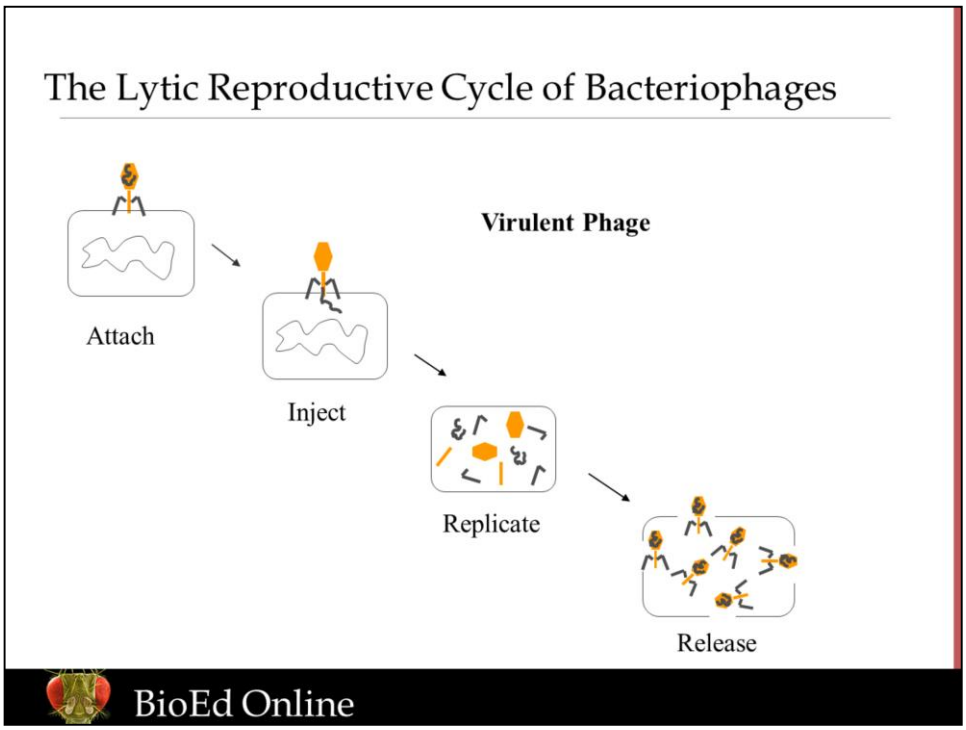

The Lytic Reproductive Cycle of Bacteriophages

The reproductive cycle of viruses that infect bacteria, called bacteriophages, or simply phages for short, are known in great detail. Phages can undergo two alternative life cycles: lytic and lysogenic. Bacteriophages that reproduce through a lytic cycle end up killing their host cell. Lytic bacteriophages attach to the cell wall of a bacterial cell and inject viral DNA into the cell. The phage takes over the cell's metabolic machinery, degrades the cell's DNA, and makes copies of its own genome and proteins. Once these components assemble into new phage particles, the viruses lyse, or burst open the cell, resulting in death to the bacterial host.

The alternate cycle is called a lysogenic cycle (illustrated in the next slide); in this case, the phage reproduces without killing its host. Once the virus genome enters the cell, the circularized DNA will become inserted into a host cell chromosome; phage DNA that has been incorporated into a host chromosome is referred to a prophage and is essentially "hidden" in the host cell's DNA. The prophage is replicated along with the bacterial host chromosome during cell replication. A single prophage can quickly multiply as each of the daughter cells arising from bacterial cell division will contain a copy of the prophage. On occasion, a switch from a lysogenic to a lytic cycle is triggered. This usually occurs as a result of an environmental factor, such as radiation or certain chemicals. The prophage is released from the host chromosome and returns to an active replication cycle that will lyse the host cell.

Bacteriophages that reproduce using only the lytic cycle are known as virulent phages, while phages that can undergo both modes of replication are called temperate phages. Bacteriophage T4 an example of a virulent phage; lambda is an example of a temperate phage. The study of temperate phages, and the process whereby the lysogenic or lytic pathway is activated, has led to fundamental discoveries in mechanisms that control the regulation of gene expression. Viruses that infect animal and plant cells differ in many particular aspects from bacteriophage

life cycles, but the basic pattern of reproduction is similar.

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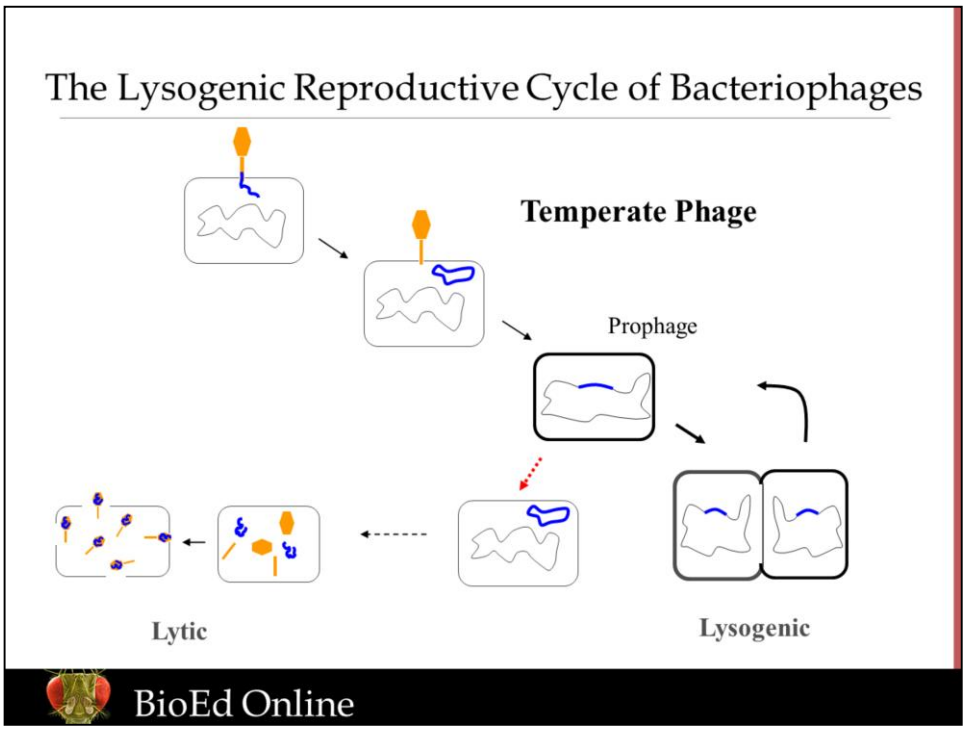

The Lysogenic Reproductive Cycle of Bacteriophages

The life cycles of viruses that infect bacteria, called bacteriophages, or simply phages for short, are known in great detail. Phages can undergo two alternate life cycles: lytic or lysogenic. Bacteriophages that reproduce through a lytic cycle end up killing their host cell (see previous slide). Lytic bacteriophages attach to the cell wall of a bacterial cell and inject viral DNA into the cell. The phage takes over the cell's metabolic machinery, degrades the cell's DNA, and makes copies of its own genome and proteins. Once these components assemble into new phage particles, the viruses lyse, or burst open the cell, resulting in death to the bacterial host.

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Viruses that infect animal and plant cells differ in many particular aspects from bacteriophage life cycles, but the basic pattern of reproduction is similar.

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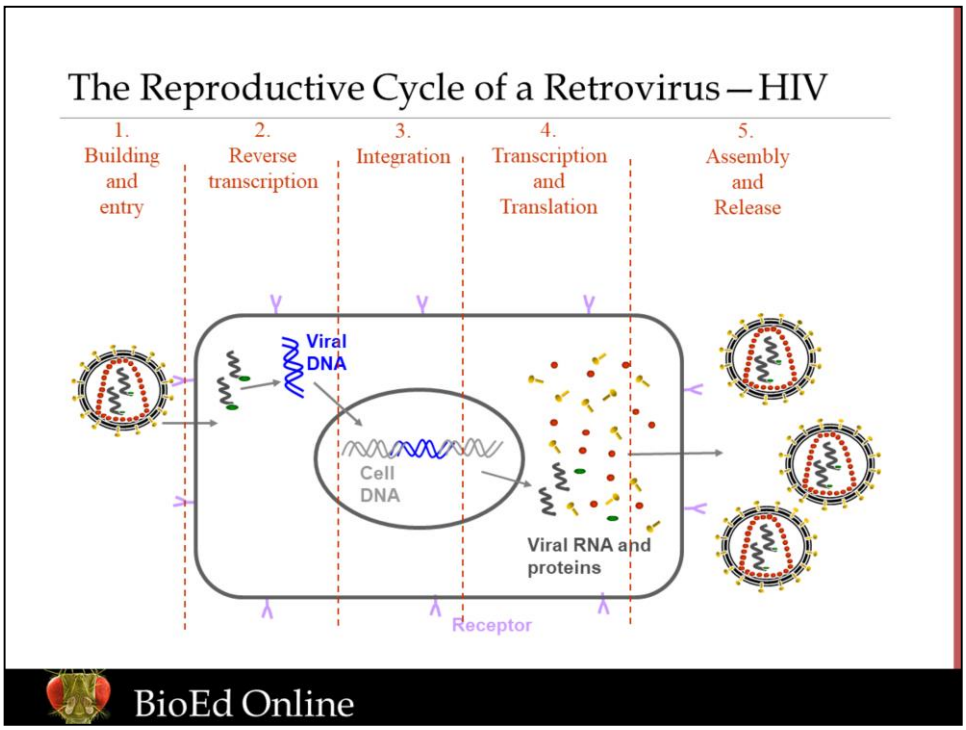

The Reproductive Cycle of a Retrovirus—HIV

There are many variations on the basic scheme of the virus life cycles described in the last two slides. As one example, we will choose HIV (human immunodeficiency virus), the virus that causes AIDS. HIV has a complicated life cycle that, while following the basic pattern, has some interesting and unique features. HIV is an enveloped RNA virus. It is a member of the retrovirus family. All members of this family contain RNA genomes that are converted into double-stranded DNA before new viruses can be made. These viruses have a "reversed" flow of genetic information and must convert RNA to DNA (hence the name retro) to reproduce. This process, is in contrast to the central dogma of molecular biology that states that information is passed from DNA, to RNA, to protein. Because cells do not have an enzyme that will generate new DNA from the existing virus RNA, retroviruses carry their own enzyme, called reverse transcriptase (shown in green), that makes double-stranded DNA copies from the information encoded in the RNA genome.

As with all viruses, HIV must first enter a cell before it can begin to reproduce. The HIV envelope glycoproteins bind to a specific receptor, called a CD4 molecule, found on the surface of white blood cells, usually T cells. The viral envelope fuses with the plasma membrane of the cell, and the capsid, containing two copies of viral RNA and two copies of the reverse transcriptase enzyme, enters the cell. The capsid proteins are removed (in a step called uncoating) and the reverse transcriptase begins the process of making a double-stranded DNA copy of the viral genome. The double-stranded viral DNA then travels from the cytoplasm into the nucleus of the cell, where it becomes integrated into the host cell DNA with the help of a viral protein called integrase. Viral DNA incorporated into the cellular DNA is called a provirus, analogous to the prophage of a lysogenic bacteriophage. In this state, it can be duplicated along with cellular DNA. Proviral genes are transcribed into RNA using the host cell transcription machinery. The RNA is then exported from the nucleus to the cytoplasm, where it serves as messenger RNA for the translation of viral proteins. The RNA molecules

also function as genomes for the new viruses that are produced. The viral proteins and RNA assemble into viral particles and bud from the cell, acquiring an envelope in the process. The particles become mature, infectious viruses after undergoing an additional step involving a virus protein, referred to as protease, that cuts the long pieces of newly made virus proteins into smaller functional units.

Because the reproductive cycle of HIV relies on several virus proteins to produce new infectious viruses, steps requiring these proteins have been targeted in the design of drugs that interfere with virus replication. Current anti-HIV drugs block the entry, reverse transcription (AZT is one example of a drug that blocks this step), and protease steps. Research on drugs to block other parts of the HIV reproductive cycle is ongoing.

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Image Reference:

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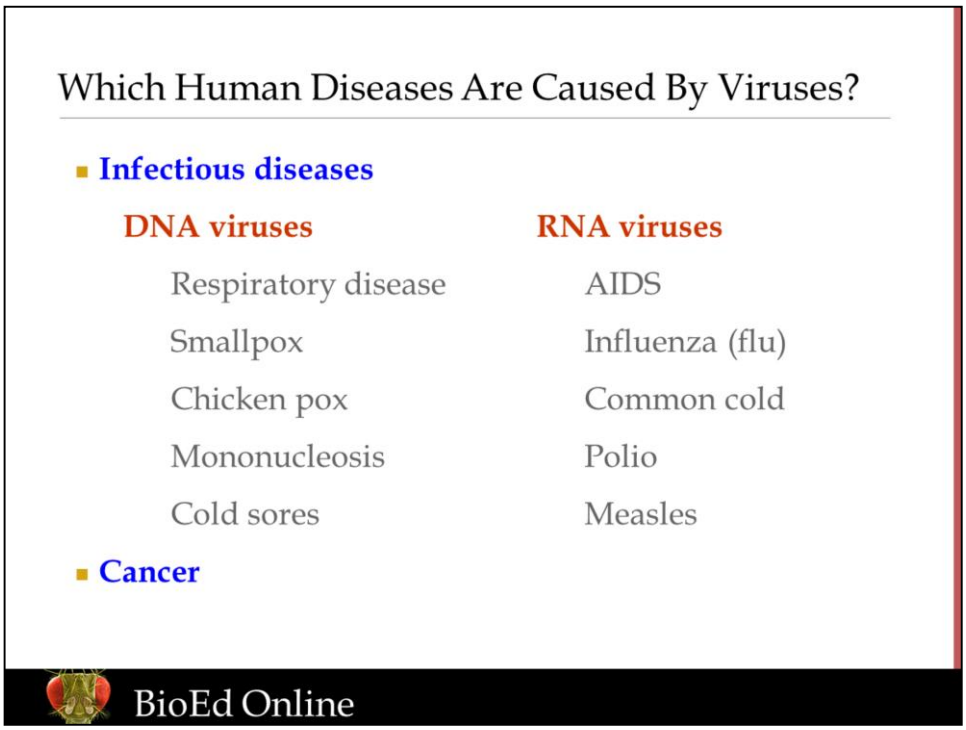

Which Human Diseases Are Caused By Viruses?

Viruses cause diseases in the many organisms that they infect. This slide lists some of the more well-known infectious diseases of humans caused by DNA and RNA viruses. Viruses also cause significant problems in animals and plants.

Some viruses, referred to as "tumor viruses," also can cause cancer. The cancer-causing abilities of some tumor viruses have been demonstrated only in animals. However, there is growing evidence that certain viruses cause specific types of human cancers. For example, some types of papillomavirus, a DNA virus, have been identified as a cause of cervical cancer. HTLV-1, a retrovirus, causes a type of adult leukemia.

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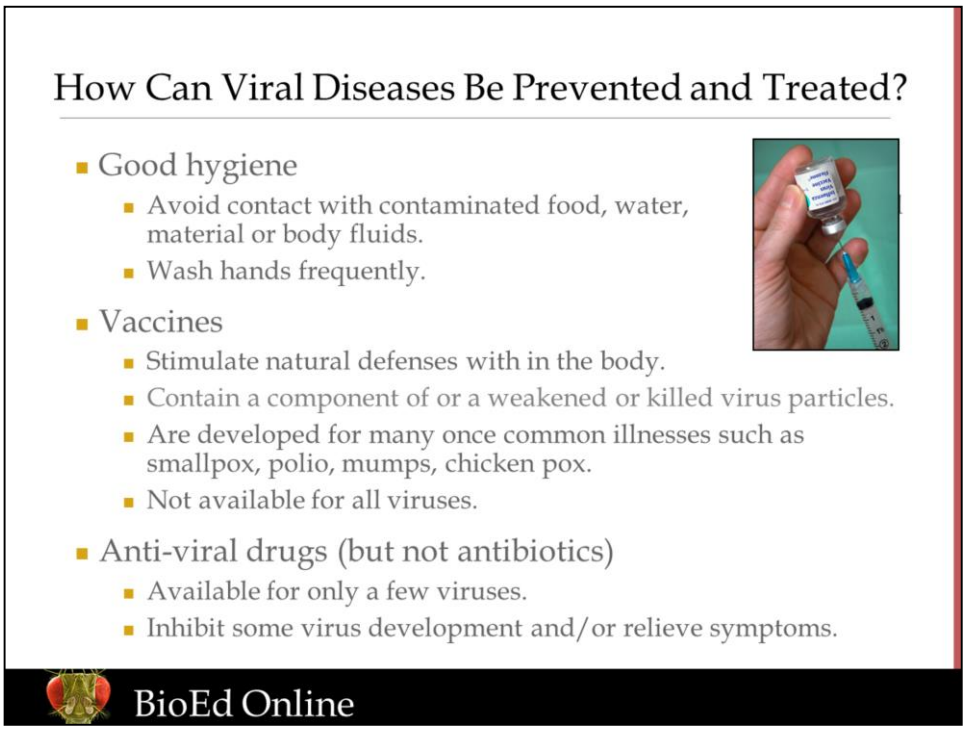

How Can Viral Diseases Be Prevented and Treated?

There are a number of different routes by which a person can become infected with a virus. To contract some viruses, humans must come in direct contact with a source of infection, such as contaminated food, water, fecal material, or body fluids. Other viruses are transmitted through the air. Viruses that cause diarrheal disease, for example, usually are spread via a fecal-oral route or through ingestion of contaminated food. Alternately, viruses that cause respiratory infections, such as the flu, are often spread by coughing and sneezing. Good hygiene and frequent hand washing are simple but effective ways to reduce the spread of viruses and other microorganisms.

The most successful method to prevent viral infections is through vaccines. Vaccines stimulate the body's natural defenses—the immune system—to combat viral infections. They consist of components of a virus, or weakened or killed whole virus particles. Many childhood viral infections virtually have been eliminated (at least in the developed world). Remarkably, the viral disease, smallpox, has been eliminated from the human population through vaccination. However, vaccines are not available for all viral diseases. For example, a vaccine against HIV is being sought urgently. Some viruses, such as HIV, mutate rapidly, making vaccine development extremely challenging.

Unfortunately, once viral infections occur, there is little that can be done to cure these diseases. In contrast to bacterial infections, antibiotics are useless against viral infections. For a few viruses, antiviral drugs exist that can relieve some symptoms of the disease. Drugs that inhibit HIV reproduction have been developed, but while these drugs may improve a patient's quality of life for some time, they are not a cure, and eventually HIV-infected individuals will succumb to the disease.

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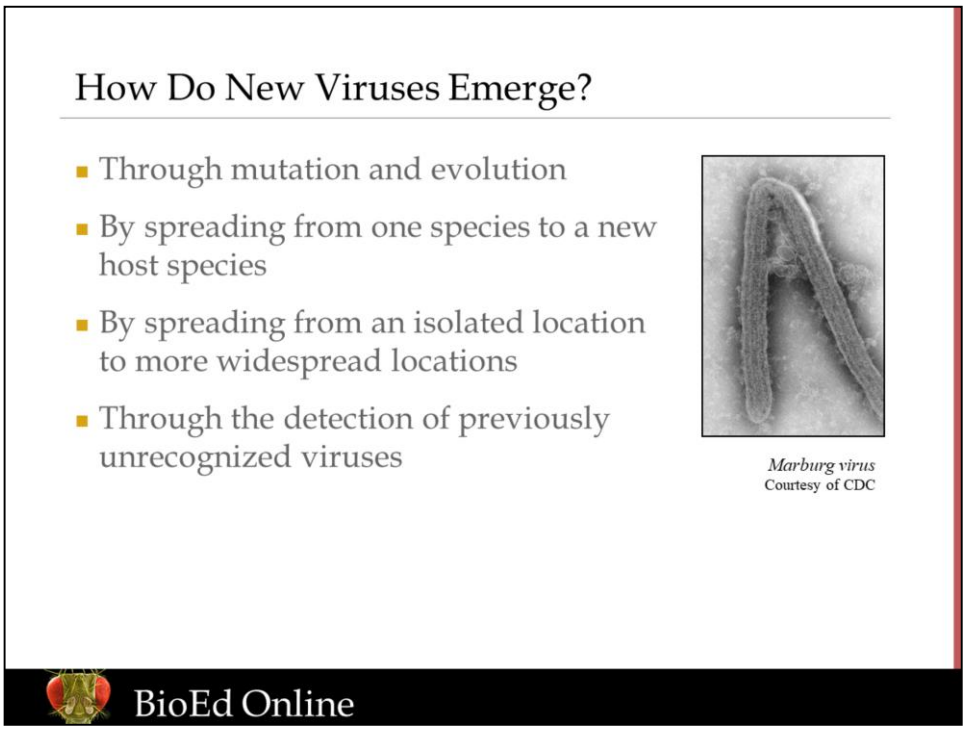

How Do New Viruses Emerge?

An emerging virus is one that has either recently appeared in a population or is rapidly expanding its range of hosts and geographic locations. Viruses, especially RNA viruses, acquire mutations and evolve over time. When viruses accumulate a significant number of changes in their genetic material, they may no longer be recognized by a host's immune system. Therefore, they may be seen as a "new" virus. Influenza virus, which causes the flu, mutates rapidly and can cause seasonal epidemics; this is the reason a flu shot is necessary every year.

Changes in a virus due to evolution also can lead to a change in the host range of a virus, in which case a virus may become capable of infecting a new species. For example, the 1918 bird flu virus mutated enough that it acquired the ability to infect humans, with devastating consequences. Viruses also can be introduced into new hosts and new geographic locations as a result of human activity. As the human population expands into previously uninhabited areas, there is increased contact between humans and animals. Many human emergent viruses have their origins in animals.

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Image Reference:

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Are There Infectious Agents Simpler Than Viruses?

Viroids and prions are even more simple than viruses. Viroids have only nucleic acid without a protein coat, while prions are composed of protein but do not contain any associated nucleic acid. Viroids can cause plant diseases, such as potato tuber spindle disease and apple scar skin disease. Prions cause mad cow disease and related diseases in humans and animals.

References:

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Introduction to Viruses - Summary

- Viruses are distinct from living organisms
- Viruses are very diverse
- Many important diseases that affect humans are caused by viruses
- New viruses are constantly emerging
- Development of new vaccines and ways to control viruses is important

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