**I-Classification and Nomenclature of Viruses**

**II-Replication of Viruses**

**III-Effects of Viruses on Cells**

**Viral Taxonomy**

**Classification of Viruses**

**The earliest efforts to classify viruses were based on common clinical and pathogenic properties, common organ tropism and host species, and common ecological, transmission characteristics,** size, the type of nucleic acid they contain**,** the structure of the capsid and the number of protein subunits in it.

It also means that when a new species of known virus family or genus is investigated it can be done in the context of the information that is available for other members of that group.

**I-Classification and Nomenclature of Viruses**

Viruses are mainly classified byphenotypic characteristics, such as morphology, nucleic acid type**,** mode of replication**,** host organismand the type of disease they cause. Viruses are classified on different bases:

**(1)-According to their nucleic acid into:**

a-DNA viruses

b-RNA viruses

**(2)-According to the disease they caused into:**

a-Generalized disease viruses

ex. Measles, dengue, vaccinia, yellow fever, chicken pox,

entereovirus.

b-Viruses affected certain organs

ex. 1-CNS or neural disease viruses (Rabies,Poliomyelitis)

2-Viruses of Respiratory System (Orthomyxoviruse,

Rhinoviruses,Coronaviruses, Paramyxoviruses).

3-Viruses of skin and mucous membrane

(Orf, Herpesvirus).

4-Viruses of eye infection (adenoconjuctivitis)

5-Viruses of liver infection (Hepatitis viruses).

6-Viruses of salivary glands (Cytomegalovirus,mumps).

7-Viruses of digestive tract. (Rota virus, Coronavirus,

Adenovirus, enterovirus).

8-Sexually transmitted viruses (herpes simplex, hepatitis, AIDs)

**9-Viruses transmitted via insects, like** Arboviruses (Arthropod born viruses)Dengue fever virus, Yellow fever virus

**The Origen of Names of Viruses**

Names of viruses may be derived from..

**a-shape of the virus**

Corona = crown like

Rhabdo = rod like

Arena = sand like

Toga = cloak

Rota = wheel

Pico = small

Calici = cup-like

Parvo = small

Orbi = ring

**b-site of multiplication**

Adeno = gland

Rhino = upper respiratory tract

Myxo = mucous

Pneumo = air

**C-Names derived from lesions**

Pox = pock lesions

Flavi = yellow fever

Morbilli = plague

Herpes = creeping from snake

Aphtho = vesicle

**D-According to an enzyme**

Retro = reverse transcriptase

**E-Derived from different names**

Papova = Papilloma, Polyoma, Vacculating

Reo = Respiratory enteric orphan(not associated with any known dis).

**F-Geographic area or town**

Bunya = Bunyayera in Uganda

**The Advance Classification of Viruses**

Without a classification scheme each newly discovered virus would be like a black box, everything would have to be discovered and rediscovered.

The development of a classification scheme is therefore an important and certain consequence. The current classification scheme allows most newly described viruses to be labeled. In the best cases much can be assumed about the biology of the virus.

In 1966 international committee on taxonomy of viruses (ICTV) was established. The universal system of viral taxonomy is set at the levels of order, family, subfamily, genus, and species.

1-Orders ended with suphex *virales*

Families ended with suphex *viridae*

Subfamilies ended with suphex *virinae*

Genera ended with suphex *virus*

Species

Types

Subtypes

Strains

Variants

Example:

Order *Mononegaviralis*  **(Italic started with uppercase litter)**

Family 1-*Paramyxoviridae*  =

2-*Rhabdoviridae =*

3-*Filoviridae*  =

Genus (Genera of *Paramyxoviridae*)

1-*Paramyxovirus genus*  =

2-*Morbillivirus genus*  =

3-*Pneumovirus genus*  =

Species (species of *Paramyxovirus* genus)Parainfluenza virus

Types1, 2, and 3 paramyxoviruses.

The  [Ebola virus from Kikwit](http://www.cdc.gov/mmwR/preview/mmwrhtml/00037078.htm) is classified as:

- Order *Mononegavirales*

- Family *Filoviridae*

- Genus *Filovirus*

- Species: *Ebola virus Zaire*

**Classification of the viruses according to ICTV**

**1- Virion morphology, including**

**-size,**

**-shape,**

**-type of symmetry,**

**-presence or absence of peplomers,**

**-presence or absence of membrane.** (the smallest one, parvovirus..18-20 nm )&large virus ( Poxvirus, 300-400 nm).

**2-Virus genome properties, including**

**-type of nucleic acid(DNA or RNA)**

**-Size of genome in kilobases(kb)**

**-Stranded(single or double)**

**-Liner or Circular**

**-Sense (positive, negative, ambisense)**

**-Nucleotide sequence, G+C**

3- Physicochemical properties of the virion including

-Molecular mass

-Buoyant density

-PH Stability

-Thermal stability

Susceptibility to physical and chemical agents

4- Virus protein properties, including,

-Number, size and function activities of structural and nonstructural proteins

-Amino acid sequence

-Modification(glycosylation, phosphorylation)

-Special function(transcripates, reverse transcriptase, neuraminidase, fusion activity).

5- Genome organization and replication, including

-Gene order

-Strategy of replication9patterns of transcription, translation)

* Cellular sites(accumulation of proteins, virion assembly, virion release).

6- Antigenic properites

7- Biologic properites, including,

Natural host range

-Mode of transmission

-Vector relationships

-Pathogenicity

-Tissue tropisms

**The Baltimore classification system in modern classification.**

**David Baltimore** classification (first defined in 1971) is a classification system that places viruses into one of seven groups depending on a combination of their [nucleic acid](http://en.wikipedia.org/wiki/Nucleic_acid) ([DNA](http://en.wikipedia.org/wiki/DNA) or [RNA](http://en.wikipedia.org/wiki/RNA)), strandedness (single-stranded or double-stranded), [Sense](http://en.wikipedia.org/wiki/Sense_(molecular_biology)), and method of [replication](http://en.wikipedia.org/wiki/Viral_replication)

**I: Double-stranded DNA** (Adenoviruses; Herpesviruses; Poxviruses, etc).

**II: Single-stranded (+)sense DNA** (Parvoviruses)  
**III: Double-stranded RNA** (Reoviruses; Birnaviruses)  
I**V: Single-stranded (+)sense RNA** (Picornaviruses; Togaviruses, etc)  
**V: Single-stranded (-)sense RNA** (Orthomyxoviruses, Rhabdoviruses, etc)  
**VI: Single-stranded (+)sense RNA with DNA intermediate in life-cycle**(Retroviruses)  
**VII: Double-stranded DNA with RNA intermediate** (Hepadnaviruses)  
This group of viruses also relies on reverse transcription, but unlike the Retroviruses, this occurs inside the virus particle on maturation. On infection of a new cell, the first event to occur is repair of the gapped genome, followed by transcription.

**II-Replication of Viruses**

Stages of viral replication

1-Attachment

2-Penetration

3-Uncoating

4-Viral synthesis

5-Assembly

6-Release

7-Latency

8-Transformation

**1-Attachement**

In most cases, specific attachment proteins on the surface of viruses bind to specific receptors on the surface of animal cells. Cellular receptors are differ for different viruses but are usually either glycoproteins or glycolipids.

The specific interaction between attachment proteins and cellular receptors is a major determinant of the host-range, or tropism of the virus. Some viruses have a very narrow host range, meaning that they can only infect one or a small number of cell types, while others have broad host ranges, meaning that they can infect a large number of different cell types.

In some cases the virus binds protein sequences(e.g. Picornaviruses) and in others oligosaccharides (e.g. Orthomyxoviruses and Paramyxoviruses).

Receptor binding is believed to reflect fortuitous configurationally homologies between a virion surface structure and a cell surface component. For example, human immunodeficiencyvirus 9HIV) binds to the CD4 receptor on the cells of the immune system, the nicotinic acetyle cholin receptor and the neural cell adhesion molecule(CD56) are receptor for Rhabdoviruses.

The presence or absence of receptors plays an important determining role in cell tropism and viral pathogenesis. Not all cells in a susceptible host will express the necessary receptor; for example, Poliovirus is able to attach only to cells in the CNS and intestinal tract of primates. Each susceptible cell may contain up to 100,000 receptor sites for a given virus.

Understanding these virus/cell interactions can be important in treating and/or preventing disease. For example, antibodies that bind to the viral attachment molecule or to the cellular receptor can disrupt the normal interactions and prevent the first steps of the viral life cycle, thereby preventing infection. This is an important consideration in the development of vaccines.

Viruses typically attach to cells via specific cell surface receptors. Very often, virus receptors are molecules which project some distance away from the cell surface, allowing them to be contacted more easily by viruses.

Rabies viruses are able to infect the nerve cells of all mammals because their receptors are common to neural cell of all mammals. Also, **the cells of some organs and tissues are more susceptible than others to infection with certain viruses. This is called tissue tropism.**

**2-Penetration:**

Following attachment, virions can enter cells by one of two main mechanisms:

**1-Endocytosis:** Many viruses enter cells via receptor mediated endocytosis . In this pathway, viruses bind to receptors at coated pits. The coated pits pinch off to form coated vesicles, which are uncoated and then fuse with endocytic vesicles. As they go through this process, the endosomes become more acidic.

Acidification within the vesicle triggers changes in virion proteins and surface structures. For example, for Picornavirus the capsid protein VP4, leads to release of the viral RNA from the virion into the cytoplasim. Similarly, at the acidic pH of the endosome, the hemagglutinin molecule of influenza virus undergoes a conformational change, which enables fusion to occur between the viral envelope and the endosomal membrane, leading to release of the viral nucleocapsid into the cytoplasm. Many other non-enveloped and enveloped viruses undergo comparable changes.

**2-Fusion with Plasma Membrane**

The F (fusion) glycoprotein of paramyxoviruses causes the envelope of these viruses to fuse directly with the plasma membrane of the cell, even at pH 7. This allows the nucleocapsid to be released directly into the cytoplasm. A number of other enveloped viruses have the ability to fuse the host cell plasma membrane with their own envelope, thereby gaining entry of their nucleic acid.



**growth analysisof the virus can be divided into several phases:**

1-**Adsorption of virus (initial phase).**

2. **Eclipse phase**. This lasts for 10-12 hours, and it corresponds to the period during which the input virus becomes uncoated. As a result, no infectious virus can detected during this time (any infectious virus detected is simply virus that is still stuck on the cell membrane).

3. **Synthetic phase**. This starts around 12 hours post-infection and corresponds to the time during which new virus particles are assembled.

4**. Latent period**. During this period, no extracellular virus can be detected. After ~18 hours, extracellular virus is detected. Ultimately, production will reach a maximum plateau level,

In order for a virus to replicate, viral proteins must be synthesized by the host cell protein-synthesizing machinery. Therefore, the virus genome must be able to produce a usable m RNA.

The unique feature of viral multiplication is that soon after interaction with the host cell, the infecting virion disrupted and its measurable infectivity is lost. This phase of growth cycle is called eclipse period; its duration varies depending on both the particular-virus and the host cell, and its followed by an interval of rapid accumulation of infectious progeny virus particles.

**Eclipse period** The period of time between infection by a virus and the appearance of the mature

virus within the cell.

Differences between the two viruses shown include the fact that WEE(western equine enceplitis) replicates more rapidly than adenovirus.

But that it does so to lower titers. In addition, WEE is an enveloped virus.

This means that WEE must acquire its envelope from the host cell membrane during budding, in order for it to become infectious. Consequently, the level of intracellular infectious WEE is low. In contrast, adenovirus is non-enveloped, and therefore its infectivity is not dependent on budding from the host cell membrane. Consequently, the levels of infectious intracellular adenovirus can be very high. Indeed, they can be considerably higher than the levels of cell-free virus, suggesting that adenovirus is highly cell-associated.

**3-Uncoating**

Uncoating occurs concomitantly with or shortly after penetration, which means a physical separation of the viral nucleic acid t become function.

With some viruses, the genome is completely released from the capsid during or after penetration for example (Picornavirus) whereas in others, may be released as nucleocapsid such as such as retroviruses and reoviruses.

These capsids have undergone some conformational changes during infection that allow viral gene expression and/or replication to begin, and the resulting structures are sometimes known as partially uncoated particles.

Since almost all DNA viruses replicate in the nucleus of infected cells, they must be targeted there. In many cases the entire nucleocapsid enters the nucleus, where uncoating then takes place.

For viral genes to become available for transcription, it is necessary that virions be at least partially uncoated. In the case of **enveloped RNA** viruses that enter by fusion of their envelope the nucleocapsid is discharged directly into the cytoplasm and **transcription** commences from viral nucleic acid still associated with this structure.

With the **non-enveloped icosahedral reoviruses**, only certain

capsid proteins are removed and the viral genome expresses all its functions without ever being released from the virion core. For some viruses that replicate in the nucleus, the later stages of uncoating occur there rather than in the cytoplasm.

In some cases, as soon as the viral nucleic acid enter the host cell, the cellular metabolism is required exclusively toward the synthesis of new virus particles and the cell will be destroyed.

In other cases, the metabolic processes of the host cell are not altered significantly, although the cell synthesizes viral proteins and nucleic acid, and the cell is not killed.

After synthesis of viral nucleic acid and viral proteins, the components assemble to form new infectious virions. The yield of infectious virus per cell ranges, from modest numbers to more than 100,000 particles.

The duration of virus replication cycle also varies widely, from 6-8 hours(Picornaviruses) to more than 40 hours (some herpesviruses).

**4-Viral Synthesis**

The essential viral replication is that **specific mRNA** must be transcribed from the **viral nucleic acid** for the successful expression and duplication of genetic information.

Once this is accomplished, virus use cell components to **translate the mRNA**.

Various classes of viruses use different pathways to synthesize the mRNA depending upon the structure of the viral nucleic acid. Some viruses (e.g. Rhabdoviruses, Paramyxoviruses, Orthomyxoviruses) carry RNA polymerases to synthesized

m RNAS. RNA of this type are called **negative stranded(negative sense)viruse.**

In Retroviruses (ssRNA) carry **reverse transcriptase** which used to synthesize DNA(proviral DNA).

In Picornaviruses and Togoviruses (+ssRNA) they carry an **nucleic acid which act as mRNA**

**A-Transcription of early mRNA**

In DNA viruses DNA dependent RNA polymerase (Transcriptase) is responsible for the transcription of mRNA. In RNA viruses, and if the N.A. is positive polarity, it can act directly as mRNA. If the viral N.A. is negative polarity, it carried its own RNA dependent RNA polymerase that transcripts a positive strand from negative strand. This newly formed RNA acts as mRNA.

**B-Translation of early proteins**

The formed early mRNA moves to cellular ribosome to be translated into viral proteins required for viral replication. They are mostly enzymes required for replication of viruses or shutdown proteins to stop all the cellular activity.

**C-Replication of Viral N.A.**

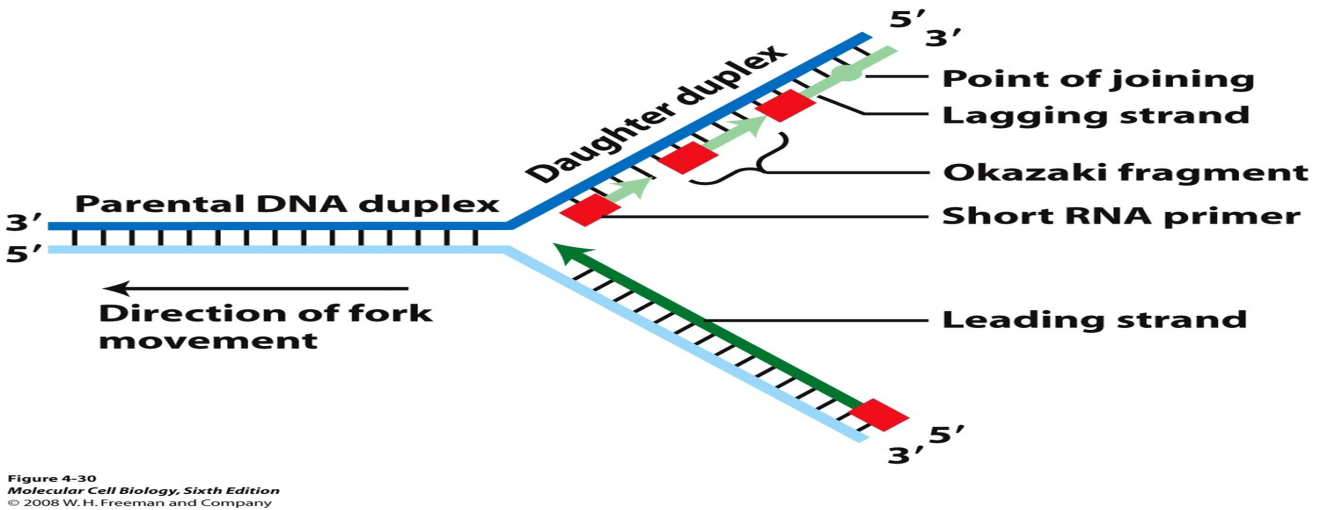
The synthesis of viral nucleic acid may involve transcription into replicative or intermediate phases and may require the co-operation of primers, promoters, and group of enzymes which included polymerases, replicases and ligases. It is not uncommon for early viral proteins to act as primers by binding to the terminal end of the genome and initiating replication. Replication of the new complimentary N.A starand proceed in 5´ to 3´ terminal direction and start at the 3´ end of the parental strand.

Different strategies are observed associated with the type of nucleic acid, RNA or DNA , single or double stranded.

Group 1: ds DNA

1. Non-structural early viral proteins are produced by the viral mRNA. They bind to cellular DNA and prim cellular DNA synthesis. This provides the way for subsequent intranucleir replication of the viral N.A in resting cells but also can cause oncogenesis. Two strategies of N.A. replication occur in this group. Continuous and semi –continuous, in continuous replication a terminal loop is formed on one of the two strands of the DNA and synthesis occurs in a 5´ to 3´ direction. The other parenteral strand is displaced as this occurs and acts as a template to form another ds replicative DNA. In the semi-continuous replication the synthesis of the both strands of DNA occurs. Simultaneously from one end. As new DNA is only synthesis in 5´ to 3´ direction it follow that the lower strand must be made in a serious of short sequence which are subsequently joined by ligases. Some ds DNA viruses have circular genome(papovavirus) as early viral protein initiates unwinding to a liner configuration prior to semi-continuous replication.
2. In group B viruses, as in group A, but viral NA replication occurs in the cytoplasm and the viral DNA polymerase is a structural protein.

Continuous replication, terminal loop replication dss DNA .1- The loops are formed at the end of the ssDNA.2- These allow synthesis of complementary strand of DNA .3- Cleavage of the original loop results in the ds replicative DNA.



Semicontinuous replication is suggested in the replication of dsDNA. The nucleic acid can only be red from the 3´ end, thus only short sequence (10-20 nucleotides)can be red discontinuously from the lower 5´ to 3´ strand using a primer. These sequence are then ligated to form the new DNA. The small DNA fragments formed are known as okazaki fragments.

Group 2: ssDNA viruses

They also use terminal loops to initiate a double stranded DNA. The loop is then broken to make double stranded replication DNA as a template for new viral DNA.

Group 3: ds RNA viruses

Viral m RNA is transcribed into negative RNA. This combined with m RNA to give genomic as RNA.

**Group 4 and 5: ss RNA viruses**

With positive and negative sense(polarity) reproduce their genomes by forming complete complementary transcripts which are used as templates for synthesis of the genome.

**Group 6: Retroviruses:**

Are unique a mongast +ve ssRNA viruses because they convert to dsDNA utilizing the reverse transcriptase(RT) enzyme (an RNA dependant DNA polymerase). The ds DNA then codes for new +ve ssRNAs which screw as new genome or mRNAs. The RT enzyme is a structural protein which is released into the cytoplasm during viral uncoating.

5-Assembly of Viruses

Nucleocapsid assembly occurs at the site where nucleic acid is formed. With unenveloped viruses the nucleocapsids become packed into a crystalline array of new virus particles.

In enveloped viruses, viral glycoproteins migrate from ribosomes via the endoplasmic reticulum to the host cell membrane. At the membrane, individual glycoprotein becomes grouped into cylindrical spikes or into spikes with a knob and stalk.

During the assembly of an enveloped virus the nucleocapsid aligns underneath plasma or nuclear membrane. A layer of protein (the matrix and inner coat protein) then becomes incorporated into the lipid membrane above the nucleocapsid. During this stage of envelope formation, host cell transmembrane glycoproteins are replaced by viral glycoprotein spikes. The nucleocapsid then evaginates through the spike the spiky membrane which envelope it as it buds outside.

**6- Release of virus**

Non-envelpoed viruses are released when the cell dies and disintegrates. Example: The burst of adenovirus from nucleus. Virus which incorporate plasma membrane leave the cell as they bud through the plasma membrane for example: orthomyxo, paramyxo and retroviridae. Many released virion are non-infectious(90-99%). This may result from their genome being incomplete, from their proteins being incompletely cleaved or from denaturation between release and assemble.

7- Latency

Some viruses become latent. In this situation the pro-viral DNA becomes integrated into the host cell chromosomes without viral replication, examples, Herpesvirus in ganglion cells or lymphoblasts, Retrovirus in retreculo-endothelial cells.

Latency is important because such infections can reactivate in vivo under stress. For example when cortico-steroid level rise and deepens the immune response to the virus. A cycle of viral replication then occurs with the possibility of resultant clinical disease and also the spread of infection

**8- cell transformation and viral neoplasia**

Oncogenic viruses induce neoplasia in vivo. Some Rous sarcoma viruses of chickens and bovine papilloma virus cause cell transformation of normal cell lines in vitro.

A-the cell becomes immortal and cell division continues indefinitely if nutrients and space are supplied.

B-the cells become rounded and grew to a higher density than normal cells which are contact inhibited in the monolayer.

C-chromosomal abnormalities develop (tetra-ploidy)

**III-Effects of Viruses on Cells**

The result of infection on the host cell may be:

A-Cell killing or cytopathic effectd (CPE).

B-No overt effect (non-cytocidal)

C-Transformation of cells to a neoplastic state.

**A- Cytopatogenic effet of the viruses**

1-Morphological alteration or death of infected cells.

2- Toxic effect of viral protein in host cell, and inhibition of cellular protein and cellular RNA, DNA all cause death of infected cell.

3-infected cells may fuse into syncytia

4-rounding of cells and ballooning

5-development of inclusion bodies (Negri bodies in rabies as intracytoplasmic and intranuclear antibodies in infectious canine hepatitis.

6- Release of viruses rupture the membrane of the cell causing death of the cell.

**Causes of CPE**

A- cell shutdown

Picornaviruses-have cell shutdown proteins

B-physical damage to cell membranes.

-insertion of viral proteins and glycoproteins in plasma membrane or nuclear membrane.

-budding of viruses from both membranes.

-rupture of membranes

C-Altered plasma membranes

The insertion of viral proteins in plasma membrane of host cells has three aspects:

Firstly: fusion proteins may lead to syncytium formation.

Secondly: inserted viral proteins appear as foreign antigens to the immune system.

Thirdly: viral HA proteins enable red cells to adhere to virus infected cells in culture which is called hemadsorption.

D-damage to cell lysosomal membranes

components of viral synthesis may be toxic to the cell and destroy lysosomal membranes and thereby release autolytic enzymes, which cause cell rounding, death and final dissolution of dead cell.

**B- Non-overt effect (non cytocidal)**

The virus or its nucleic acid in latency replicates but without damaging the cell in 3 situations:

A-steady state infection.

All cells become infected but continue to divide and continually replicate virus e.g. leukemia viruses and some non-cytocidal strains of bovine viral diarrhea virus.

B-carrier cell cultures.

a minority of cells are infected and the CPE may be transient,e.g. feline panleukopenia virus which replicates only if cells are at the DNA synthesis (S) phase.

C-latency infections.

Viral NA is integrated into chromosomal DNA as provirus like in herpes viruses and retroviruses.

**C- cell transformation and viral neoplasia**

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