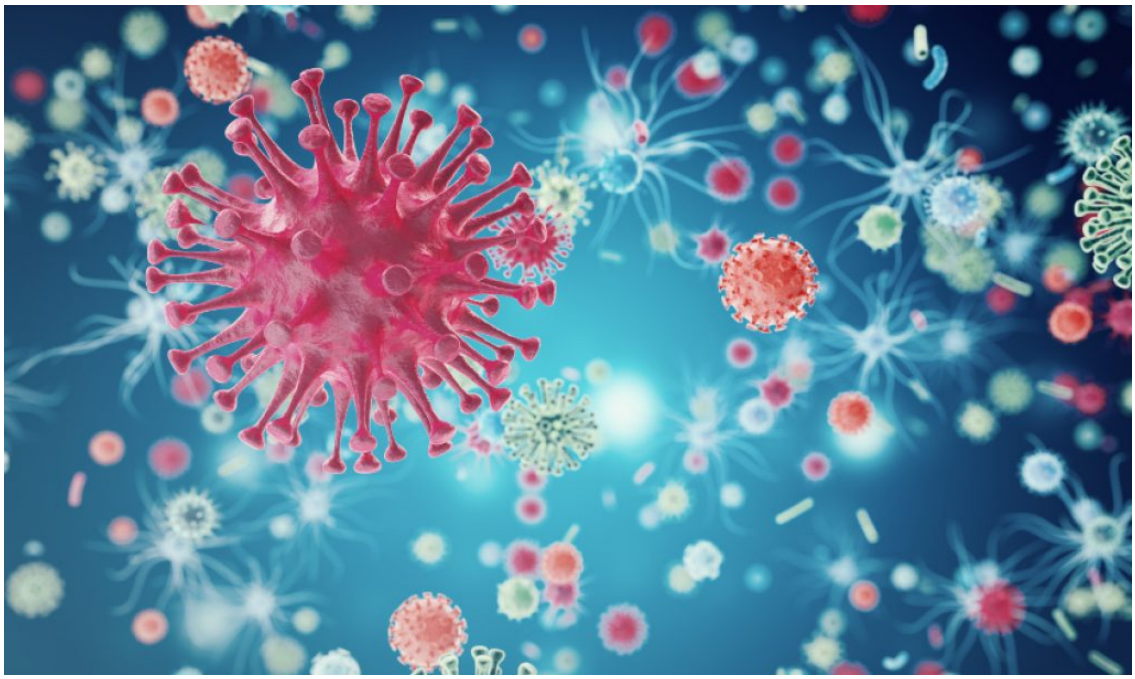
Viruses



A French-Canadian was one of the early pioneers of the basic biology of viruses - Felix D'Herelle.

"Viruses are bad news wrapped in protein" - Sir Peter Medawar

Viruses are obligate intracellular parasites, they have to infect a cell, "hijack" control of the cell and cause it to make new copies of the virus. Viruses are not cells, for that reason most biologists do not regard them as being "alive". Viruses are very small, much smaller than eukaryotic cells, much smaller than bacteria.

Viruses do not have cytoplasm, do not have a metabolism. Some viruses do house one or a few enzymes, but this is not an indication that they have a metabolism, they do not. The AIDS virus(HIV) for instance, is a retrovirus, this means that it copies its RNA genome into DNA that is then integrated with the host cell DNA. In order to achieve this copying from RNA to DNA an HIV virus carries a unique enzyme called reverse transcriptase.

Viruses are essentially nucleic acid within a capsule made of protein.

The viral genome contains far fewer genes than cell genomes, from less than a dozen (as in the influenza virus) to a few hundred at most, as opposed to thousands or tens of thousands in cell genomes.

The viral genome can be DNA or RNA, but not BOTH.

The protein shell or capsule of viruses is called a **capsid**, and is composed of many

smaller protein subunits called **capsomeres** (sometimes spelled as capsomers).Some viruses have many glycoprotein "spikes" which dot their capsid surfaces and act to

attach the virus to specific receptor sites on the host cell membrane.

The capsid has a distinctive shape, it can be **Polyhedral**, or **filamentous**, or a **complex** capsid composed of a number of capsid shapes.

Some viruses that infect animals have an outer lipid membrane derived and modified from the cell that was forced to replicate and release the virus - it functions in making the virus more infectious and is called the envelope. Viruses that infect cells that also have a rigid cell wall (such as bacteria, fungi, plant cell etc) do not form an envelope. All types of cells have viruses that infect them. Viruses are generally specific as to what type of cell they will infect. Viruses that infect potato do not infect us, viruses that infect one genus of animal generally do not infect another (there are well known exceptions to this rule though – like flu viruses!) So, viruses that infect animal cells have a host range and within that range they have a viral specificity - which refers to what cell types they can infect.

Note that bacteria are infected by viruses, and bacterial viruses are known as bacteriophage or "phage" in common usage. Bacteriophage are of great significance, they can be one means by which new and dangerous bacterial variants arise because bacteriophage can "accidently" pass virulence related genes from one bacterial species to another. And some bacteriophage contain genes for toxins that can be produced in bacteria. Bacteriophage are also critical tools in modern biotechnology research and industry. Many bacteriophage actually carry an enzyme that is found also in human tears and other body fluids, it is called lysozyme, it is used by the bacteriophage to break down peptidoglycan in the bacterial cell wall so that the phage can enter the bacterial cell. Much of the modern understanding of how ALL viruses replicate and infect was taken from studies with the T even phage that infect bacteria.

When a virus infects a cell and directs that cell to make new copies of itself, it is a very different process than cell reproduction and is therefore NOT called reproduction - it is called virus replication.

There are five stages in virus replication: (This was mostly worked out using bacteriophage infections of bacteria, and the terminology applied to the bacteriophage infection cycle is used here, and of course, this is a continuous process, the "steps" are imposed by humans so that we can understand this continuous process);

1. **Attachment**- specific attachment of the virus to the host cell, it attaches because it binds with specific molecules on the cell wall surface of the bacterium, the same principle of specific recognition of a binding or attachment site is found with viruses that infect animal and other cells that do not have a cell wall, and in that case it is molecules projecting from the target cell membrane that act as recognition sites so that the virus will attach to the cell.

2. **Penetration** - the virus (or in some cases - just its genome) enters the cell. When a cell has a cell wall (bacteria, fungi, plant cells, algal cells) the usual strategy is for insertion of just the genome of the virus into the cell cytoplasm, cell walls are rigid and difficult for entire virus particles to penetrate. In animal cells, the entire virus enters.

3. **Synthesis** - viral genes are transcribed and then direct the host cell membrane to

make components of the virus. In many cases the first step is the destruction of the host cell

genome, followed by transcription and translation of viral nucleic acid that results in generation of virus components.

4. **Maturation** - the viral components assemble into complete virus copies, this is a thermodynamic process, it is not directly (as far as I can gather) controlled, it is just that there is a thermodynamically favourable tendency for the different virus particle components to associate in the correct way to form a functioning virus particle.

5. **Release** - the new viruses are released, which may or may not kill (lyse – this word means to burst in this context) the host cell. In some cases, as with cells that have cell walls, the virus has to direct lytic processes that lyse or burst the cell by first damaging the cell wall. In other cases, as with animal cells that lack a cell wall, there may be an immediate release of virus particles that bursts and kills the host cell, or the virus can escape from the host cell by forming an envelope derived from the host cell membrane, and this can be done in a way (essentially exocytosis) that does not cause host cell destruction, at least not immediately, so that many viruses leave the cell in this fashion.

The immediate viral infection, replication and exiting of newly replicated viruses from cells, with the destruction of the host cell is called the lytic cycle.

In some cases viruses penetrate and infect a cell but do not immediately direct the synthesis of new viruses, instead, they integrate into the host cell genome without killing the host cell, they insert their genes into the DNA in the host cell chromosomes, and the viral genes are “quietly” copied along with the host cell genome as it reproduces. When a bacterial virus genome is in this integrated form it is called a prophage. If a bacterium is growing and reproducing while it contains a prophage it is said to be in a lysogenic cycle of growth. At some later stage, a matter of perhaps days, and sometimes years, a stimulus (uv light is an example) triggers the virus genome to activate to begin replication of new viruses, when this occurs the bacterium is now in a lytic cycle.

As mentioned, when this delayed integrated mode of virus infection is found in bacteria the practice is to call it a lysogenic cycle, but when a similar thing occurs in animal cells such as ours, it is often called a latent infection. This terminology can be a bit confusing, since it is possible to have a virus infection described as latent when there are actual free virus particles present but not causing disease, and in other cases the term latent infection is used when no actual virus particles are evident and the viral genome remains integrated and inactive in the host cell genome. Often, in animal virus infections, where the viral genome has integrated with the host genome, the viral genome so inserted is referred to as a provirus. The AIDS virus - HIV - undergoes a prolonged provirus phase. As mentioned, the term latent is also applied to whole, formed viruses in animal cells that are not active, they are dormant and can be triggered, often years later, to become active and promote disease, the classic example is shingles, this is caused by viruses that had previously caused chicken pox, and when the patient recovered, viruses remained in some of the nerve cells in the body and activate much later on to cause the painful blistering condition called shingles.

Viruses that cause infections in animals often cause a characteristic and diagnostic cytopathic effect (CPE) when they are grown in artificial animal cell tissue culture. The cultured animal cells form a sheet, one cell thick, that adheres at the bottom of the container of nutrient fluid. Viruses added to the culture cause "holes" to appear in the sheet when they infect cells, by causing dead infected cells in the sheet to detach from the bottom of the container, as well as causing the cells to change in shape. Animal viruses in cell culture are also often observed to cause the formation of large multinucleate cells that are a result of the fusion together of numerous cells, these are called syncytia, which are commonly observed in the cytopathic effect. The CPE often involves the production of diagnostic inclusion bodies inside infected cells, a classic example is the dark tiny Negri bodies, these are granules that are found in nerve cells infected with rabies. Inclusion bodies are often masses of viral nucleic acids or proteins.

I mentioned before that some animal viruses possess an outer lipid membrane - the envelope (sometimes also called a coat). When such a virus is replicated in an animal cell it is released from that cell in a process of exocytosis, which does not kill the cell. In that case the virus retains that small piece of the host cell membrane that encloses it while it is exiting the cell, inserts some viral proteins into it, and it becomes the viral envelope. Possession of that envelope allows fusion of the virus into the cell membrane of a new host cell - the envelope assists in infection. "Naked" animal viruses do not have an envelope, they generally have many spikes of glycoprotein which recognise and bind the virus to host cell receptors.

Some viruses can cause birth defects - eg., Rubella. Some viruses can cause cancer - eg., human papillomavirus, some strains of which cause genital warts, and some types of which cause cervical cancer - there is a new vaccine that is touted as giving excellent protection against cervical cancer caused by the papillomavirus, and there are plans to give mass vaccinations to pre-adolescent females.

Except for extreme cases involving the very old or the immune compromised, until recently there has been little option for treatment of virus infection with drugs. Some powerful anti-nucleic acid (DNA or RNA) replication drugs (these are usually nucleotide analogues) have been used for decades to treat established flu in people who are at very high risk of fatal infection – such as the very old in whom the flu can be life threatening, but they can have serious side effects and there are now many reports of resistance. The last 5 years or so have seen the development and use of some effective drugs against an established flu infection that work in a different way, these tend to be agents that block receptor interactions, and will be mentioned when we discuss the flu – Canada has established large stocks of doses of one of these agents.

Penicillin, tetracycline, and the other antibiotics used for bacterial infections are USELESS for treating viral infections.

The MAIN defence against viral infections is the immune system, and also by activation of the immune system to recognise the virus PRIOR to infection, by vaccination (immunization).