Replication of Viruses (Life cycle of virus)

Stages of viral replication:

1-Attachment

2-Penetration

3-Uncoating

4- Gene expression and biosynthesis

5-Assembly

6-Release

1-Attachement to host cell:

The first stage in viral infection is attachment of virus to specific receptor on the surface of host cell:

A- Receptor molecules **differ for different viruses**. For example, HIV attaches to CD4 receptor on helper T-cell and Rabies virus binds to acetylcholine receptor.

B- The attachment of virus **determines the organ specificity** such as hepatitis virus infect liver, influenza virus infect respiratory tract, and so on.

C- The specificity of attachment **determines the host rang** of viruses. Some viruses have the narrow range, whereas others have abroad ranged.

2-Penetration:

Following attachment, virions can enter cells by one of the following ways:

A- Translocation of virion across plasma membrane.

B- Endocytosis: in which the virus is accumulated inside cell.

C- Fusion with Plasma Membrane

The virus fuses directly with the plasma membrane of the cell, and enter into host cell.

3-Uncoating

Uncoating occurs concomitantly with or shortly after penetration, **Uncoating is removing the capsid proteins**. Uncoating may be occurring **in cytoplasm** or **in nucleus**. A low pH within the vesicle and presence of cellular enzymes which lead to dissolve the proteins of capsid , then result in uncoating and release of viral nucleic acid into infected host cell. The viral nucleic acid may remain in cytoplasm or migrate to nucleus.

4-Gene expression and biosynthesis:

Virus cannot replicate by binary fission or mitosis, but they replicate by complex process. When the viral genome released inside living host cell, the virus is control on host cell biosynthesis, inhibition of macromolecules synthesis and use the energy of host cell in synthesis of viral macromolecules.

The gene expression involves:

A- **Replication of viral genome** (synthesis of viral nucleic acids).

The **DNA viruses** replicate **in nucleus** (except **pox viruses** in **cytoplasm)**, whereas the **RNA viruses** are replicate in the **cytoplasm** (except **retro viruses** and **influenza virus** in **nucleus**).

B- **Transcription of viral mRNA**: synthesis of mRNA in viruses in various pathways, transfer of genetic information from parental genome to mRNA is called transcription.

C- **Translation of mRNA (synthesis of viral proteins):** Once the mRNA of either DNA viruses or RNA viruses is synthesized, and it translated by ribosome of host cell into viral protein.

5-Assembly of Viruses

The virus produces many copies of their nucleic acid and proteins. The newly synthesized viral genome and structural proteins are assembling to form many progeny viruses.

The packaging of viral nucleic acid into capsid is accruing either in cytoplasm or in nucleus of infected cell.

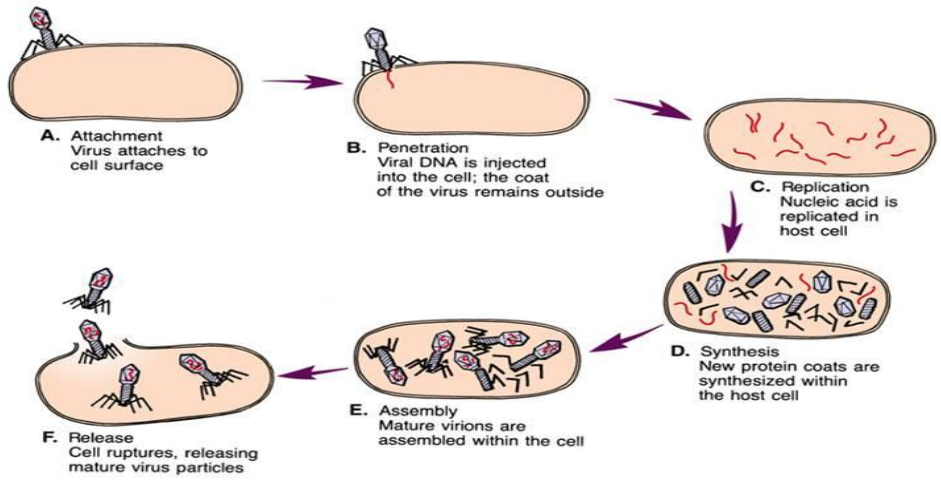
6- Release of virus

The virus mature particles are released from the infected cell by one of two processes:

A- Lysis of infected cell.

B- **Budding (without lysis)** through the outer cell membrane.

Some viruses are enveloped; they acquired their envelopes from cell membrane during releasing, while other enveloped viruses acquire their envelope from nuclear membrane of infected cell.



Viral Pathogenesis

Viral pathogenesis is the process by which a viral infection leads to disease.

Viral pathogenesis is an abnormal situation of no value to the virus.

The majority of viral infections are subclinical. It is not in the interest of the virus to severely harm or kill the host.

The consequences of viral infections depend on the interplay between a numbers of viral and host factors.

Outcome of Viral Infection

Acute Infection

Recovery with no residue effects

Recovery with residue effects e.g. acute viral encephalitis leading to neurological sequelae.

Death

Proceed to chronic infection

Chronic Infection

1- Silent subclinical infection for life e.g. CMV, (Epstein–Barr virus) EBV.

2- A long silent period before disease e.g. HIV, SSPE, PML

3- Reactivation to cause acute disease e.g. herpes.

4- Chronic disease with relapses and exacerbations e.g. HBV, HCV.

5- Cancers e.g. (Human herpes-8)HHV-8

Factors included in Viral Pathogenesis

For pathogenic virus, there are a number of critical stages in replication which determines the nature of disease they produce which included;

1-Entry into the Host

2-Course of Infection (Primary Replication, Systemic Spread, Secondary Replication)

3-Cell/Tissue Tropism

4-Cell/Tissue Damage

5-Host Immune Response

6-Virus Clearance or Persistence

1- Entry into the host

The first stage in any virus infection. In the case of pathogenic infections, the site of entry can influence the disease symptoms produced. Infection can occur via:

A- Skin, dead cells therefore cannot support virus replication. Most viruses which infect via the skin require a breach in the physical integrity of this effective barrier, e.g. cuts or abrasions.

B- Respiratory tract- the respiratory tract and all other mucosal surfaces possess sophisticated immune defense mechanisms, as well as non-specific inhibitory mechanisms (ciliated epithelium, mucus secretion, lower temperature) which virus must overcome.

C- Gastrointestinal tract- a hostile environment; gastric acid, bile salts, etc. Viruses that spread by GI tract must be adapted to this hostile environment.

D- Genitourinary tract- relatively less hostile than the others.

E-Conjunctiva and other mucous membranes - rather exposed site and relatively unprotected

2-Course of Viral Infection

Primary Replication

After entry to potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection will remain localized at the site of entry or spread to become systemic infection.

Localized infections

Virus	primary replication

Rhinoviruses	upper respiratory tract
Rotaviruses	Intestinal epithelium
Papillomaviruses	Epidermis

Systemic Infections

Virus	primary replication	secondary replication
Enteroviruses	Intestinal epithelium	Lymphoid tissues, C.N.S
Herpesviruses	Oropharynx or G.U. tract	Lymphoid cells, C.N.S

Secondary replication

Occurs in systemic infections when a virus reaches other tissues in which it is capable of replication, e.g. poliovirus (gut epithelium- nervous in brain &spinal cord). If the virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results.

3- Spread throughout the host

Apart from direct cell-cell contact, there are 2 main mechanisms for spread throughout the host:

Via the bloodstream

Via nervous system

Virus may get into the blood stream by direct inoculation- e.g. Arthropod vectors, blood transfusion or I.V drug abuse.

The virus may travel free in the plasma (Togaviruses, Enteroviruses) or in association with red cells (Orbiviruses) platelets (Herpes simplex virus). As above, spread to nervous system is preceded by primary viaremia.

4- Cell/ Tissue tropism

Tropism- the ability of a virus to replicate in particular cells or tissues- is controlled partly by the route of infection but largely by the interaction of a virus attachment protein(V.A.P) with a specific receptor molecule on the surface of a cell and has considerable effect on pathogenesis.

5- Host immune response

Has a major impact on the outcome of an infection. In the most cases the virus is cleared completely from the body and results in complete recovery. In other infections, the immune response is unable to clear the virus completely and the virus persists. In general, cellular immunity plays the major role in clearing virus infection whereas humoral immunity protects against reinfection.

7- Cell /Tissue damage

Virus may replicate widely throughout the body without any disease symptoms, if they do not cause significant cell damage or death. Retroviruses do not generally cause cell death, being released from the cell by budding rather than by cell lysis and cause persistent infections, even being passed vertically to offspring if they infect the germ line.

Conversely, Picornaviruses cause lysis and death of the cells in which they replicate, leading to fever and increased mucus secretion in the case of Rhinoviruses, paralysis or death (usually due to respiratory failure) for Poliovirus.

8- Viral Clearance or Persistence

The majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of chronic persistence infections.

1- True Latency -the virus remains completely latent following primary infection e.g. Herpes simplex virus.

2- Persistence e- the virus replicates continuously in the body at a very low level e.g. (HIV).