College of Veterinary Medicine

VIROLOGY

I-Classification and Nomenclature of Viruses
II-Replication of Viruses
III-Effects of Viruses on Cells

We can differentiate **ssDNA from that of dsDNA** by **acridine orange staining**:

dsDNA → Yellow-green

ssDNA → red to orange

We can differentiate single stranded RNA from double stranded RNA by the use of acridine orange stain

dsRNA → yellow to orange

ssRNA → red to orange

We can differentiate RNA from DNA by the use of digestion enzymes like, RNAse for RNA and DNAse for DNA.

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 by phenotypic characteristics, such as **morphology**, **nucleic acid type**, mode of **replication**, **host organism** and the type of **disease they cause**.

Viruses are classified on different bases:

Criteria of Classification

1-According virus genome properties including:

A- Nucleic acid (DNA or RNA)

B- Size of genome in kilobases(KB).

C- Stranded(single or double)

D-Whether liner or circular

E- Segment(number, size)..

2-Virion morphology, including:

A- Size

B- Shape

C- Type of symmetry

D- Presence or absence of peplomers

E- Presence or absence of membrane.

3-Physicochemical properties of the virion, including

A- Molecular mass

B- buoyant density

C- PH stability

D- Susceptibility to physical and chemical agents, especially **ether** and **detergents.**

4- Virus proteins properties including

A- Number, size, and functional activities of structural and nonstructural proteins

B- Amino acid sequence

C- Modifications(glcosylation, phosphorylation)

D- Special functional activities(transcriptase, reverse transcriptase, neuraminidase, fusion activities.

5-According to the disease they caused into:

a-Generalized disease viruses: ex. Measles, dengue, vaccinia, yellow fever, chicken pox,

b-Viruses affected certain organs:

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

2-Viruses of Respiratory System (Orthomyxoviruse, Rhinoviruses).

3-Viruses of skin and mucous membrane (Orf, Herpesvirus).

4-Viruses of eye infection (adenoconjuctivitis).

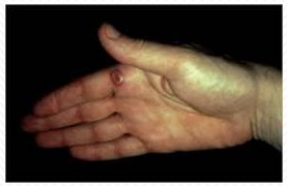
5-Viruses of liver infection (Hepatitis viruses).

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

7-Viruses of digestive tract. (Rota virus, enterovirus).

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

9)-Viruses transmitted via insects, like Arboviruses (Arthropod born viruses)



6-There is an old classification of viruses according to such class can be grouped into:

A-Enteroviruses: for examples; Coronavirus, Rotavirus, adenovirus.

B-Respiratory viruses: for examples; Orthomyxo viruses, Paramyxo viruses.

C-Virus transmitted by insect (Arbo viruses): for examples; dengue fever virus, Yellow fever viruses.

The Origen 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**

The Origen Names of Viruses

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 =	=	Latent
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 disease)

F-Geographic area or town

Bunya = Bunyayera in Uganda

The name (Papova) derives from three abbreviations: Pa for papillomavirus, Po for polyomavirus, and Va for "vacuolating belonged to simian vacuolating virus 40 or SV40, which is now known to be part of the polyomavirus genus.

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. Lower levels, such as subspecies, strains and variant.

- **Taxonomy from Order downward**

Viruses are classified into:

Orders	**ended with**	***virales***
Families	**ended with**	***viridae***
Subfamilies	**ended with**	***virinae***
Genera	**ended with**	***virus***
Species		
Types		
Subtypes		
Strains		
Variants		

Classification

- **Example:**
-
- **Order** ***Mononegaviralis*** **(Italic started with uppercase letter)**
- **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 is classified as:

- Order *Mononegavirales*
- Family *Filoviridae*
- Genus *Filovirus*
- Species: *Ebola virus Zaire*

The Advance Classification of Viruses

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The establishment of an order is based on the inference that the virus families it contains have most likely evolved from a common ancestor.

The majority of virus families remain unplaced.

As of 2012, seven orders, 96 families, 22 subfamilies, 420 genera, and 2618 species of viruses have been defined by the ICTV.

The 7 orders are the(Caudovirales, Herpesvirales, Ligamenvirales, Mononegavirales, Nidovirales, Picornavirales, and Tymovirales).

These orders span viruses with varying host ranges. The Ligamenvirales, infecting archaea, are the most recent addition to the classification system.

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 (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication.

Named after David Baltimore, a Nobel Prize-winning biologist, these groups are designated by Roman numerals.

Other classifications are determined by the disease caused by the virus or its morphology, neither of which are satisfactory due to different viruses either causing the same disease or looking very similar.

In addition, viral structures are often difficult to determine under the microscope. Classifying viruses according to their genome means that those in a given category will all behave in a similar FASHION, offering some indication of how to proceed with further research


David Baltimore

The Baltimore classification, developed by David Baltimore, by this classification they put the viruses into families, depending on

The structure and Type of Nucleic Acid (N.A.)

This classification places viruses into seven groups:

I-dsDNAvruses (e.g. Adenoviruses, Herpesviruses, poxviruses, Papillomavirus, Polyomavirus).

II- ssDNA viruses(+)senseDNA(e.g. Parvoviruses).

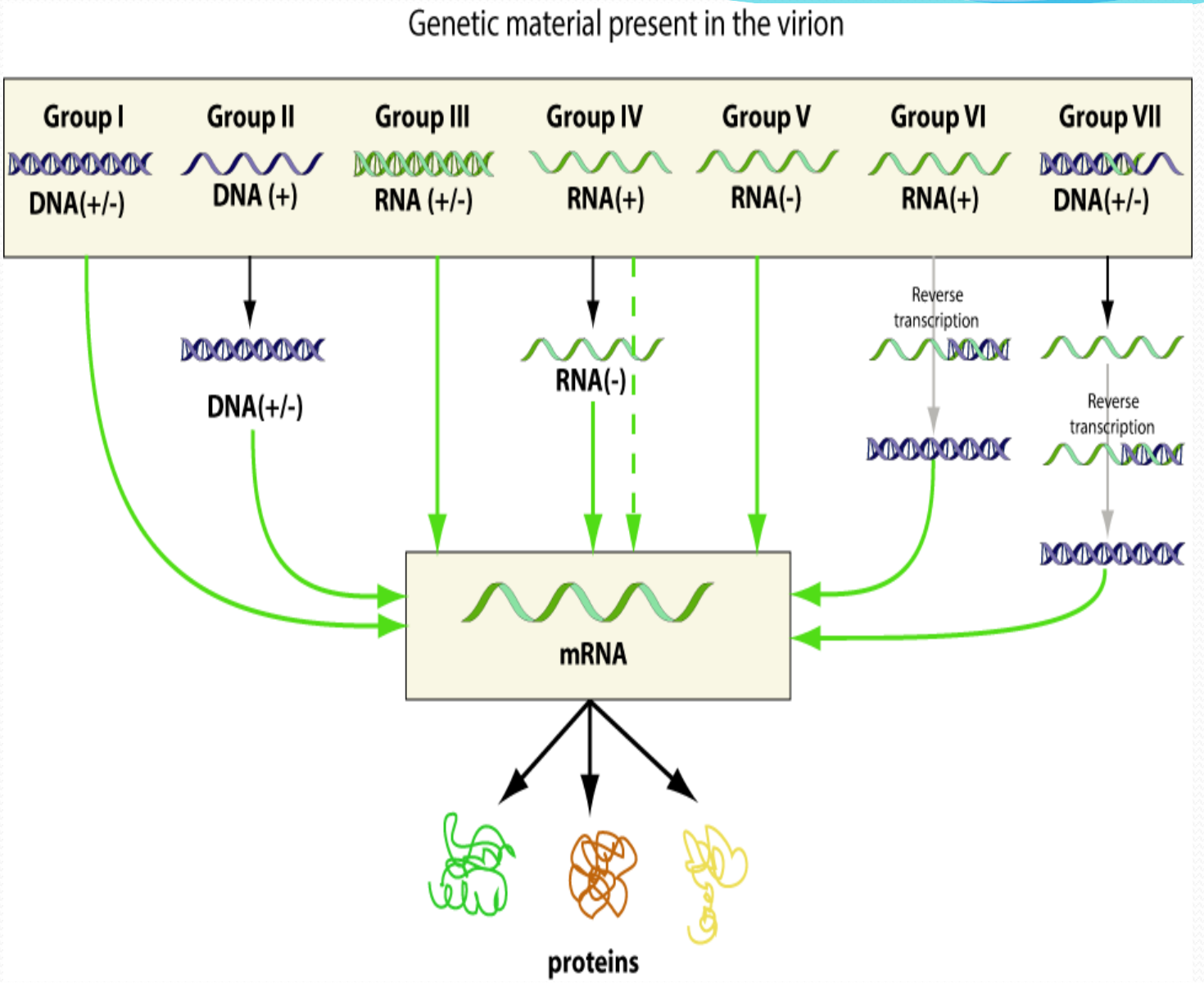
III- dsRNA viruses (e.g. Reoviruses, Birnaviruses).

IV- (+)sense ssRNA viruses (e.g. Picornaviruses, Togaviruses, Coronavirus, Flavivirus).

V- (-) sense ssRNA viruses (e.g. Orthomyxoviruses, Rhabdoviruses, Paramyxovirus).

VI- ssRNA-RTviruses (+) sense RNA with DNA intermediate in lifecycle (e.g. Retroviruses).

VII-ds DNA –RT viruses (e.g. Hepadnaviryses).


Genetic material present in the virion
Group I
DNA(+/-)
Group II
DNA (+)
Group III
RNA (+/-)
Group IV
RNA(+)
Group V
RNA(-)
Group VI
RNA(+)
Group VII
DNA(+/-)
DNA(+/-)
RNA(-)
Reverse transcription
Reverse transcription
mRNA
proteins

V·T·E	Baltimore (virus classification)
DNA	I: dsDNA viruses
	II: ssDNA viruses
RNA	III: dsRNA viruses
	IV: (+)ssRNA viruses (primarily icosahedral)
	V: (-)ssRNA viruses (primarily helical)
RT	VI: ssRNA-RT viruses
	VII: dsDNA-RT viruses

Group I: Double-stranded DNA viruses:

These types of viruses must **enter the host nucleus before they are able to replicate**. Furthermore, these viruses **require host cell polymerases to replicate the viral genome** and, hence, are highly dependent on the cell cycle. Proper infection and production of progeny requires that the cell be in replication, as it is during replication that the cell's polymerases are active. The virus may induce the cell to forcefully undergo cell division, which may lead to transformation of the cell and, ultimately, cancer. **Examples include Herpesviridae, Adenoviridae, and Papovaviridae.**

There is only one well-studied example in which a class 1 virus is not replicating within the nucleus: **the Poxvirus family**, a highly pathogenic virus that infects vertebrates and includes the smallpox virus. The mRNA is transcribed in the normal way from viral DNA using the host transcriptase enzymes, into two types of mRNA's:

1) early mRNA, transcribed prior to the synthesis of viral DNA, and
2) late mRNA, transcribed from progeny DNA.

Group II: Single-stranded DNA viruses

Viruses in this category include the **Anelloviridae, Circoviridae, and Parvoviridae** (which infect vertebrates), **the Geminiviridae and Nanoviridae** (which infect plants), and the **Microviridae** (which infect prokaryotes). Most of them have circular genomes (the parvoviruses are the only known exception).

Viruses that replicate via RNA intermediates need an RNA-dependent RNA-polymerase to replicate their RNA, but animal cells do not seem to possess a suitable enzyme. Therefore, this type of animal RNA virus needs to code for an RNA-dependent RNA polymerase.

Group III: Double-stranded RNA viruses:

As with most RNA viruses, this class replicates in the "Core" **capsid that is in cytoplasm**, **not** having **to use the host replication polymerases to as much a degree as DNA viruses**. This family includes 2 major families, the Reoviridae and Birnaviridae.

Replication is monocistronic and includes individual, segmented genomes, meaning that each of the genes codes for only one protein, unlike other viruses that exhibit more complex translation.

Group IV & V: Single-stranded RNA viruses

The ssRNA viruses belong to Class IV or V of the Baltimore classification. They could be grouped into **positive sense or negative** sense according to the sense of polarity of RNA. The single stranded RNA is **the common feature** of these viruses. The replication of viruses happens **in the cytoplasm or nucleus** (for segmented class V viruses

Group IV: Single-stranded RNA viruses - Positive-sense:

The positive-sense RNA viruses and indeed all RNA defined as positive-sense can be directly **accessed by host ribosomes to immediately form proteins**. These can be divided into two groups, both of which reproduce in the cytoplasm: **Viruses with polycistronic mRNA** where the genome RNA forms the mRNA and is translated into a polyprotein product that is subsequently cleaved to form the mature proteins. All of which are different mechanisms with which to produce proteins from the same strand of RNA. Examples of this class include the families Astroviridae, Caliciviridae, Coronaviridae, Flaviviridae, Picornaviridae, Arteriviridae, and Togaviridae.

In these viruses, the virion (genomic) RNA is the same sense as mRNA and so functions as mRNA. This mRNA can be translated immediately upon infection of the host cell.

Group V: Single-stranded RNA viruses - Negative-sense:

The negative-sense RNA viruses and indeed all genes defined as negative-sense **cannot be directly accessed by host ribosomes to immediately form proteins**. Instead, they must be transcribed by viral polymerases into a "readable" form, which is the positive-sense reciprocal. These can also be divided into two groups: Viruses containing nonsegmented genomes for which the first step in replication is transcription from the (-)-stranded genome by the viral RNA-dependent RNA polymerase to yield monocistronic mRNAs that code for the various viral proteins. A positive-sense genome copy is then produced that serves as template for production of the (-)strand genome. Replication is within the cytoplasm. Viruses with segmented genomes for which replication occurs in the nucleus and for which the viral RNA-dependent RNA polymerase **(RdRp)** produces monocistronic mRNAs from each genome segment. The largest difference between the two is the location of replication. Examples in this class include the families Arenaviridae, Orthomyxoviridae, Paramyxoviridae, Bunyaviridae, Filoviridae, and Rhabdoviridae (the latter of which includes the rabies virus).

Group VI: Positive-sense single-stranded RNA viruses that replicate through a DNA intermediate ssRNA-RT virus:

A well-studied family of this class of viruses include the **retroviruses**. One defining feature is the use of **reverse transcriptase** to convert the **positive-sense RNA into DNA**. Instead of using the RNA for templates of proteins, they use DNA to create the templates, which is spliced into the host genome using integrase. Replication can then commence with the help of the host cell's polymerases.

Group VII: Double-stranded DNA viruses that replicate through a single-stranded RNA intermediatedsDNA-RT virus:

This small group of viruses, exemplified by the **Hepatitis B** virus (which is in the Hepadnaviridae family), have a double-stranded, gapped genome that is subsequently filled in to form a covalently closed circle (cccDNA) that serves as a template for production of viral mRNAs and a subgenomic RNA. The pregenome RNA serves as template for the viral reverse transcriptase for production of the DNA genome.

-The virus are Not cells

Smallest infectious agent (20nm to 300 nm)

smallest RNA virus: Picornavirus

smallest DNA virus: Parvovirus

largest virus: Poxvirus

Most of viruses have spherical shapes **EXCEPT**

Rhabdovirus: bullet-shaped, **Poxvirus: brick-shaped**

Bacteriophage: tadpole-shaped

Tobacco Mosaic virus: rod-shaped

Do not undergo mitosis or binary fission

Do not have cell wall & ribosome

Sensitive to interferon

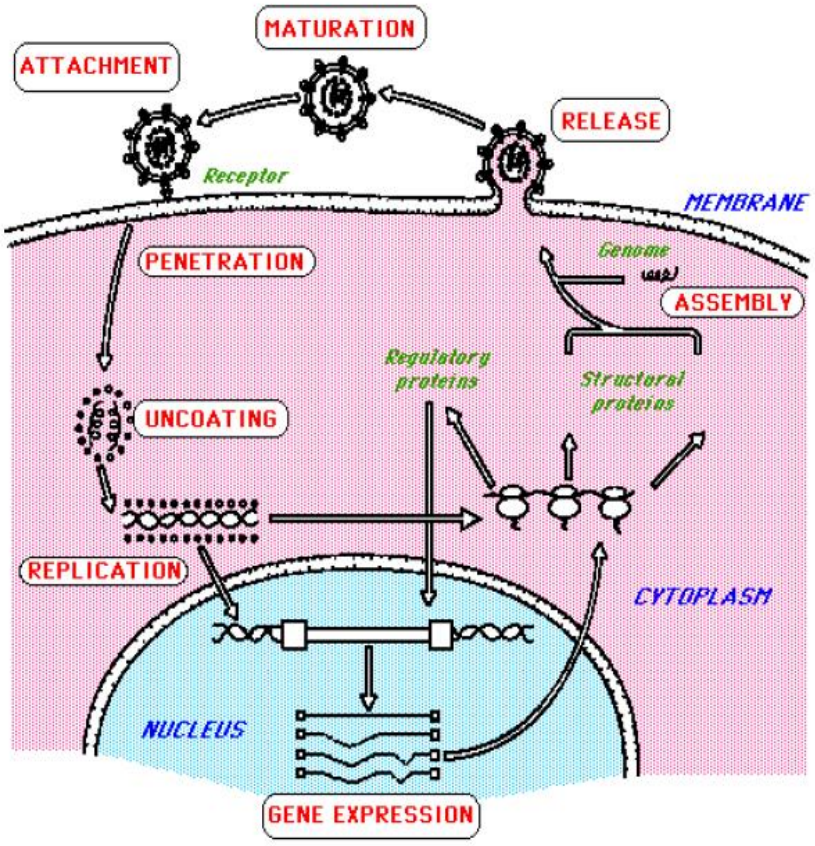
viral nucleic acid (genome) contain the genetic material necessary for replication either a dna **or** rna maybe single-stranded or double-stranded.

Replication of Viruses

Stages of viral replication

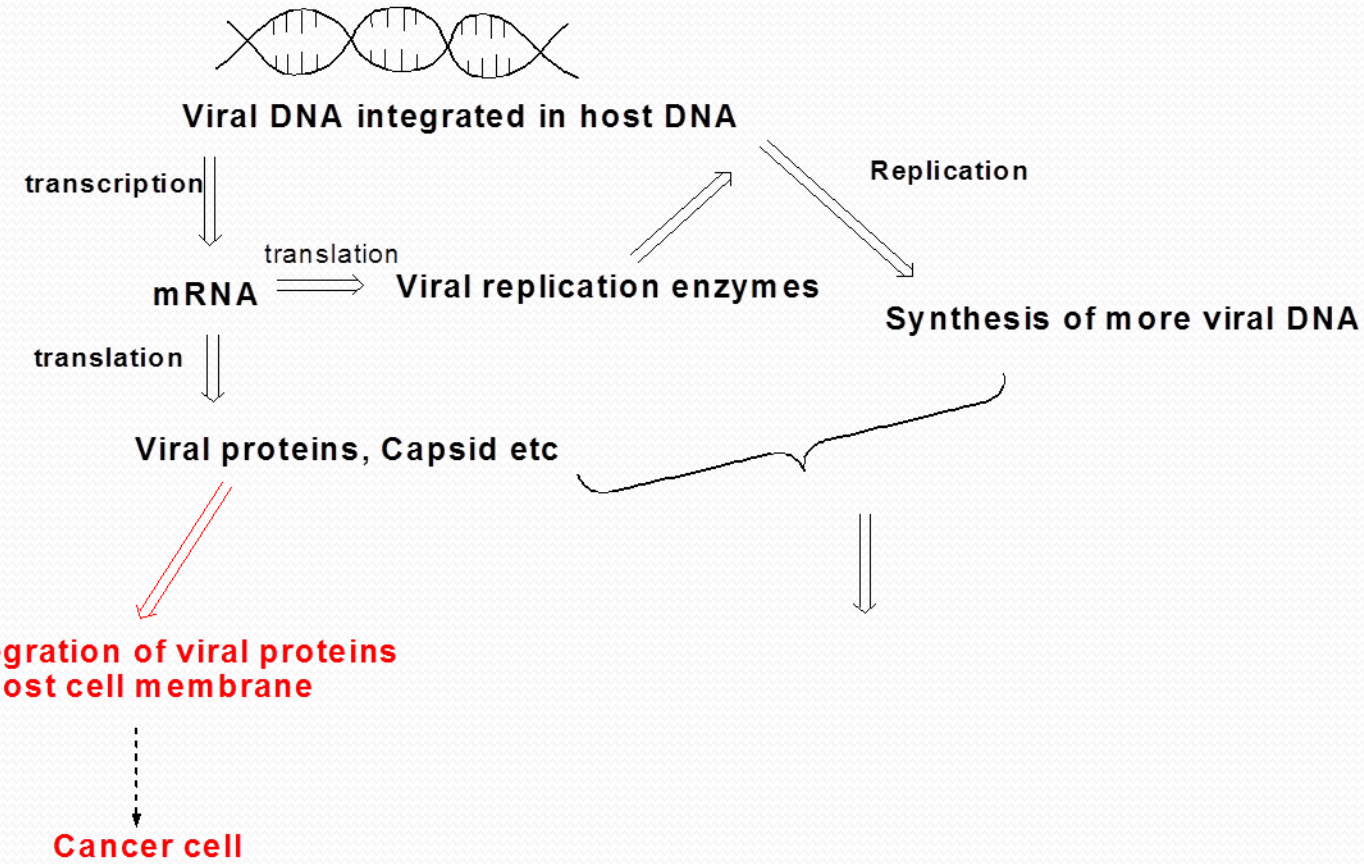
- 1-Attachment
- 2-Penetration
- 3-Uncoating
- 4-Viral synthesis
- 5-Assembly
- 6- Release
- 7-Latency
- 8-Transformation

As the virus obligate intracellular parasites, Virus must enter and replicate in living cells in order to "reproduce" themselves. This "growth cycle" involves specific attachment of virus, penetration and uncoating, nucleic acid transcription, protein synthesis, maturation and assembly of the virions and their subsequent release fro



Stages of replication - DNA virus

Attachment, penetration, uncoating, transfer of DNA to cell nucleus



Oncogenic viruses

1-Attachment:

In most cases, specific attachment **proteins on the surface of viruses bind to specific receptors site on the surface of a 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. Also, the cells of some organs and tissues are more susceptible than others to infection with certain viruses. This is called tissue tropism.

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. This is partially determined by whether the receptor for the virus is expressed on many or a limited number of cell types. Some examples of specific viruses and their known or probable cellular receptors are given in the following table.

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.

Virus	Viral Attachment Molecule	Likely Cellular Receptor	Target Cell Type
Rabies virus (*Rhabdoviridae)*	Glycoprotein(G protein)	Acetylcholine receptor	Neuron
Rotavirus	**VP7**	**Sialic acid containing glycoprotein**	**Many cell types**
pseudorabies virus *Herpesviridae*	**gIII**	Heparin sulfate proteoglycans	Many cell types
Influenza A virus Orthomyxoviridae	Hemagglutinin (HA)	Sialic-acid containing glycoproteins	Respiratory epithelium cell
HIV	**CD4 on T-Cell**	ICAM(intracellular adhesion molecules)	**Upper respiratory epithelial certain cells of the immune system, including T cells, which help other lymphocytes identify and destroy pathogens. cells cells**

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**. **Most naked virus** enter the cell by this route.

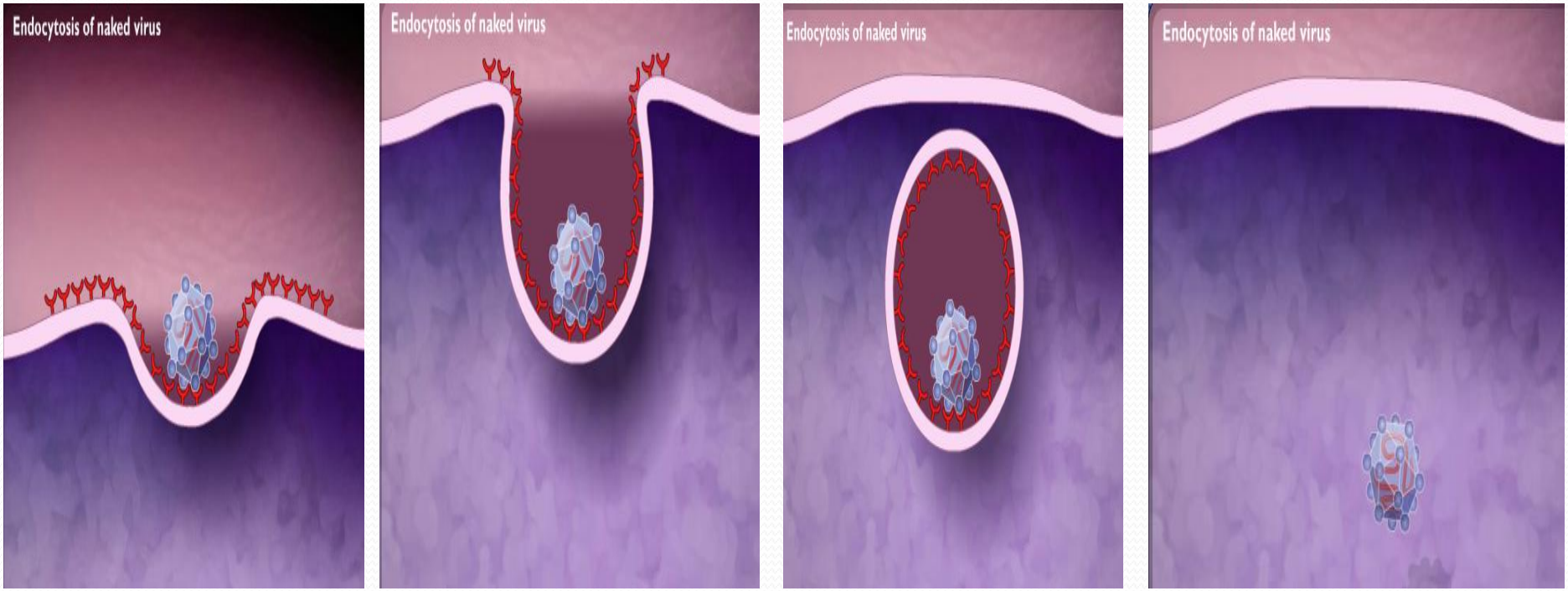
2-Fusion with Plasma Membrane

The F (fusion) glycoprotein of paramyxoviruses or herpesvirus 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.

A naked virus

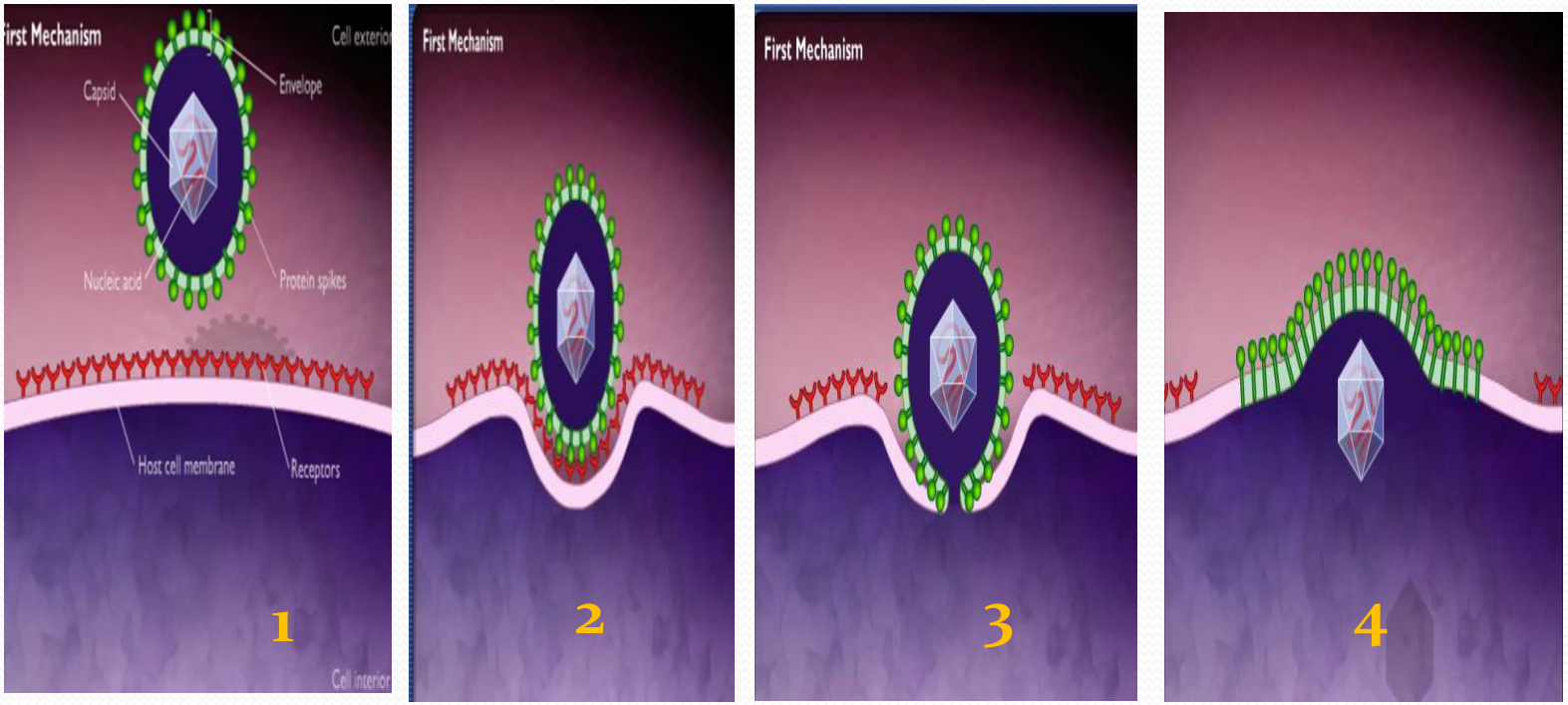
A naked virus enters the cell by endocytosis, since the virus has no envelope it cannot fuse with the plasma membrane, after being engulfed the viral nucleic acid is released from the endocytic vesicle. The nucleic acid then separates from the capsid



Enveloped viruses:

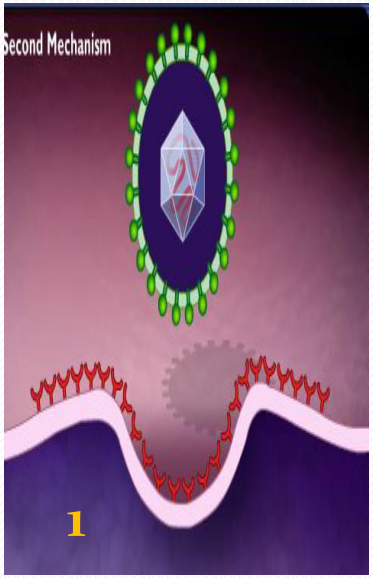
There are two mechanisms by which enveloped viruses enter host cells.
In one of the mechanisms, the virion attaches to host cell receptors by specific proteins on its surface, called spikes.

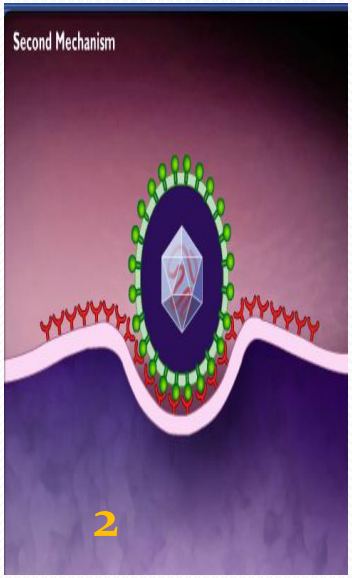
The envelope of the virus fuses with the plasma membrane of the host and the nucleocapsid is released directly into the cytoplasm. The nucleic acid then separates from the protein coat.

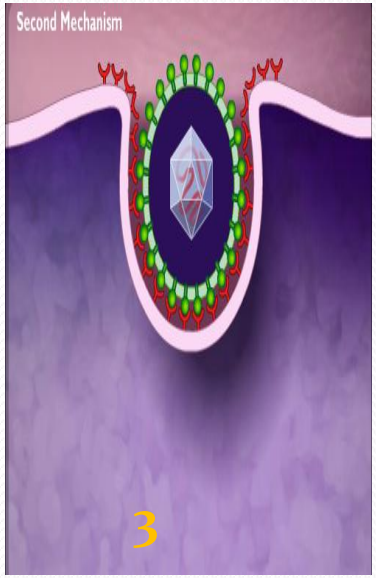


In the second mechanism, the enveloped virus adsorbs to the host cell by specific proteins on its surface and the virion is taken in by endocytosis. In this process, the host cell plasma membrane surrounds the whole virion and forms a vesicle.

The envelope of the virion then fuses with the plasma membrane of the vesicle and the nucleocapsid is released into the host's cytoplasm. The capsid protein is then removed, releasing the nucleic acid of the virus.







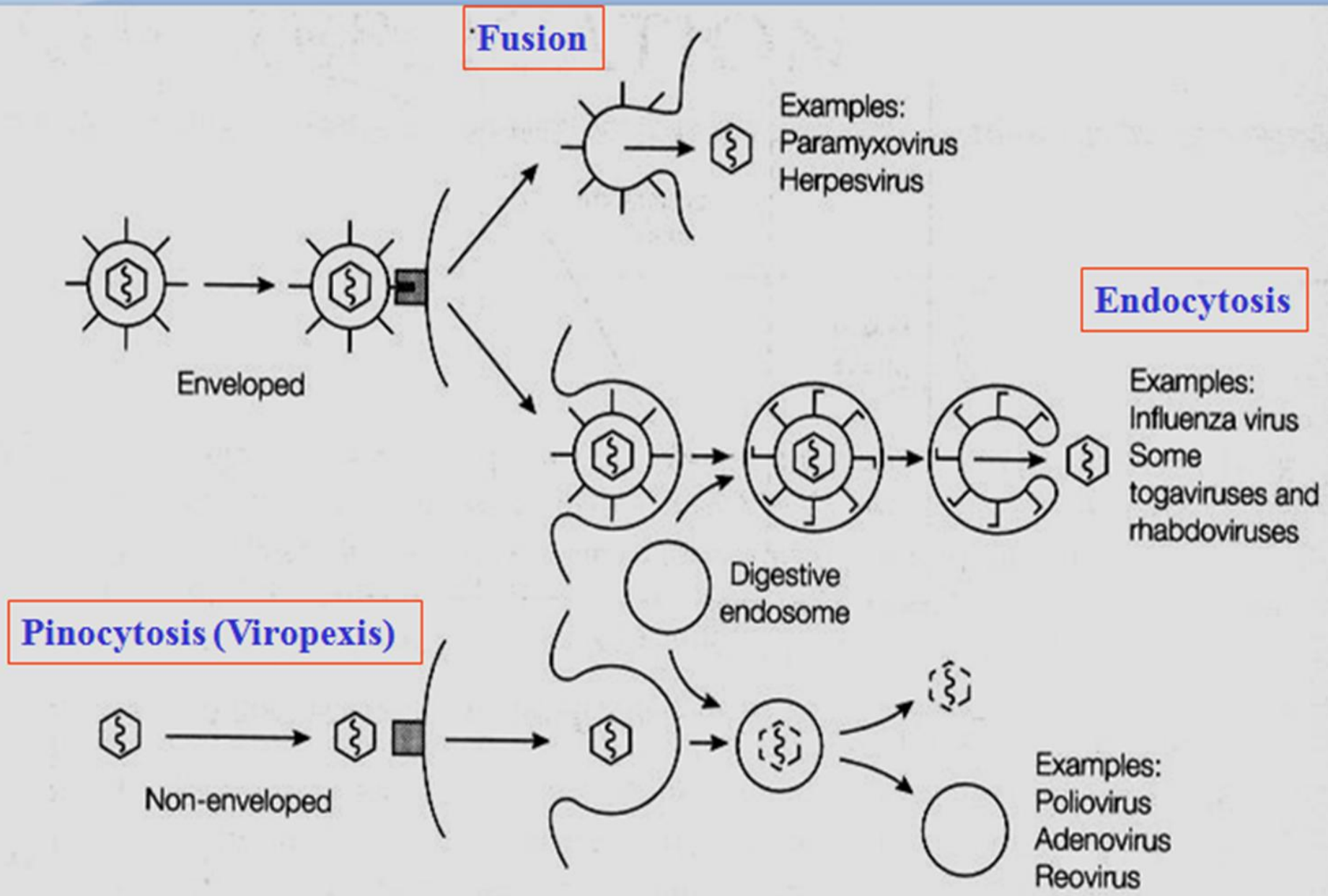
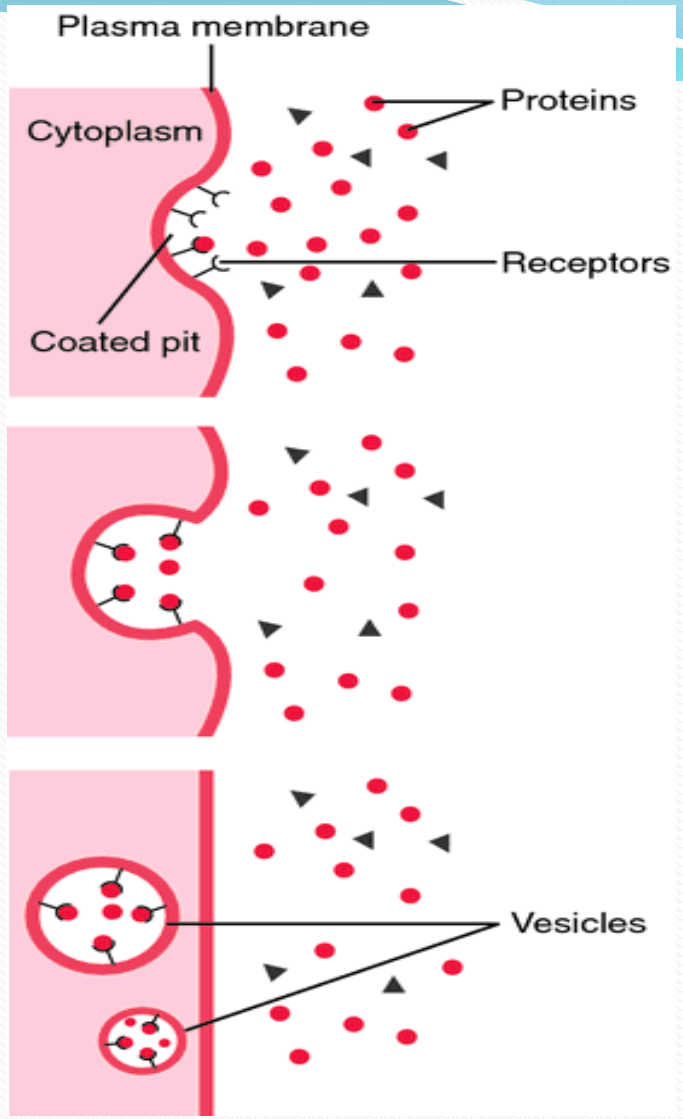


Fig. 2. Methods of virus entry. From Harper, D., Molecular Virology, 2nd edn, © *BIOS Scientific Publishers Limited, 1998.*



pinocytosis

a mechanism by which cells ingest extracellular fluid and its contents; it involves the formation of invaginations by the cell membrane, which close and break off to form fluid-filled vacuoles in the cytoplasm.

3-Uncoating

Uncoating occurs concomitantly with or shortly after penetration, which means a physical separation of the viral nucleic acid from the outer structural components of the virion so that it can function.

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

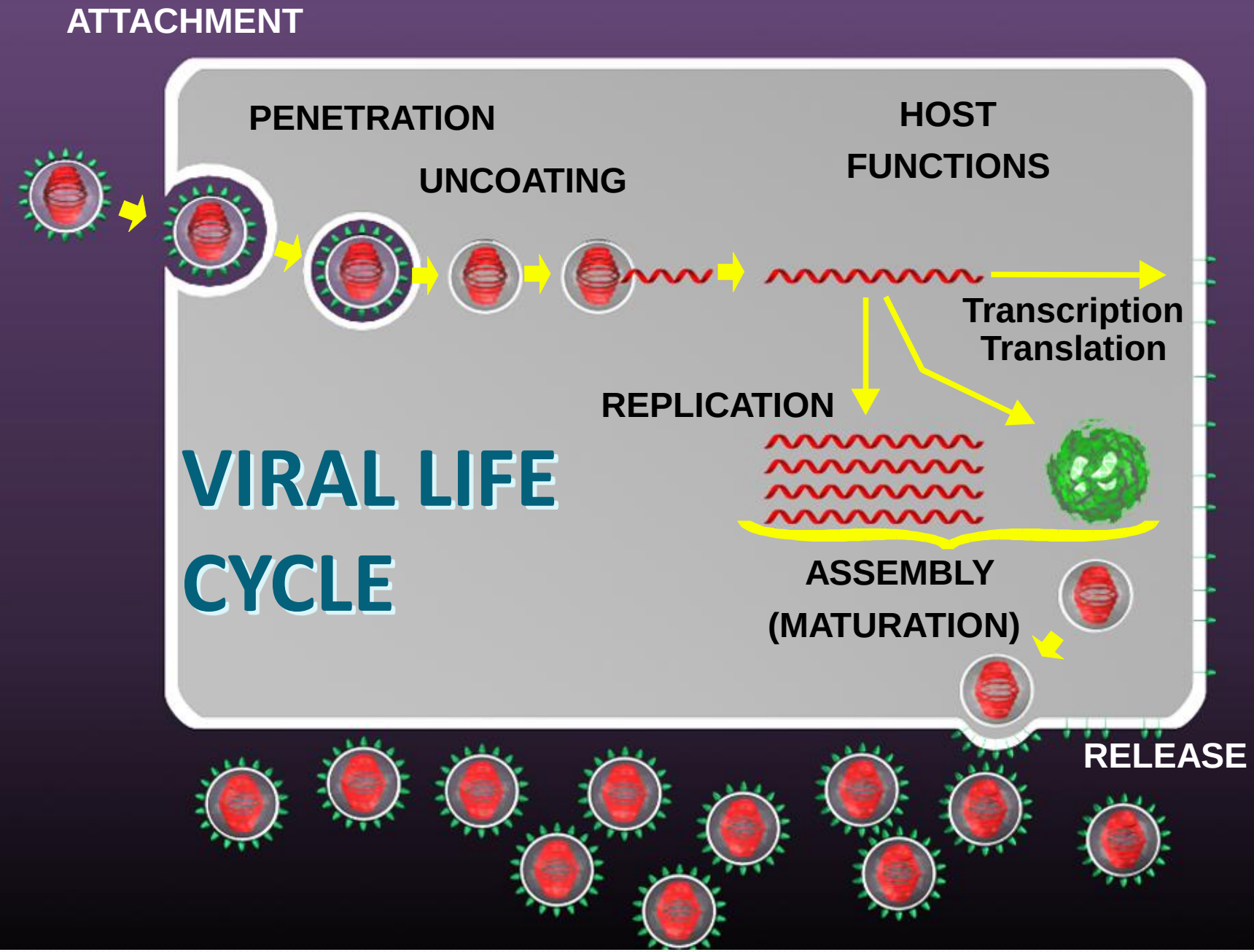
These capsids have undergone some conformational changes during infection that allow viral gene expression and/or replication to begin, and the resulting structures are sometimes known as partially uncoated particles.

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.


ATTACHMENT
PENETRATION
UNCOATING
HOST
FUNCTIONS
Transcription
Translation
REPLICATION
VIRAL LIFE
CYCLE
ASSEMBLY
(MATURATION)
RELEASE

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 synthetic phase of the viral replicative cycle follows after uncoating of the viral genome.

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**.

Note about Retroviral (HIV)

Endogenous retroviruses are always in the state of a provirus. When a (**nonendogenous)** retrovirus invades a cell, the RNA of **the retrovirus is reverse-transcribed** into DNA by reverse transcriptase, then inserted into the host genome by an integrase.

Retroviral integrase (IN) is an enzyme produced by a retrovirus (such as HIV) that enables its genetic material to be integrated into the DNA of the infected cell

Integration occurs following production of the double-stranded viral DNA by the viral RNA/DNA-dependent DNA polymerase reverse transcriptase.

The main function of IN is to insert the viral DNA into the host chromosomal DNA, a step that is essential for HIV replication. Integration is a point of no return for the cell, which becomes a permanent **carrier of the viral genome (provirus**). Integration is in part responsible for the persistence of retroviral infections. After integration, the viral gene expression and particle production may take place immediately or at some point in the future. The timing, it is presumed, depends on the activity of the chromosomal locus hosting the provirus.

A-Transcription of early mRNA

In DNA viruses: depend on DNA dependent RNA polymerase enzymes (Transcriptase) is responsible for the transcription of mRNA.

In RNA viruses, and if the N.A. is positive polarity, it can act directly act as mRNA for proteins synthesis, such virus are also can cause the infection by their nucleic acid. It means that the N.A is infectious.

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 strand 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

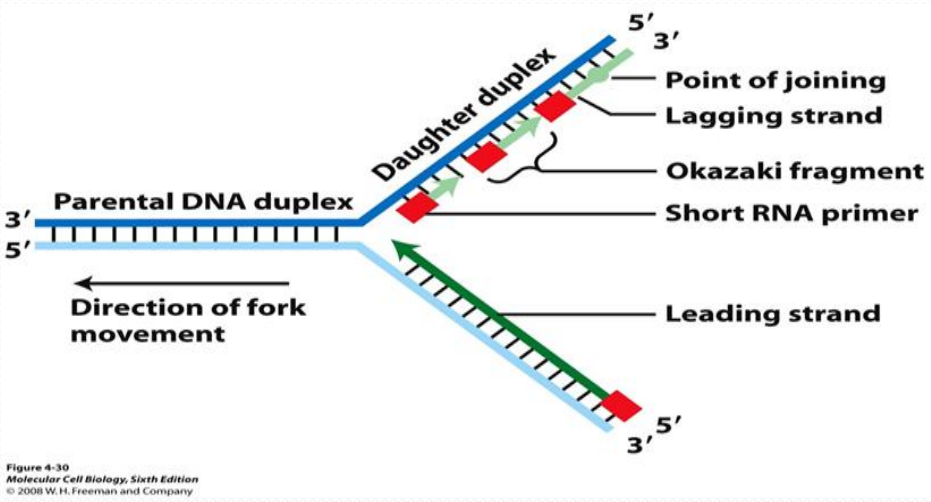
Group 1: ds DNA: **Viral protein** synthesis: virus mRNA is translated on cell ribosomes into two types of virus protein.

Structural: the proteins which make up the virus particle are manufactured and assembled.

Non – structural: not found in particle, mainly enzymes for virus genome replication.

A- **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 intranuclear 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 dsDNA viruses **have circular** genome(**papovavirus**) as early viral protein initiates unwinding to a liner configuration prior to semi-continuous replication.



B- 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, as a bove.

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(Parvoviridae)

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 mRNA is transcribed into negative RNA. This combined with mRNA to give genomic as RNA. The mRNA used in translation is synthesized from the negative strand of the dsRNA. Each negative strand produces many positive strands.

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 among a +ve ssRNA viruses because they convert to dsDNA utilizing the reverse transcriptase(RT) enzyme (an RNA dependant DNA polymerase). The dsDNA 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 uncoting.

D-Transcription of late mRNA

Viral NA will transcribed newly mRNA known as late mRNA.

E-Synthesis of Viral Proteins

Viral proteins are translated from viral mRNA at the ribosomes in the cytoplasm. Each length of viral mRNA either codes for one protein or for several proteins. In the latter case the translation product is a polyprotein which becomes cleaved into several viral protein, example: The single protein of FMDV yields the 4 capsid proteins VPA 1-4. Viral proteins mature between synthesis at the ribosomes and assembly into the virus particle.

5- Assembly of viruses

Nucleocapsid assembly occurs at the site where nucleic acid is formed (**The nucleus for the most DNA viruses** or the **cytoplasm for most RNA viruses**). With **non-enveloped viruses** the nucleocapsid become packed into crystalline array of new virus particles.

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

During the assembly of enveloped virus the nucleocapsid aligns under neath plasma or nuclear membrane. A layer of protein(the matrix or inner coat protein)then becomes incorporated into the lipid membrane a bove the nucleocapsid. It can be considered as attracting viral glycoprotein spikes into this area. During this stage of envelope formation host cell transmembrane glycoproteins are replaced by viral glycoprotein spikes. The nucleocapsid then evaginates through the spike membrane which envelope it as and buds outwards.

6- Release of virus

Newly synthesized viral genomes and capsid polypeptides assemble togather to form progeny viruses.

- **In general, non-envelpoed** viruses are released when the cell dies and disintegrates. Example: The burst of adenovirus from nucleus.
- **Enveloped viruses mature** by budding process. Virus –specific envelope glycoprotein are inserted into cellular membranes; viral nucleocapsids then bud through the membrane at these modified sites;
- 1- Budding frequently occurs at the plasma membrane fro example: orthomyxo, paramyxo and retroviridae.
- Other virus like Coronavirus and Bunyavirus budding through R.E Reticulium or Golgi apparatus and then transport to the surface and release by exocytosis.
- 3- Herpes virus bud through inner lamella of nuclear membrane and accumulate in the space between the two membranes and release by exocytosis or by cytolysis.

Many released virions 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. Enveloped viruses are not infectious until they have acquired their envelopes? why

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 depress 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).

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.

Kind of Cytopathic Effect of the viruses(CPE)

1-Morphological alteration or death of infected cells.

2- Toxic effect of viral protein in host cell, inhibition of cellular protein cause death of 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.

What CPE caused

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 fro 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.

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 culture

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-latent infection

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