Medical Virology

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General Virology

- Conception
- Viruses
- Virion
- Size and Shape
- Structure
- Replication
- Viral Variation
- Classification

Conception

- **Virology is the bioscience for study of viral nature, and the relationship between viruses and hosts. Viruses often cause serious diseases, relate to some cancers and congenital deformities, also can be used as tool for genetic engineering.**

- 3000BC

History

- Smallpox was endemic in China by 1000BC. In response, the practice of **variolation** was developed. Recognizing that survivors of smallpox outbreaks were protected from subsequent infection, variolation involved inhalation of the dried crusts from smallpox lesions like snuff, or in later modifications, inoculation of the pus from a lesion into a scratch on the forearm of a child.

Definition of Virus

Viruses may be **defined** as **acellular organisms** whose **genomes** consist of **nucleic acid**, and which obligately **replicate inside host cells** using **host metabolic machinery** and **ribosomes** to form a **pool of components** which assemble into particles called **VIRIONS**, which serve to **protect the genome** and to **transfer it to other cells**

Viral Properties

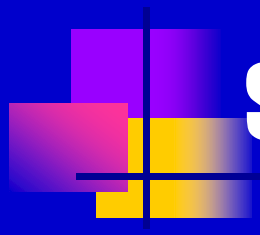
- Viruses are inert (nucleoprotein) filterable Agents
- Viruses are obligate intracellular parasites
- Viruses cannot make energy or proteins independent of a host cell
- Viral genome are RNA or DNA but not both.
- Viruses have a naked capsid or envelope with attached proteins
- Viruses do not have the genetic capability to multiply by division.
- Viruses are non-living entities

Consequences of Viral Properties

- Viruses are not living
- Viruses must be infectious to endure in nature
- Viruses must be able to use host cell processes to produce their components (viral messenger RNA, protein, and identical copies of the genome)
- Viruses must encode any required processes not provided by the cell
- Viral components must self-assemble

Challenges the way we define life

- viruses do not respire,
- nor do they display irritability
- they do not move
- they do not grow
- they do most certainly reproduce, and may adapt to new hosts.



Size and Shape

- Methods
- Size of Viruses
- Shapes of Viruses

Methods of Analysis

Electron microscopy :
The resolution is 5nm (1nm = 10^{-9} m)

X-ray crystallography

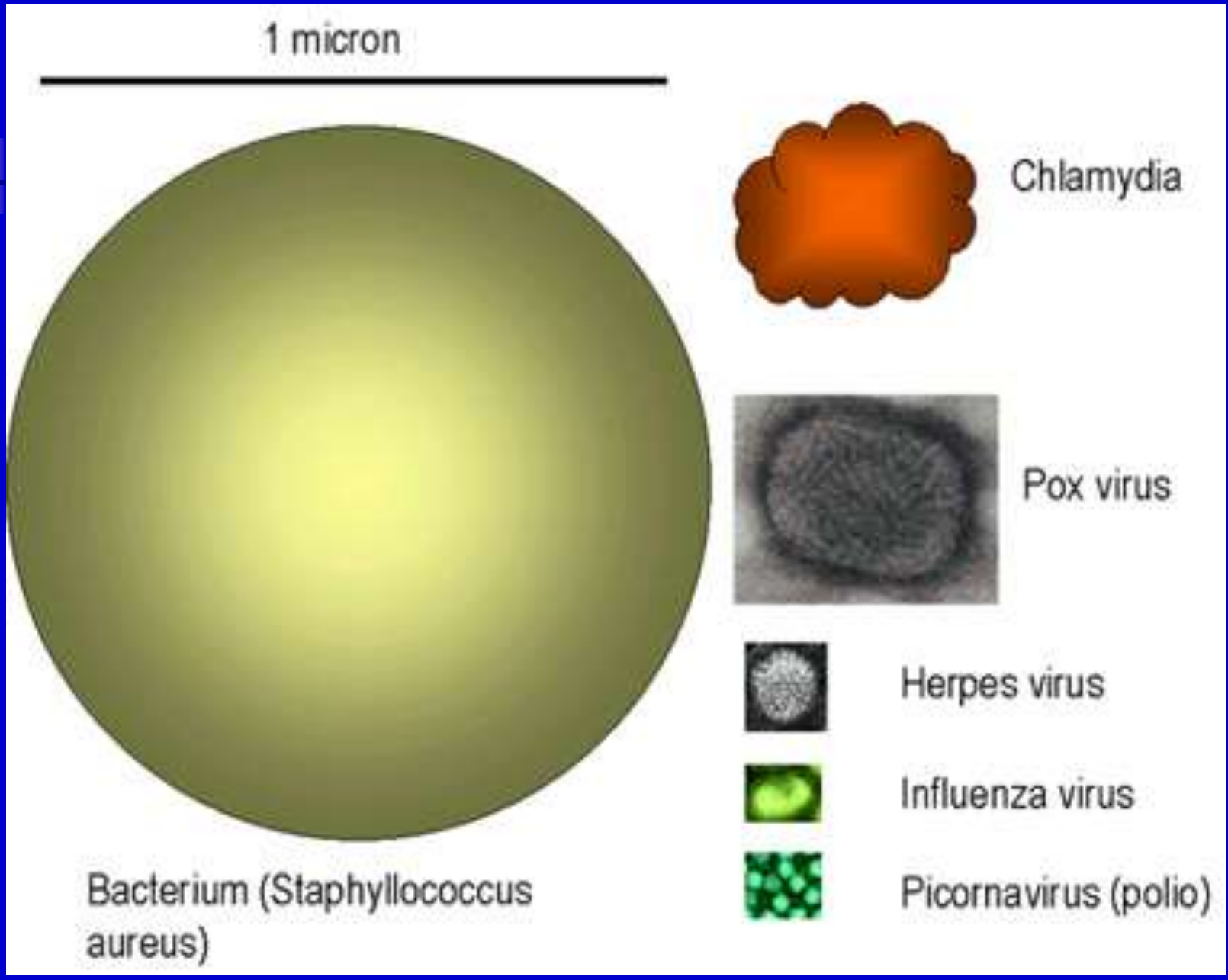
Size of Viruses

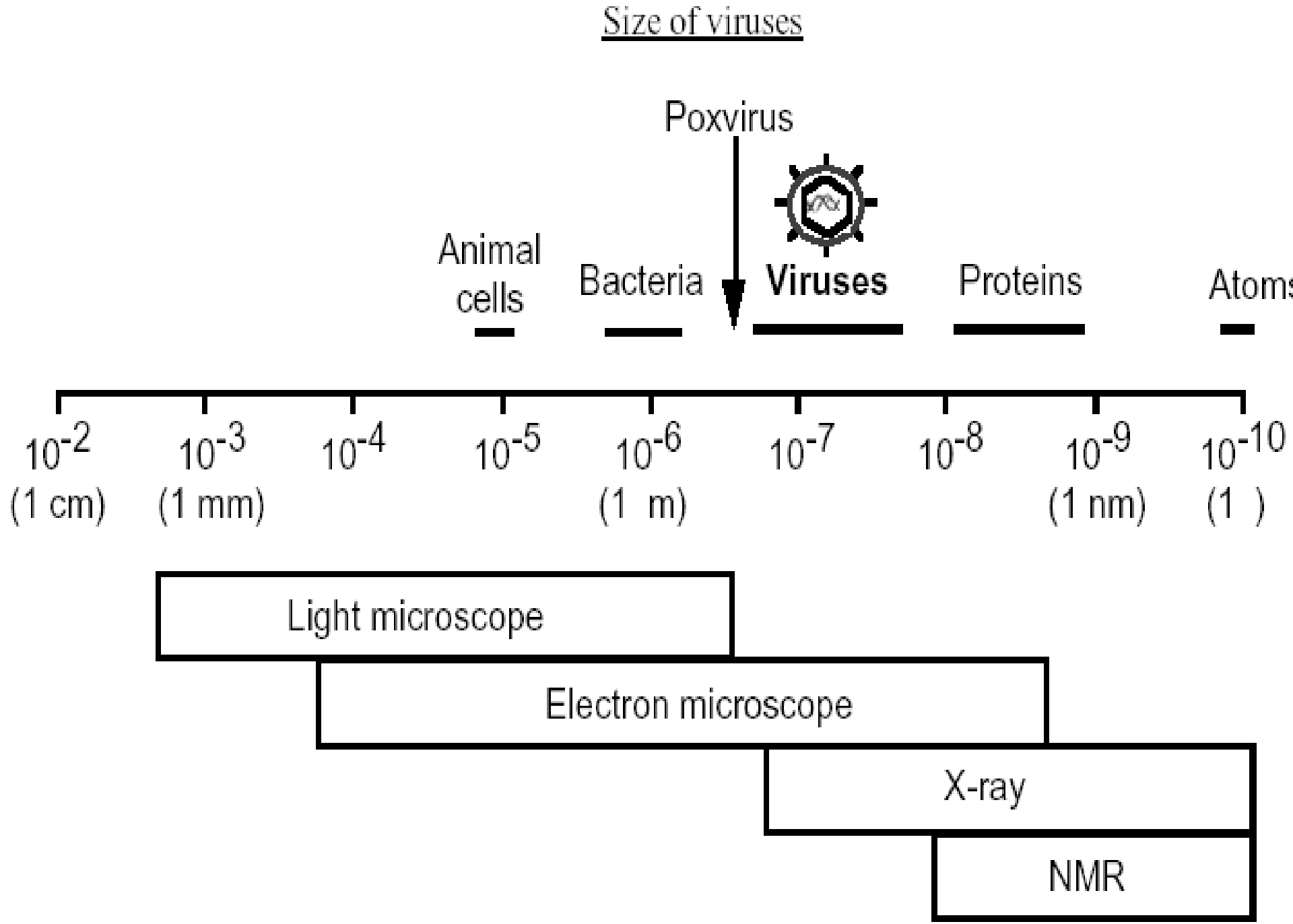
A small virus has a diameter of about 20nm.

Parvovirus

A large virus have a diameter of up to 400nm.

Poxviruses


1 micron
Chlamydia
Pox virus
Herpes virus
Influenza virus
Picornavirus (polio)
Bacterium (Staphyllococcus aureus)

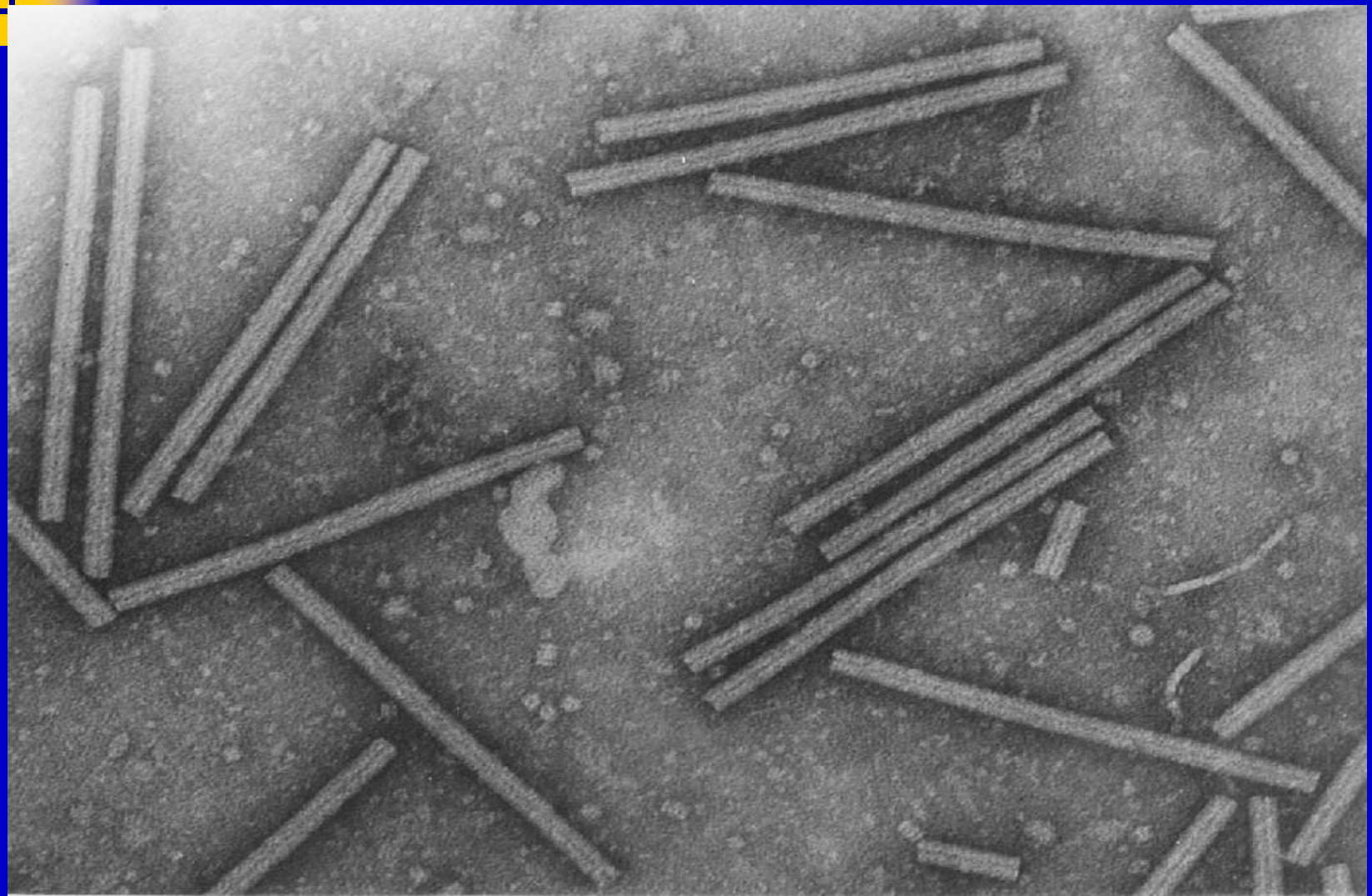

Size of viruses
Poxvirus
Animal cells
Bacteria
Viruses
Proteins
Atoms
10^{-2} (1 cm)
10^{-3} (1 mm)
10^{-4}
10^{-5}
10^{-6} (1 m)
10^{-7}
10^{-8}
10^{-9} (1 nm)
10^{-10} (1)
Light microscope
Electron microscope
X-ray
NMR

Shape of Viruses

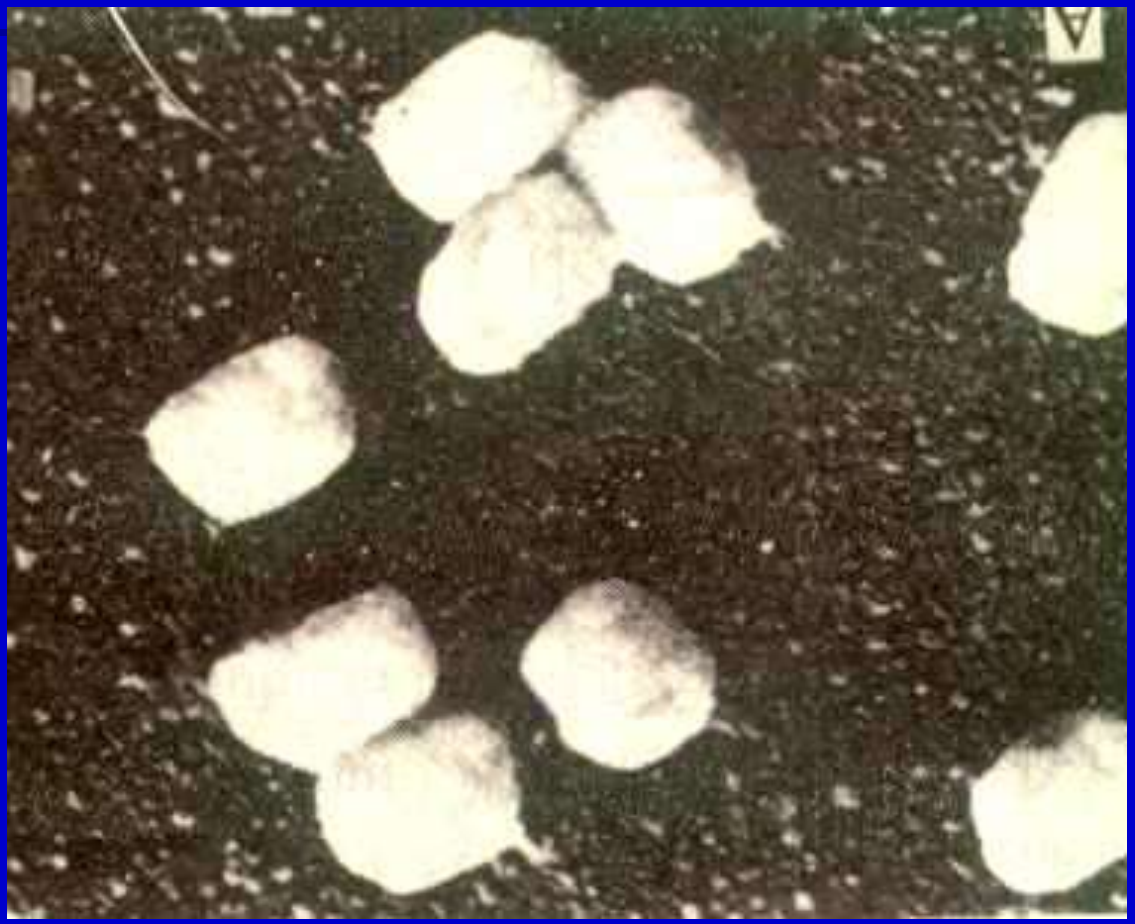
- **Spherical**
- Rod-shaped
- Brick-shaped
- Tadpole-shaped
- Bullet-shaped
- Filament

Shapes of Viruses: Spherical

Shapes of Viruses :Rod-shaped (***Rudivirus***)



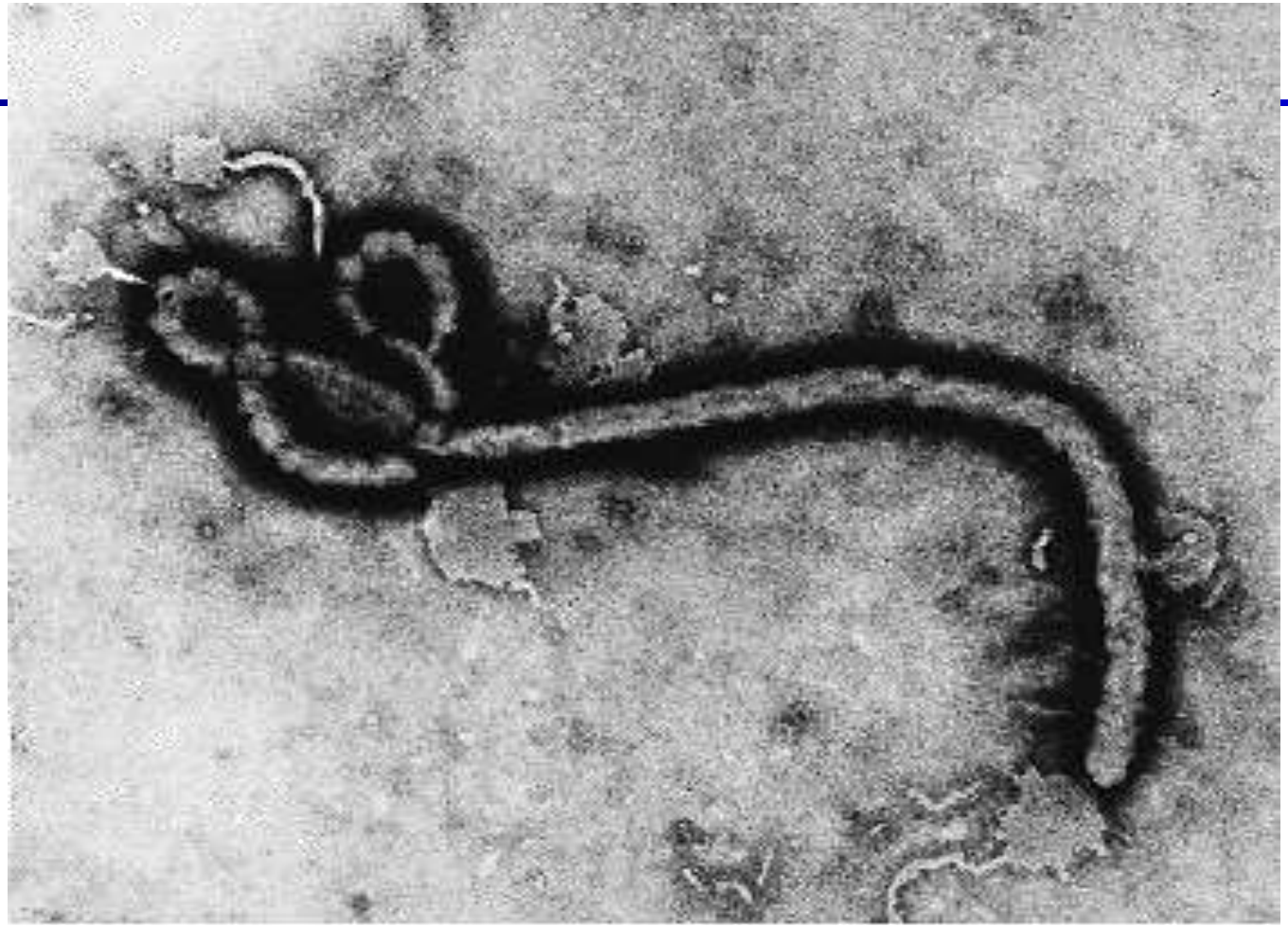
Shapes of Viruses :Brick-shaped (**Poxviridae**)



Tadpole-shaped

Shapes of Viruses :Bullet-shaped (**Rhabdoviridae), rabies**

Shapes of Viruses :Filament (**Filoviridae), Ebola virus**



Origin of viruses:

- Regressive hypothesis
- Cellular origin hypothesis
- Coevolution hypothesis

Regressive hypothesis

- Viruses may have once been small cells that parasitised larger cells.
- Over time, genes not required by their parasitism were lost.
- The bacteria rickettsia and chlamydia are living cells that, like viruses, can reproduce only inside host cells.
- They lend support to this hypothesis, as their dependence on parasitism is likely to have caused the loss of genes that enabled them to survive outside a cell.
- This is also called the *degeneracy hypothesis*, or *reduction hypothesis*.

Cellular origin hypothesis

- Some viruses may have evolved from bits of DNA or RNA that "escaped" from the genes of a larger organism.
- The escaped DNA could have come from

1- plasmids (pieces of naked DNA that can move *between* cells)

2- transposons (molecules of DNA that replicate and move around to different positions *within* the genes of the cell). Once called "jumping genes", transposons are examples of mobile genetic elements and could be the origin of some viruses.

- They were discovered by Barbara McClintock in 1950.
- This is sometimes called the *vagrancy hypothesis*, or the *escape hypothesis*

Coevolution hypothesis

This is also called the *virus-first hypothesis* and proposes that viruses may have evolved from complex molecules of protein and nucleic acid at the same time as cells first appeared on Earth and would have been dependent on cellular life for billions of years.

Viroids are important pathogens of plants. They do not code for proteins but interact with the host cell and use the host machinery for their replication

satellites virus may represent evolutionary intermediates of viroids and viruses.

- the regressive hypothesis did not explain why even the smallest of cellular parasites do not resemble viruses in any way.

- The escape hypothesis did not explain the complex capsids and other structures on virus particles.

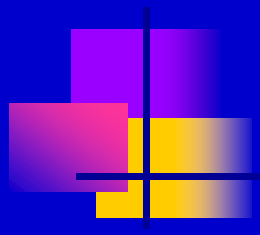
- The virus-first hypothesis contravened the definition of viruses in that they require host cells.

- Viruses are now recognised as ancient and as having origins that pre-date the divergence of life into the three domains. This discovery has led modern virologists to reconsider and re-evaluate these three classical hypotheses.

- Prions are infectious protein molecules that do not contain DNA or RNA.

- They can cause infections such as scrapie in sheep, bovine spongiform encephalopathy ("mad cow" disease) in cattle, in humans, prionic diseases include Kuru, Creutzfeldt–Jakob disease.

- Although prions are fundamentally different from viruses and viroids, their discovery gives credence to the theory that viruses could have evolved from self-replicating molecules.

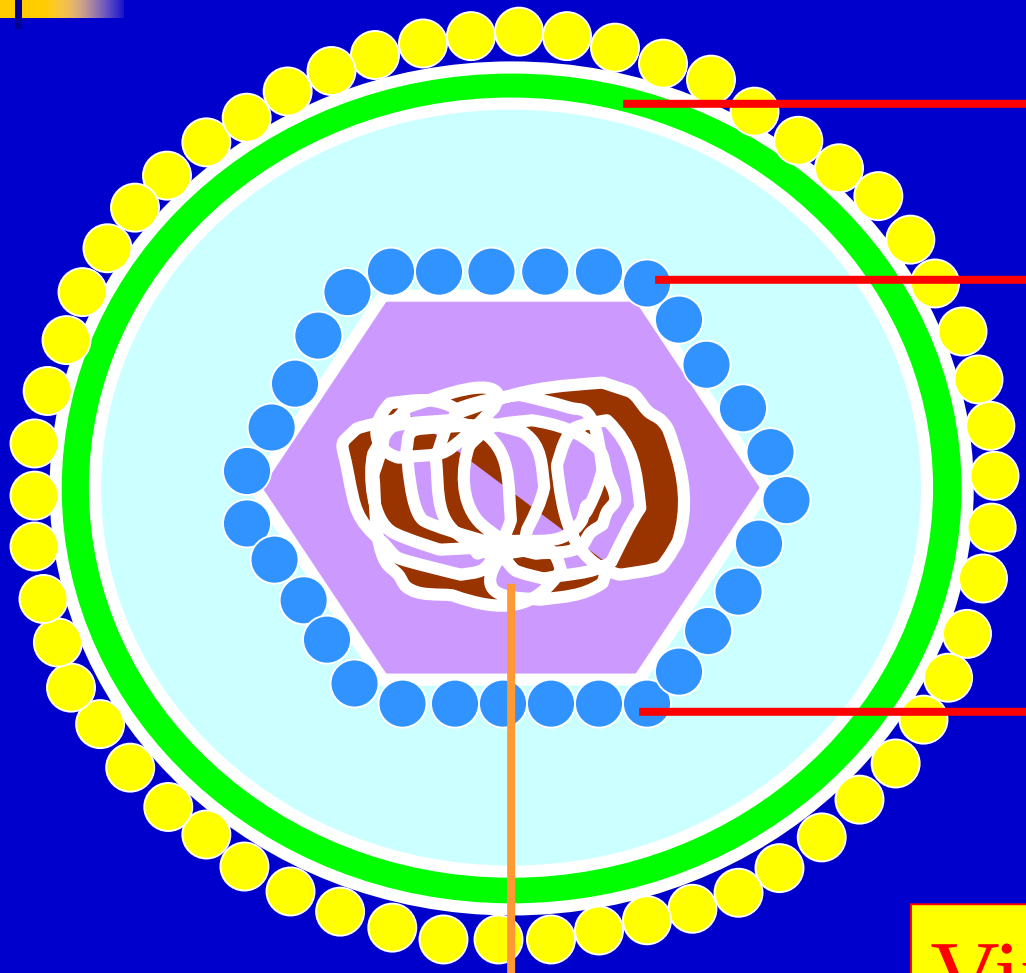


Structure of Viruses

Virion

- **the complete infectious unit of virus particle**
- **Structurally mature, extracellular virus particles.**

Virion



envelope

Capsid

Viral core

Viral core

- ***Viral core***

  The viral nucleic acid genome, In the center of the virion, : Control the viral heredity and variation, responsible for the infectivity.

Genome

- The genome of a virus can be either DNA or RNA

- DNA-double stranded (ds): linear or circular

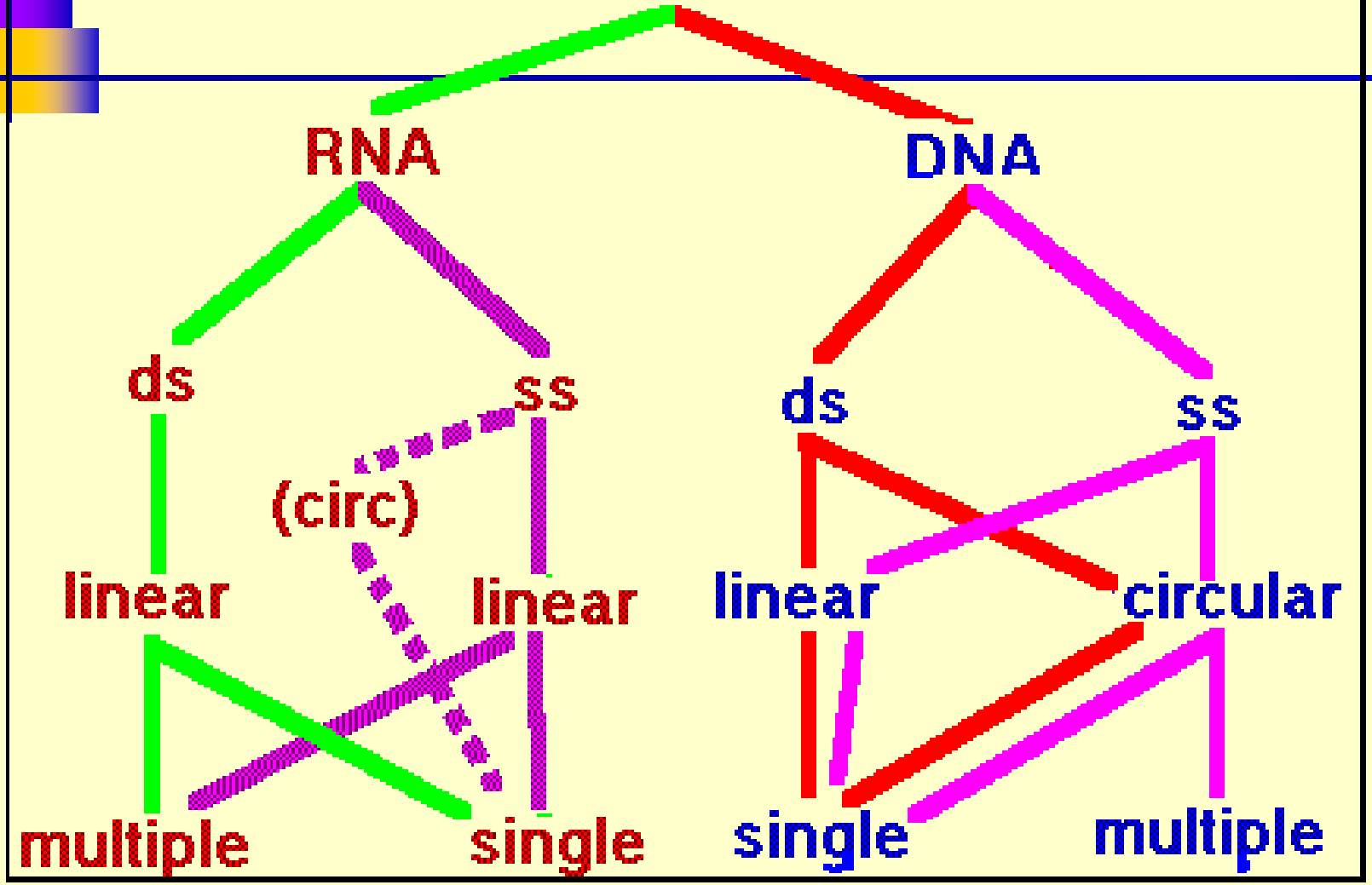
  Single stranded (ss) : linear or circular
- RNA- ss:segmented or non-segmented

  ss:polarity+(sense) or polarity –(non-sense)

  ds: linear (only reovirus family)

DNA						RNA					
double-stranded			single-stranded			double-stranded		single-stranded			
linear	circular		linear	circular		linear		linear (circular)*			
single	single	multiple	single	single	multiple	single	multiple	(+)sense		(-)sense	
								single	multiple	single	multiple

Virus Genomic Nucleic Acids



Viral Capsid

- The protein shell, or coat, that encloses the nucleic acid genome.

❖ **FUNCTIONS:**

- a. Protect the viral nucleic acid.
- b. Participate in the viral infection.
- c. Share the antigenicity

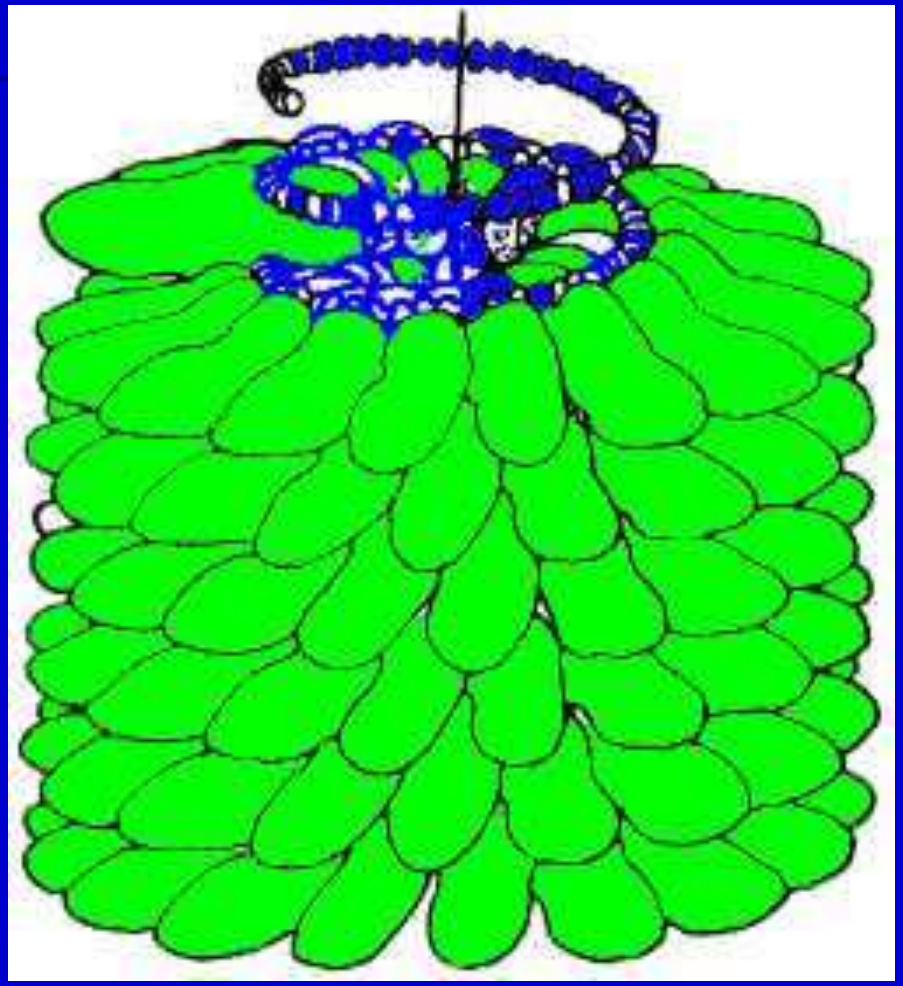
Nucleocapsid

- *The core of a virus particle consisting of the genome plus a complex of proteins.*
- *complex of proteins* = **Structural proteins +Non- Structural proteins (Enzymes &Nucleic acid binding proteins)**

Symmetry of Nucleocapsid

- Helical
- Cubic /Icosahedral
- Complex

Helical symmetry



These viruses are composed of a single type of capsomer stacked around a central axis to form a helical structure, which may have a central cavity, or tube. This arrangement results in rod-shaped or filamentous virions: These can be short and highly rigid, or long and very flexible. The genetic material, in general, single-stranded RNA, but ssDNA in some cases.

Helical

- California Encephalitis Virus
  Coronavirus
  Hantavirus
  Influenza Virus (Flu Virus)
  Measles Virus (Rubeola)
  Mumps Virus
  Parainfluenza Virus
  Rabies Virus
  Respiratory Syncytial Virus(RSV)

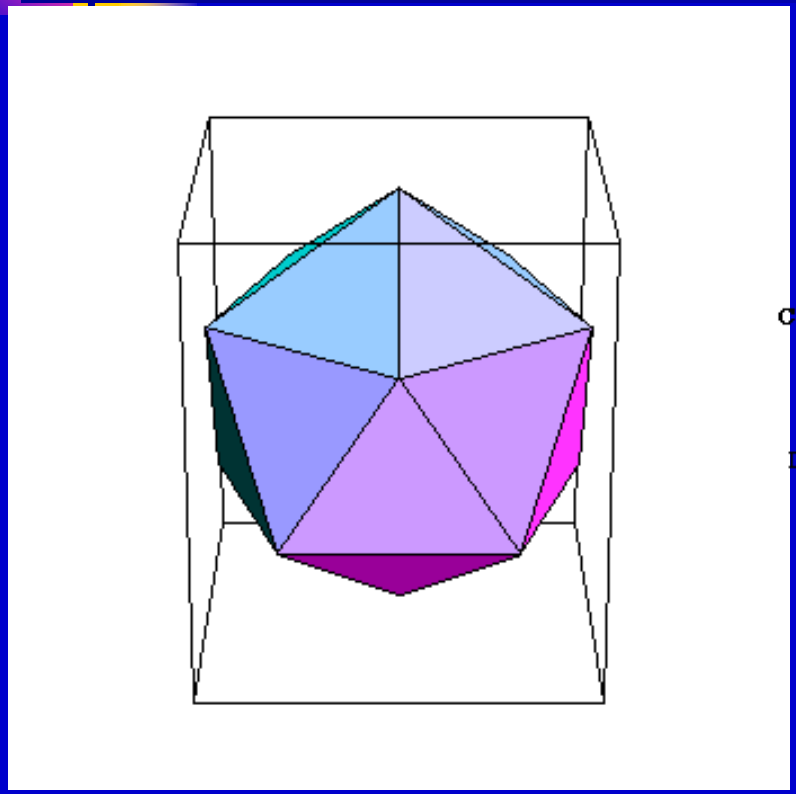
Cubic or icosahedral symmetry

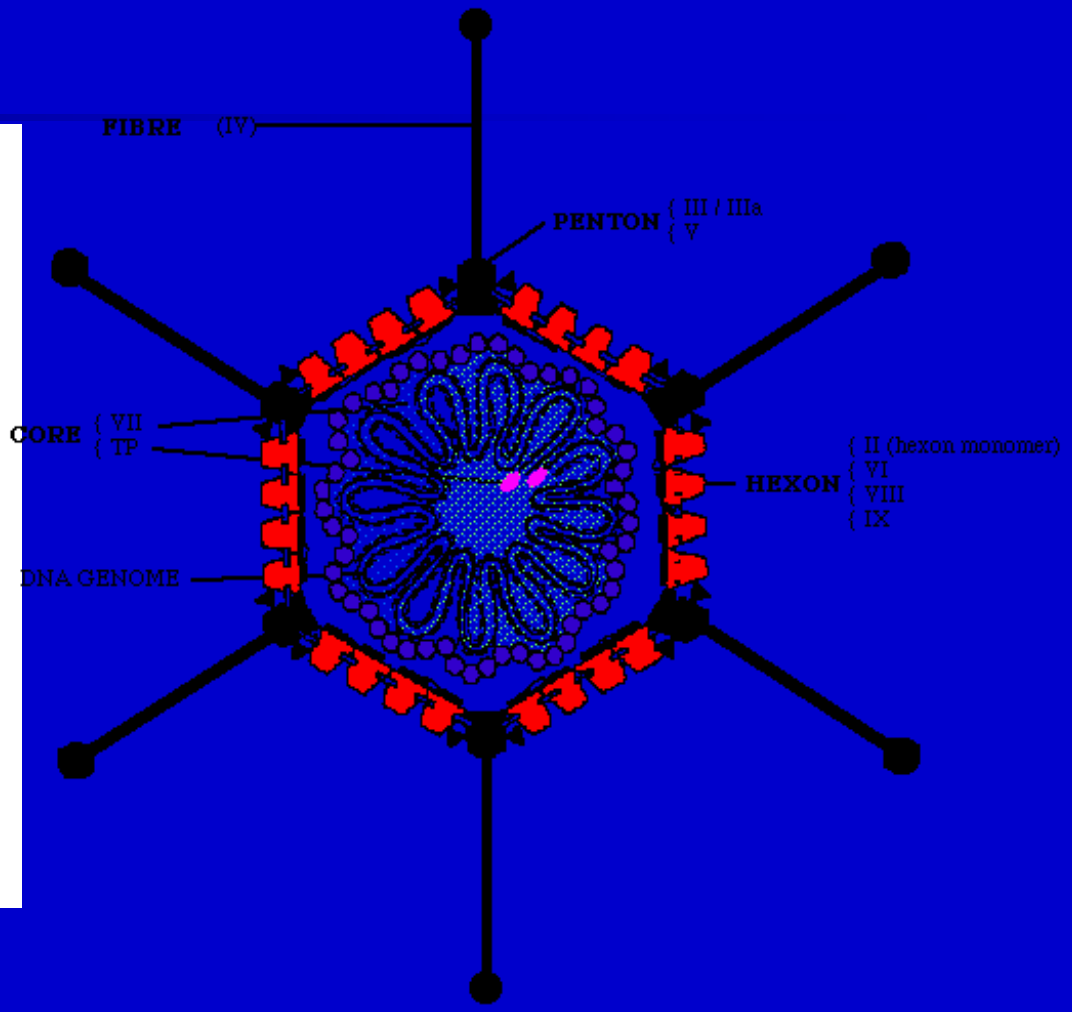
icosahedral is a solid figure with twenty plane faces, especially equilateral triangular ones.

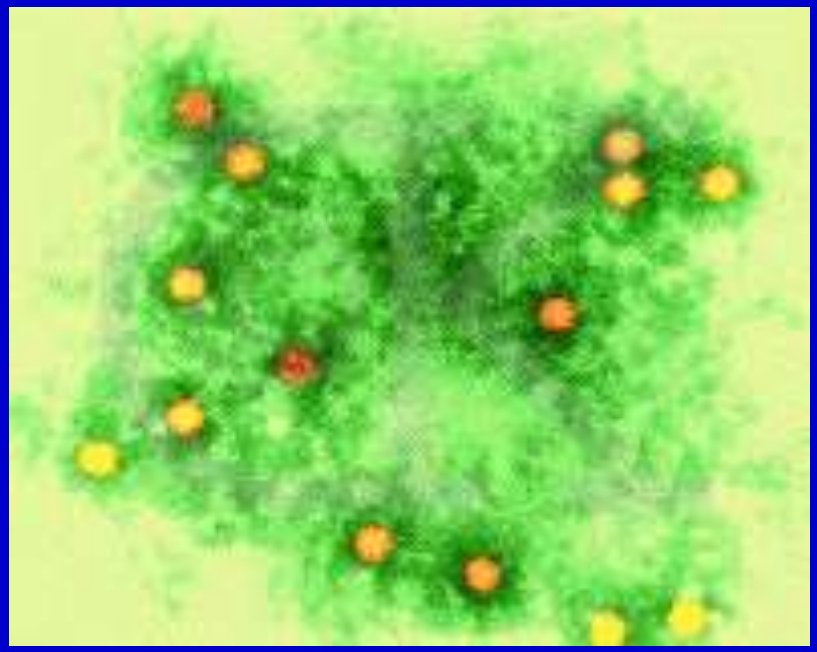
Most animal viruses are icosahedral or near-spherical with icosahedral symmetry.

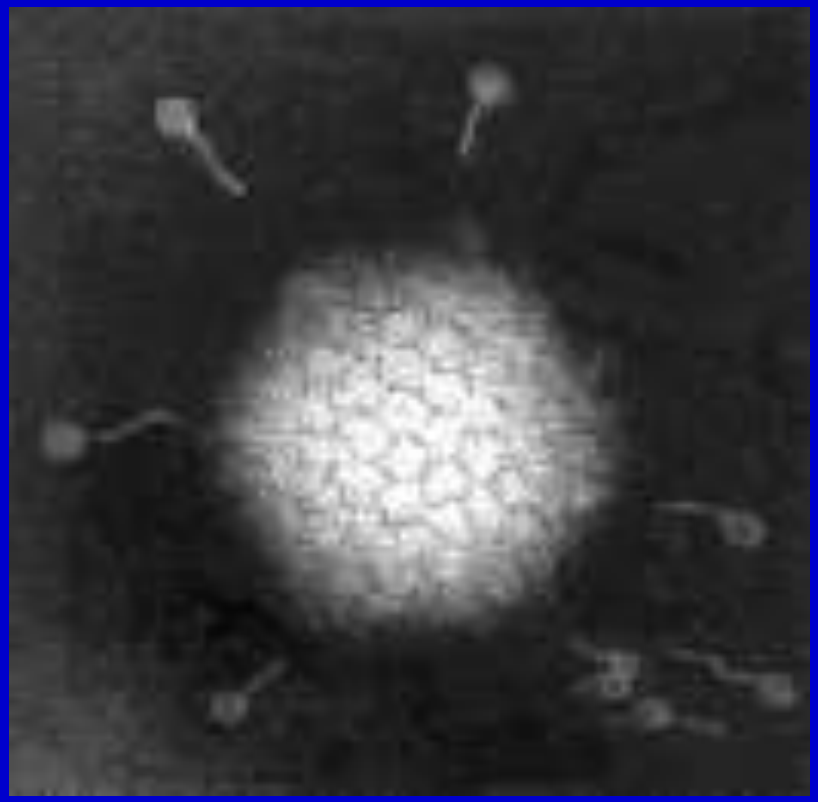
A regular **icosahedron** is the optimum way of forming a closed shell from identical sub-units.

The minimum number of identical capsomers required is twelve, each composed of five identical sub-units.




FIBRE (IV)
PENTON { III / IIIa
{ V
CORE { VII
{ TP
DNA GENOME
HEXON { II (hexon monomer)
{ VI
{ VIII
{ IX





Many viruses, such as rotavirus, have more than twelve capsomers and appear spherical but they retain this symmetry.

Capsomers at the apices are surrounded by five other capsomers and are called pentons.

Capsomers on the triangular faces are surrounded by six others and are called hexons.

Icosahedral

- Adeno-associated Virus (AAV)
  Adenovirus
  B19
  Coxsackievirus - A
  Coxsackievirus - B
  Cytomegalovirus (CMV)
  Eastern Equine Encephalitis Virus (EEEV)
  Echovirus
  Epstein-Barr Virus (EBV)
  Hepatitis A Virus (HAV)
  Hepatitis B Virus (HBV)
  Hepatitis C Virus (HCV)
  Hepatitis Delta Virus (HDV)
  Hepatitis E Virus (HEV)
- Herpes Simplex Virus 1 (HHV1)
  Herpes Simplex Virus 2 (HHV2)
  Human Immunodeficiency Virus (HIV)
  Human T-lymphotrophic Virus (HTLV)
  Norwalk Virus
  Papilloma Virus (HPV)
  Polio virus
  Rhinovirus
  Rubella Virus
  Saint Louis Encephalitis Virus
  Varicella-Zoster Virus (HHV3)
  Western Equine Encephalitis Virus (WEEV)
  Yellow Fever Virus

Complex Virus Structures

- A well known example is the tailed bacteriophages such as T4.
- The head of these viruses is cubic with a triangulation number of 7. This is attached by a collar to a contractile tail with helical symmetry.

T4 Bacteriophage

Properties of naked viruses

- Stable in hostile environment
- Not damaged by drying, acid, detergent, and heat
- Released by lysis of host cells
- Can sustain in dry environment
- Can infect the GI tract and survive the acid and bile
- Can spread easily via hands, dust, fomites, etc
- Can stay dry and still retain infectivity
- Neutralizing mucosal and systemic antibodies are needed to control the establishment of infection

Naked viruses(**Non Enveloped**)

- Adeno-associated Virus (AAV)
  Adenovirus
  B19
  Coxsackievirus - A
  Coxsackievirus - B
  Echovirus
  Hepatitis A Virus (HAV)
  Hepatitis E Virus (HEV)
  Norwalk Virus

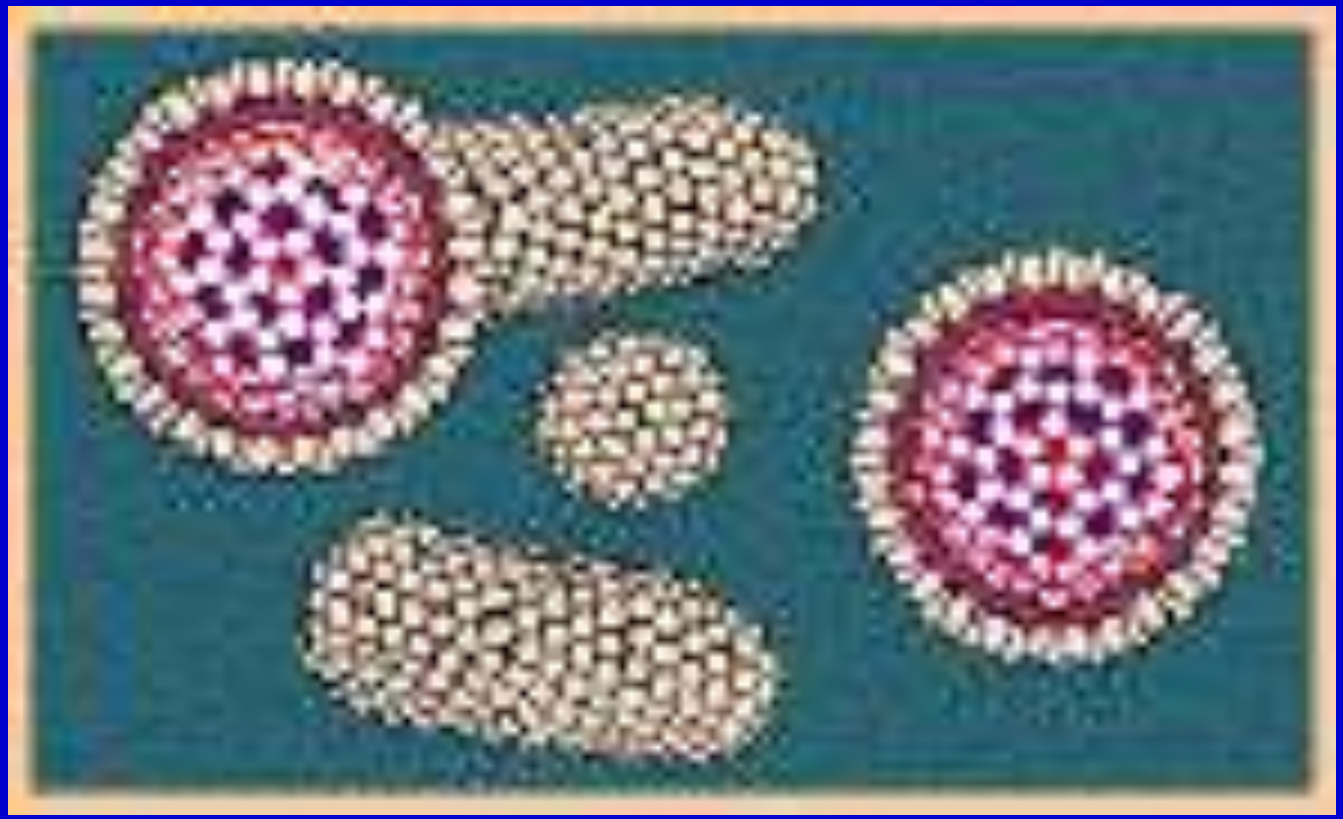
Envelope

- ***A lipid-containing membrane that surrounds some viral particles.***
- ***It is acquired during viral maturation by a budding process through a cellular membrane, Viruses-encoded glycoproteins are exposed on the surface of the envelope.***
- ***Not all viruses have the envelope***

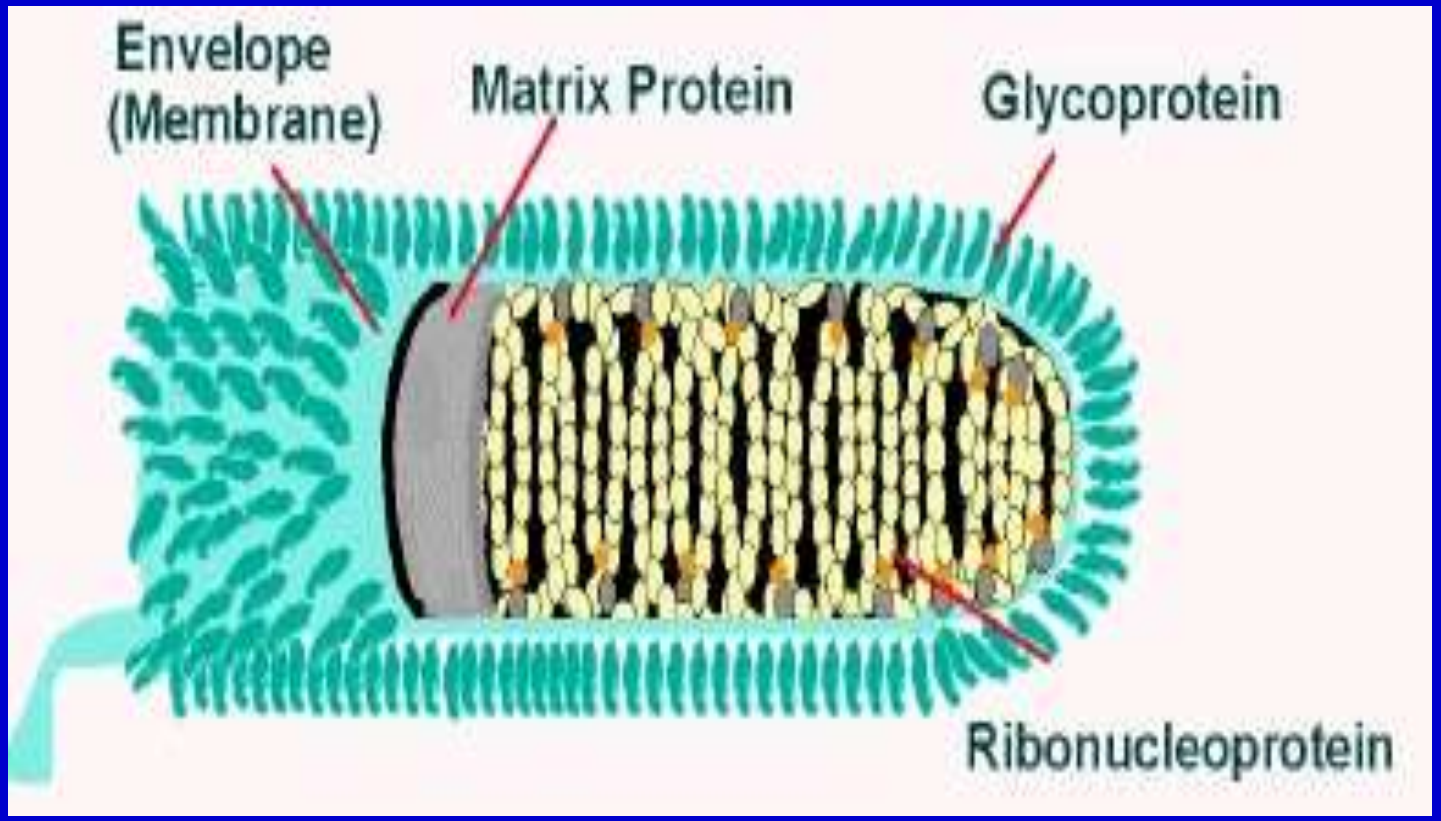
Functions of envelope

- ***Antigenicity***

  some viruses possess neuraminidase
- ***Infectivity***
- ***Resistance***



Envelope

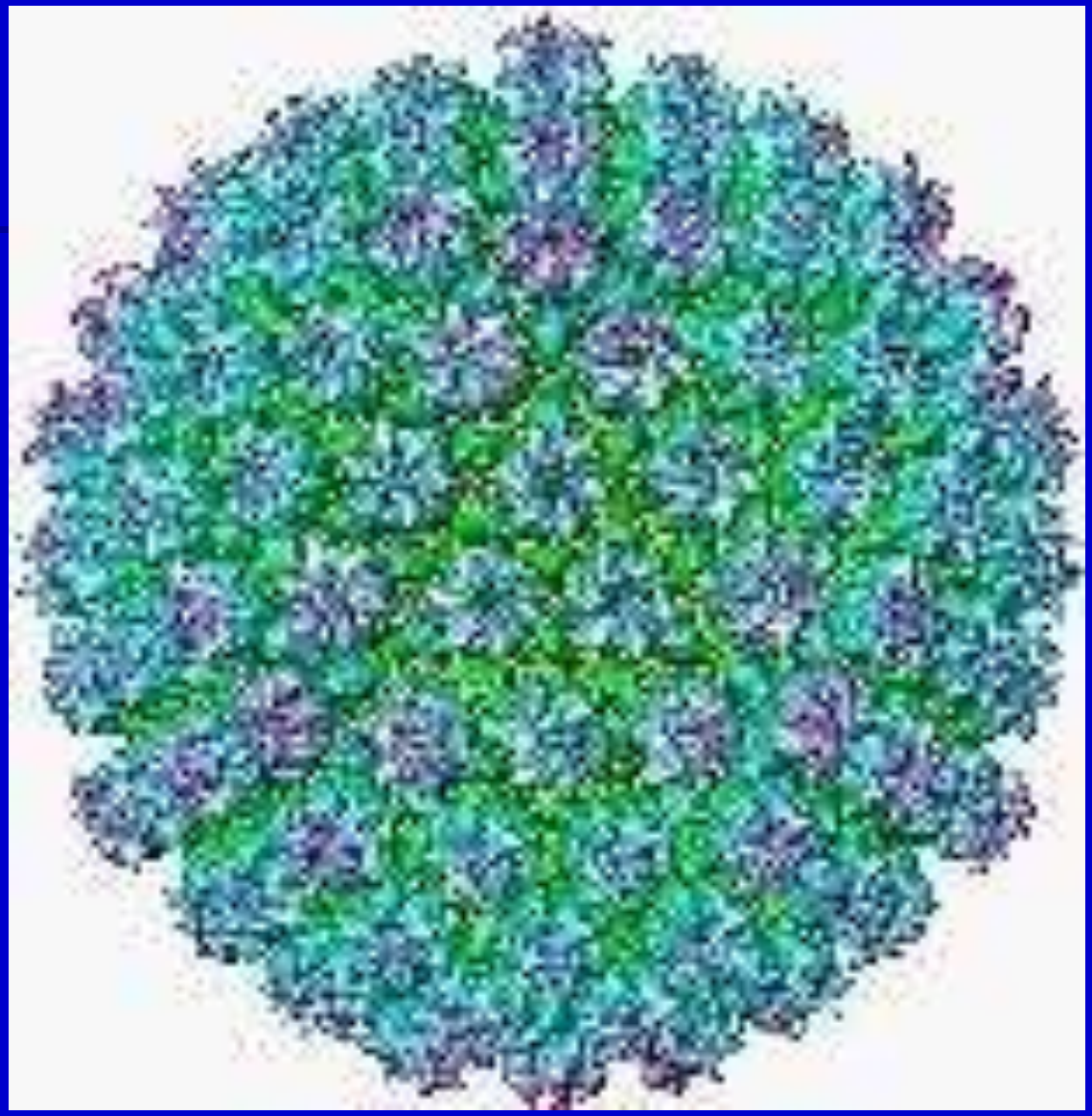

Envelope
(Membrane)
Matrix Protein
Glycoprotein
Ribonucleoprotein

Properties of enveloped viruses

- Labile in dry , arid environment
- Damaged by drying, acid, detergent, and heat
- Pick up new cell membrane during multiplication
- Insert new virus-specific proteins after assembly
- Virus is released by budding

Consequences of Properties for enveloped viruses

- Must stay moist
- Must not infect the GI tract for survival
- Must be transmitted in the protective, droplets, secretions, blood and body fluids
- Must reinfect another host cell to sustain
- Humoral and cell-mediated immunity are needed to control the infection



Enveloped

- California Encephalitis Virus
- Coronavirus
- Cytomegalovirus (CMV)
- Eastern Equine Encephalitis Virus (EEEV)
- Epstein-Barr Virus (EBV)
- Hantavirus
  Hepatitis B Virus (HBV)
  Hepatitis C Virus (HCV)
  Hepatitis Delta Virus (HDV)
  Herpes Simplex Virus 1 (HHV1)
- Rotavirus
- Rubella Virus
- Saint Louis Encephalitis Virus
  Smallpox Virus (Variola)
  Vaccinia Virus
- Herpes Simplex Virus 2 (HHV2)
  Human Immunodeficiency Virus (HIV)
  Human T-lymphotrophic Virus (HTLV)
  Influenza Virus (Flu Virus)
  Molluscum contagiosum
  Papilloma Virus (HPV)
  Polio virus
  Rhinovirus
  Varicella-Zoster Virus (HHV3)
  Venezuelan Equine Encephal. Vir. (VEEV)
  Western Equine Encephalitis Virus (WEEV)
  Yellow Fever Virus

Replication of Viruses

Replicative

- As obligate intracellular parasites, Virus must enter and replicate in living cells in order to "reproduce" itselves. This "growth cycle" involves specific attachment of virus, penetration and uncoating, nucleic acid transcription, protein synthesis, matureation and assembly of the virions and their subsequent release from the cell by budding or lysis

Initiation Phase

- Attachment
- Penetration
- Uncoating

Attachment/Adsorption

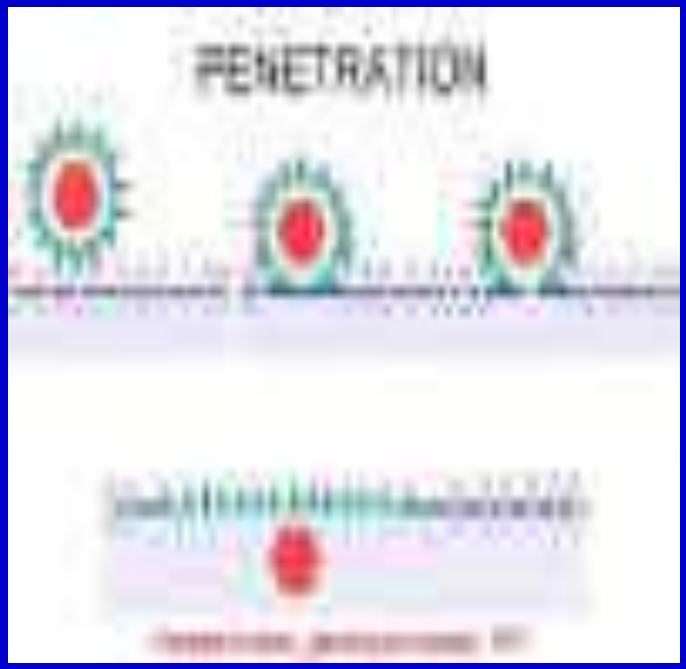
- Virus attaches to the cell surface. Attachment is via ionic interactions which are temperature-independent.
- Viral attachment protein recognizes specific receptors on the cell surface (These may be protein or carbohydrate or lipid components of the cell surface).
- Cells without the appropriate receptors are not susceptible to the virus.

PENETRATION
(Virus enters the cell)

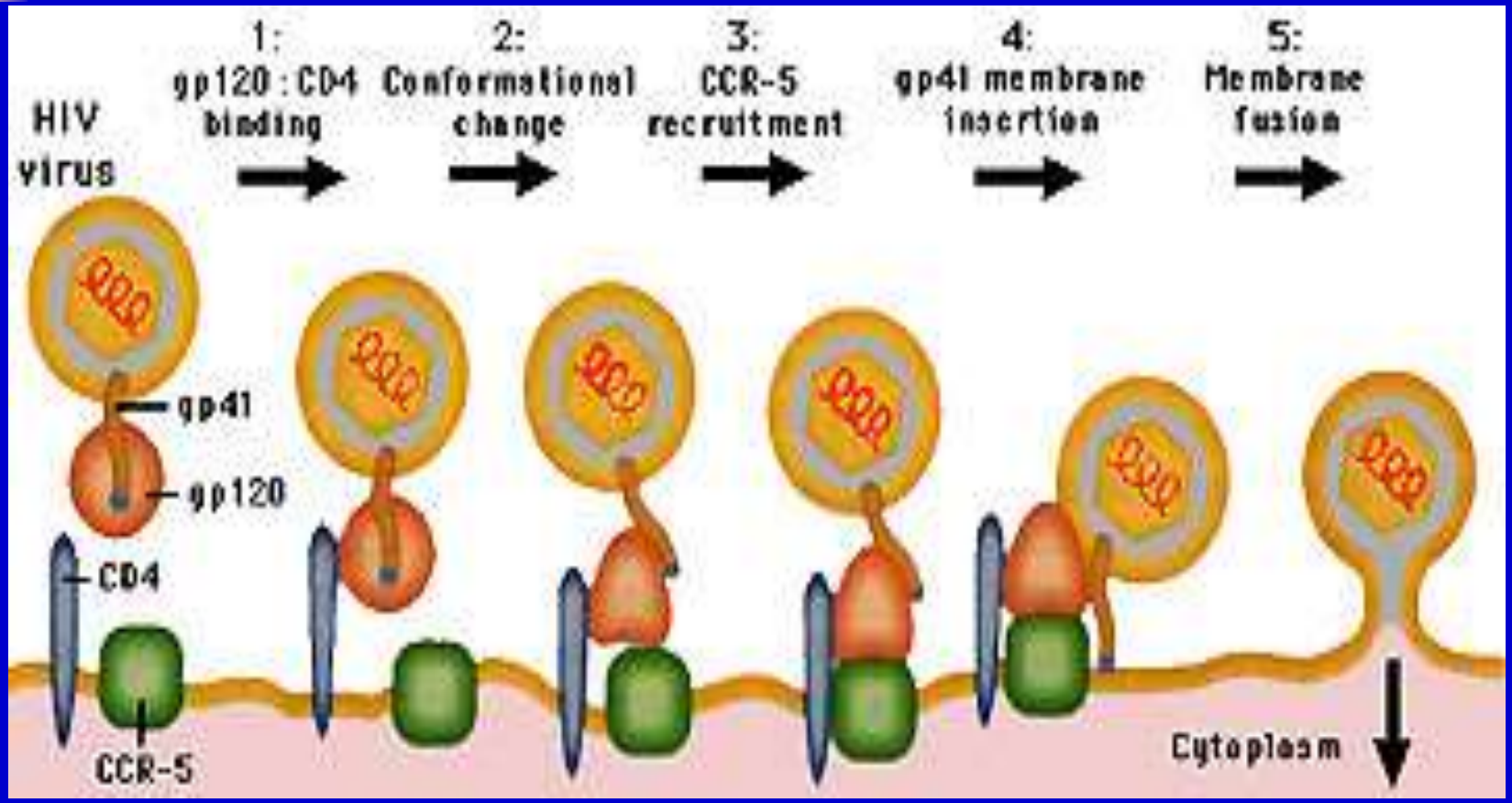
- Virions are either engulfed into vacuoles by “endocytosis” or the virus envelope fuses with the plasma membrane to facilitate entry
- Enveloped viruses
- Non-enveloped viruses

Fusing

- (A) *Entry by fusing with the plasma membrane*. Some enveloped viruses fuse directly with the plasma membrane. Thus, the internal components of the virion are immediately delivered to the cytoplasm of the cell.

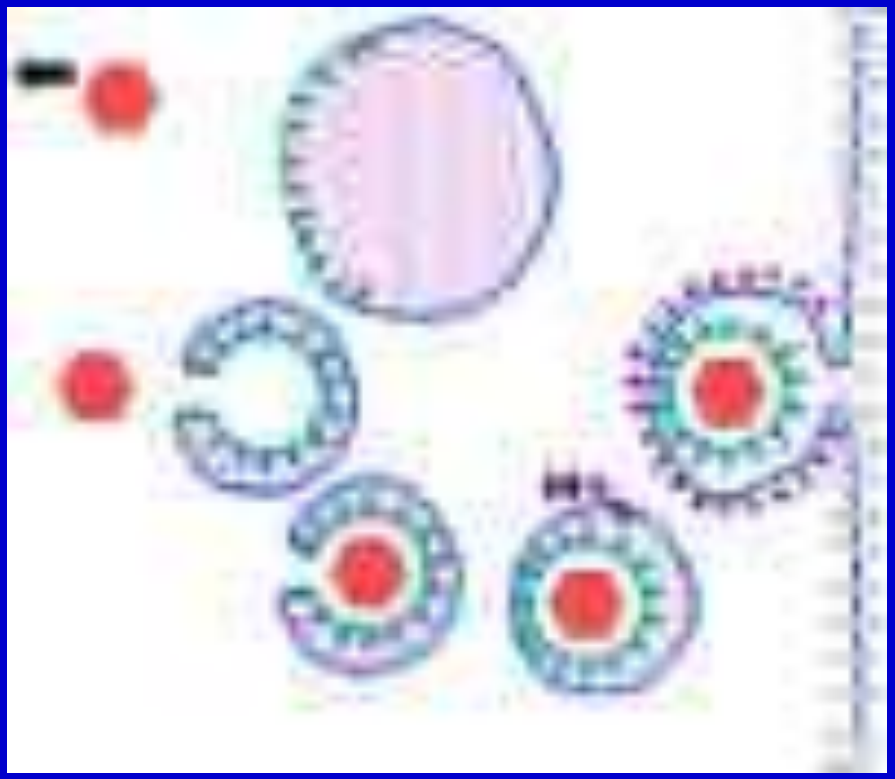


HIV

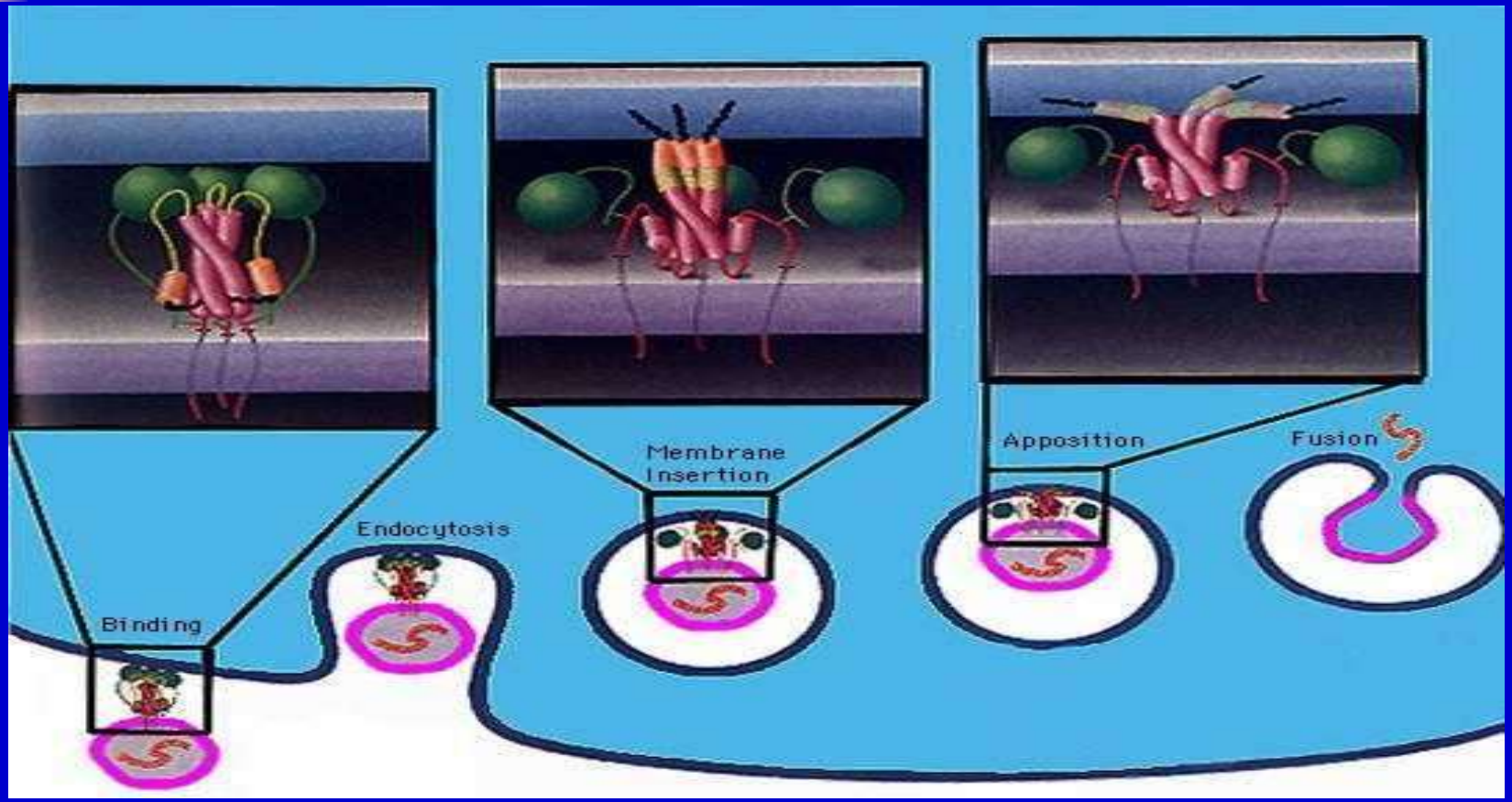

HIV virus
1: gp120 : CD4 binding
2: Conformational change
3: CCR-5 recruitment
4: gp41 membrane insertion
5: Membrane fusion
gp41
gp120
CD4
CCR-5
Cytoplasm

Endocytosis

- (B) *Entry via endosomes at the cell surface*



influenza virus



Enveloped viruses

- Some enveloped viruses require an acid pH for fusion to occur and are unable to fuse directly with the plasma membrane. These viruses are taken up by invagination as this invagination become acidified, the latent fusion activity of the virus proteins becomes activated by the fall in pH and the virion membrane fuses with the cell membrane. This results in delivery of the internal components of the virus to the cytoplasm of the cell

Non-enveloped viruses

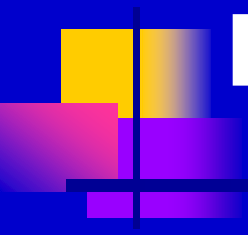
- Non-enveloped viruses may cross the plasma membrane directly
- may be taken up via clathrin-coated pits into endosomes. They then cross (or destroy) the endosomal membrane.

UNCOATING

- Nucleic acid has to be sufficiently uncoated that virus replication can begin at this stage. When the nucleic acid is uncoated, infectious virus particles cannot be recovered from the cell - this is the start of the **ECLIPSE phase** - which lasts until new infectious virions are made
- Uncoating is usually achieved by cellular proteases "opening up" the capsid

BIOSYNTHESIS

- genome synthesis
- mRNA production
- protein synthesis



Maturation assembly release

Maturation

- The stage of viral replication at which a virus particle becomes infectious; nucleic acids and capsids are assembled together.

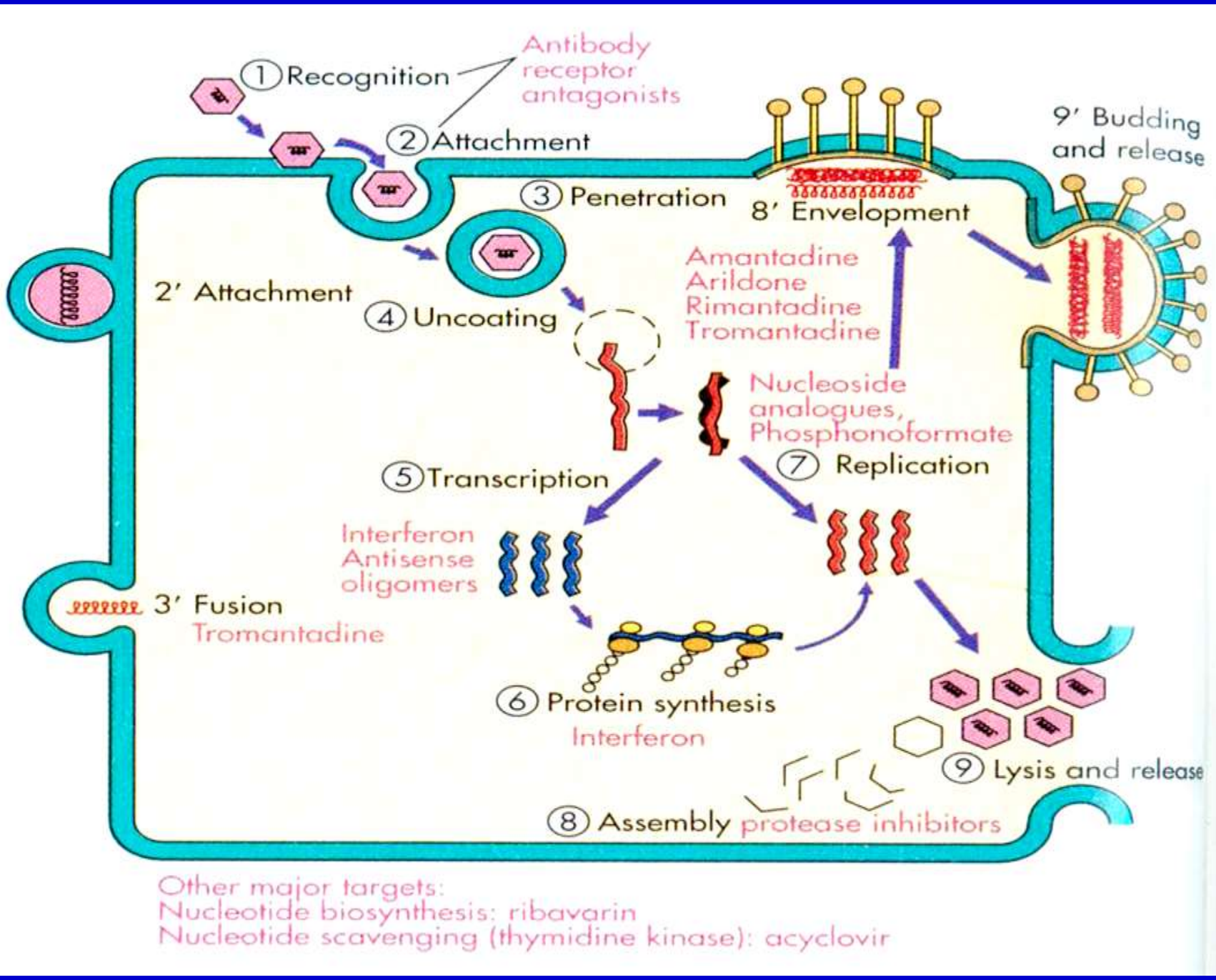
ASSEMBLY

- The stage of replication during which all the structural components come together at one site in the cell and the basic structure of the virus particle is formed.

RELEASE

- Disintegration : naked virus cause the host cell lysis
- Budding: enveloped viruses

- Budding viruses do not necessarily kill the cell. Thus, some budding viruses may be able to set up persistence


1 Recognition
Antibody receptor antagonists
2 Attachment
3 Penetration
2' Attachment
4 Uncoating
9' Budding and release
8' Envelopment
Amantadine
Arildone
Rimantadine
Tromantadine
Nucleoside analogues, Phosphonoformate
7 Replication
5 Transcription
Interferon
Antisense oligomers
3' Fusion
Tromantadine
6 Protein synthesis
Interferon
9 Lysis and release
8 Assembly protease inhibitors
Other major targets:
Nucleotide biosynthesis: ribavarin
Nucleotide scavenging (thymidine kinase): acyclovir

Products of viral replication

- Virion
- DEFECTIVE VIRUS
- ABORTIVE INFECTION
- integration

- **DEFECTIVE VIRUS**

  deficiency in some aspects of replication.

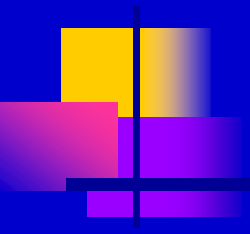
- **ABORTIVE INFECTION**

  When a virus infects a cell (or host), but cannot complete the full replication cycle (not biosynthesize their components or not assemble virions.), i.e. a non-productive infection.

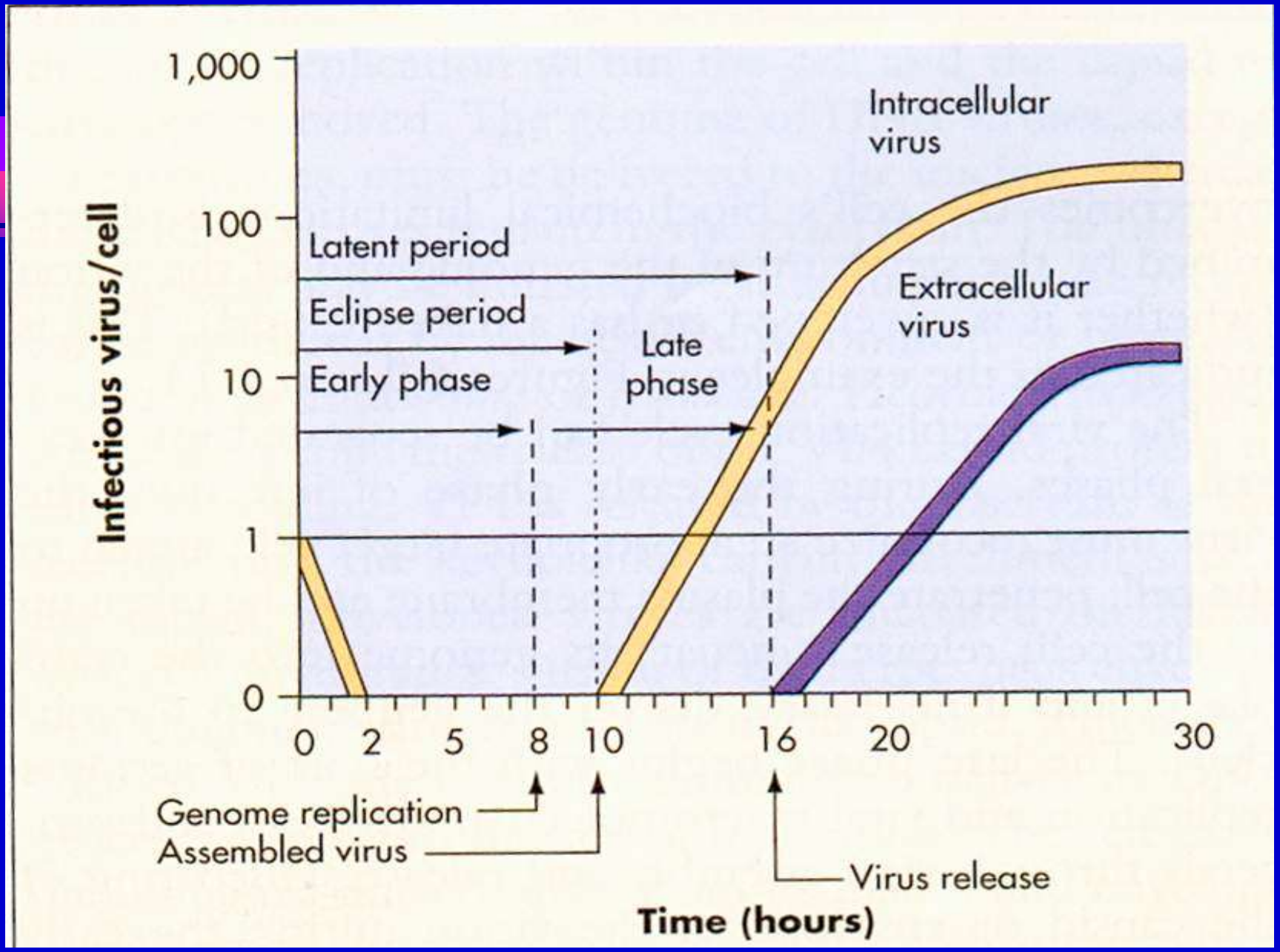
INTERFERENCE

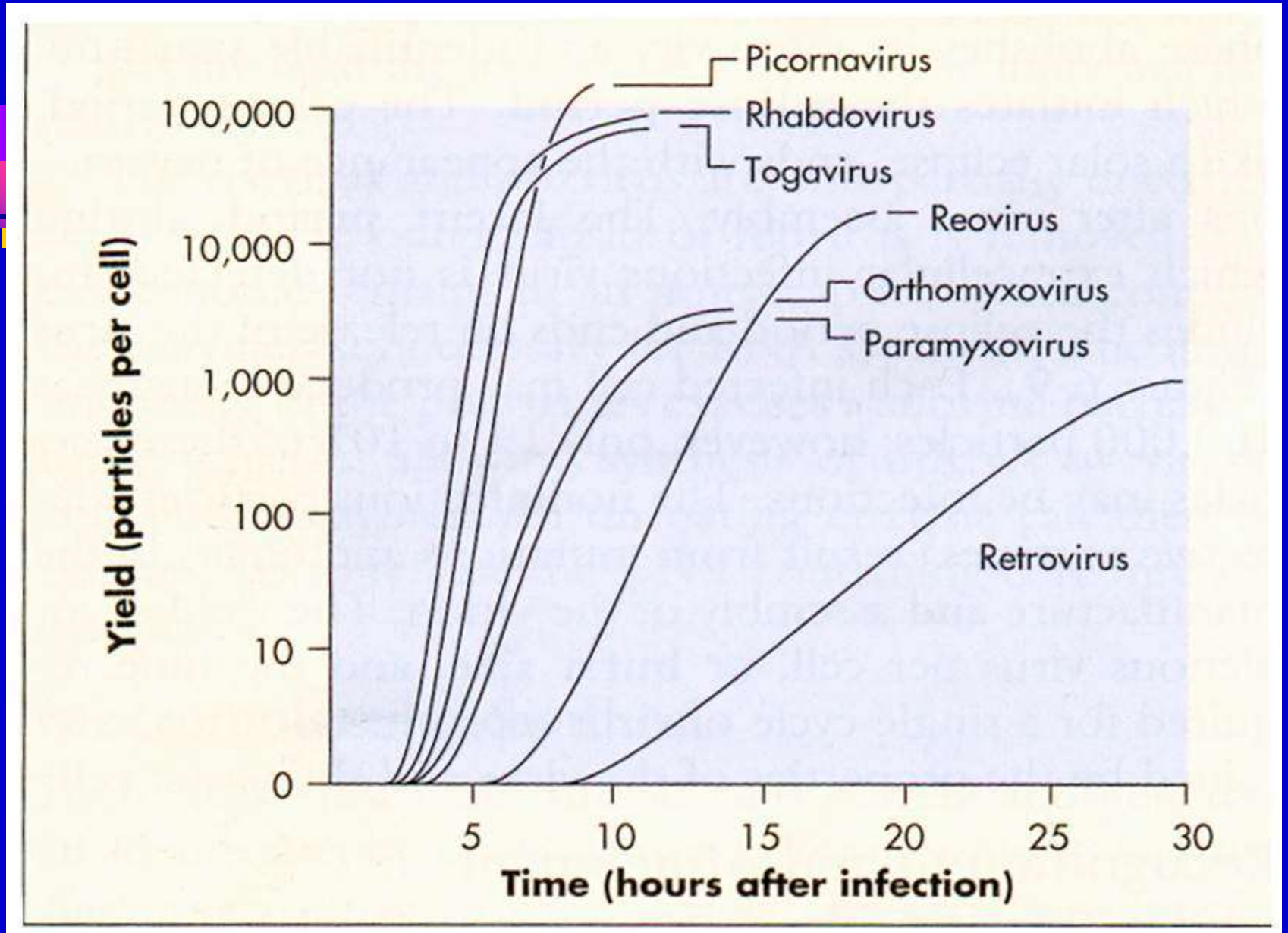
- ***Interferon, IFN***

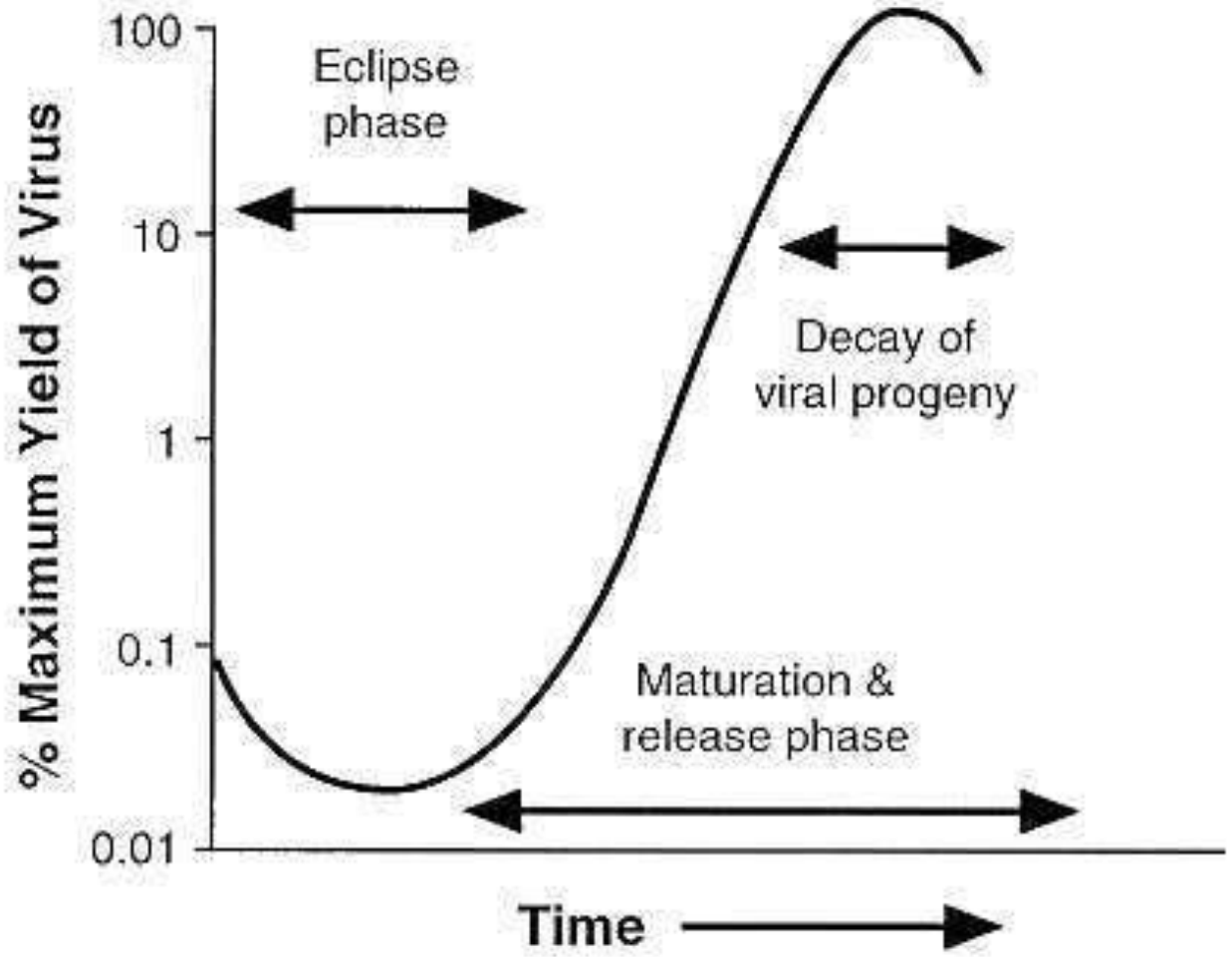
Interferons (**IFN**s) are a group of **signaling proteins** made and released by host cells in response to the presence of several pathogens, such as viruses, bacteria, parasites, and also tumor cells. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defenses.



Culture of Viruses


1,000
100
10
1
0
Infectious virus/cell
Intracellular virus
Extracellular virus
Latent period
Eclipse period
Early phase
Late phase
0
2
5
8
10
16
20
30
Genome replication
Assembled virus
Virus release
Time (hours)


Picornavirus
Rhabdovirus
Togavirus
Reovirus
Orthomyxovirus
Paramyxovirus
Retrovirus
100,000
10,000
1,000
100
10
0
Yield (particles per cell)
5
10
15
20
25
30
Time (hours after infection)


100
10
1
0.1
0.01
% Maximum Yield of Virus
Eclipse phase
Decay of viral progeny
Maturation & release phase
Time

One step growth curve to study viral replication:

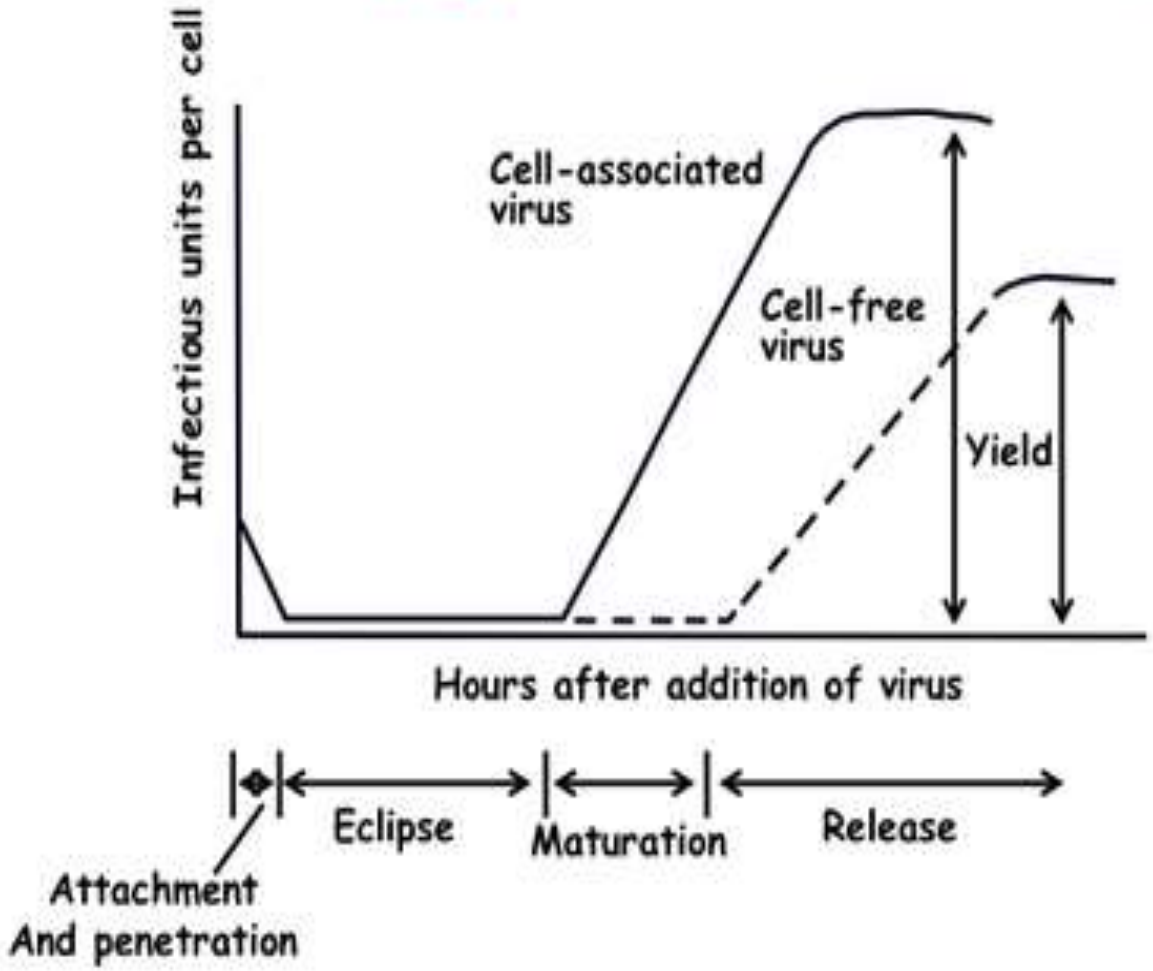
1. Adsorption of virus (initial phase).

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.

One-step growth curve-VIRUSES



Virus latency (or **viral latency**): is the ability of a pathogenic virus to lie dormant (latent) within a cell, denoted as the lysogenic part of the viral life cycle.

- A latent viral infection is a type of persistent viral infection which is distinguished from a chronic viral infection.
- Latency is the phase in certain viruses' life cycles in which, after initial infection, proliferation of virus particles ceases. However, the viral genome is not fully eradicated.
- The result of this is that the virus can reactivate and begin producing large amounts of viral progeny without the host being infected by new outside virus, denoted as the lytic part of the viral life cycle, and stays within the host indefinitely.
- Virus latency is not to be confused with clinical latency during the incubation period when a virus is *not* dormant.

System for the propagation of viruses

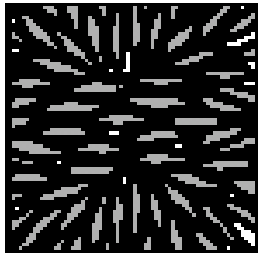
- People
- Animals : cows;chickens; mice; rats
- Embryonated eggs
- Organ and tissue culture
  - Organ culture
  - primary tissue culture
  - cell lines: diploid
  - Tumor or immortalized cell line

Comparison of primary cells versus growth transformed cells and continuous cell lines

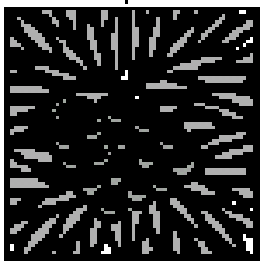
Mince tissue; digest with collagenase

Filter out clumps; pellet & wash cells

grow in culture medium with serum, antibiotics, vitamins, amino acids

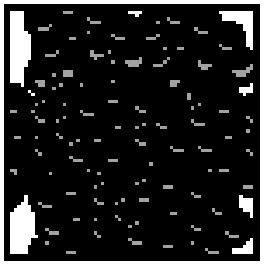


Primary cells



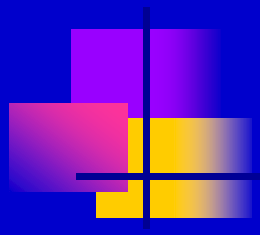
Growth transformed cells

grow out during prolonged culture as normal cells senesce



Continuous cell line

Immortalized cells; often have genetic or chromosomal abnormalities

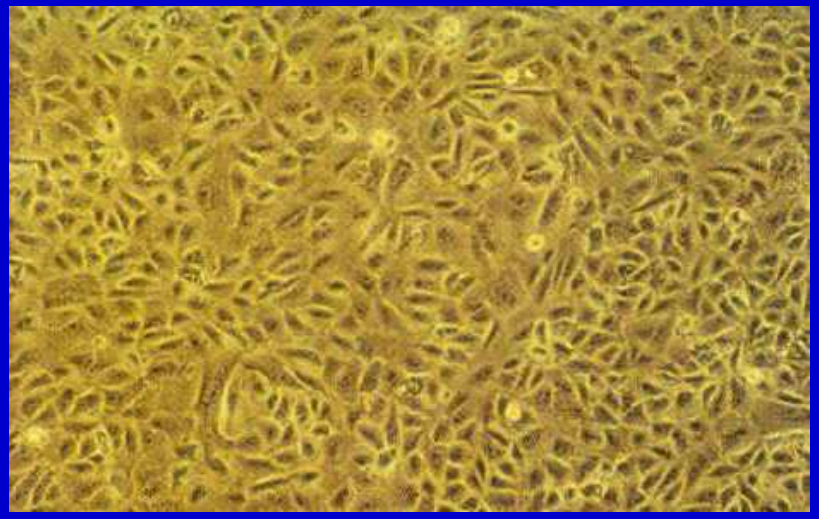


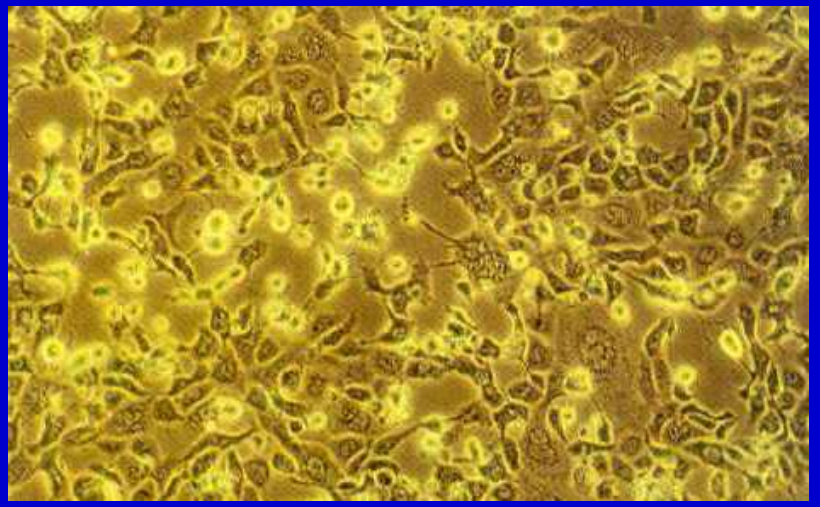
- Cytopathic effect, CPE
- Inclusion Bodies

CPE:Viral Cytopathological Effects

- Cell death
  - Cell rounding/Degeneration/Aggregation
  - Lass of attachments to substrate
- Inclusion bodies in the nucleus or cytoplasm, margination of chromatin
- Syncytia: multinucleated giant cells caused by virus-induced cell-cell fusion
- Cell surface changes
  - Viral antigen expression
  - Hemadsorption (hemagglutinin expression)

Normal cell and CPE



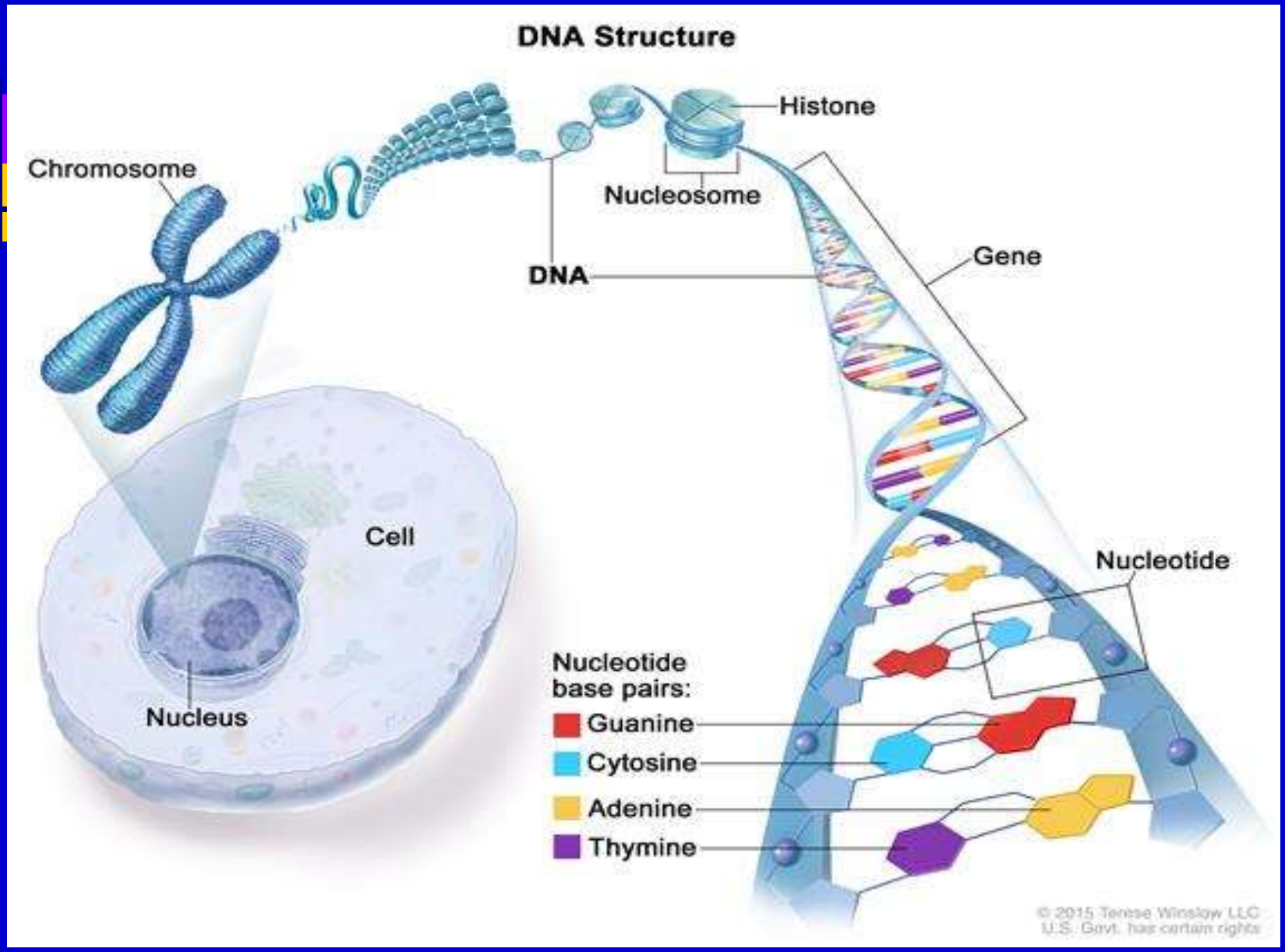


Interactions

when two genetically distinct viruses infect a cell different phenomena can result

antigenic drift: (minor changes) individual bases in the DNA or RNA mutate to other bases. Most of these point mutations are "silent" – they do not change the protein that the gene encodes – but others can confer evolutionary advantages such as resistance to antiviral drugs.

Antigenic shift occurs when there is a major change in the genome of the virus.


DNA Structure
Chromosome
Histone
Nucleosome
DNA
Gene
Cell
Nucleotide
Nucleus
Nucleotide base pairs:
Guanine
Cytosine
Adenine
Thymine
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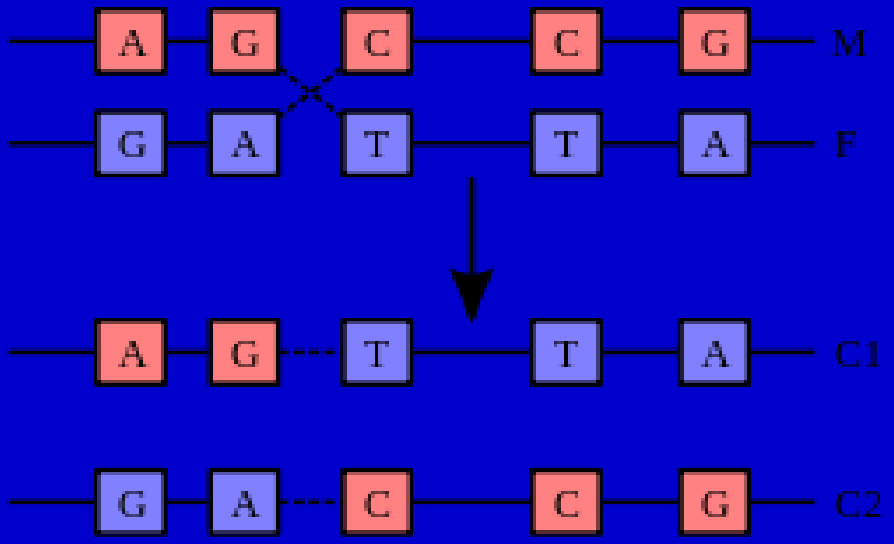
- **Recombination:** involves the exchange of genetic material either between multiple chromosomes or between different regions of the same chromosome. This process is generally mediated by homology; that is, homologous regions of chromosomes.
- Recombination involves the breakage and rejoining of two chromosomes (M and F) to produce two re-arranged chromosomes (C1 and C2).

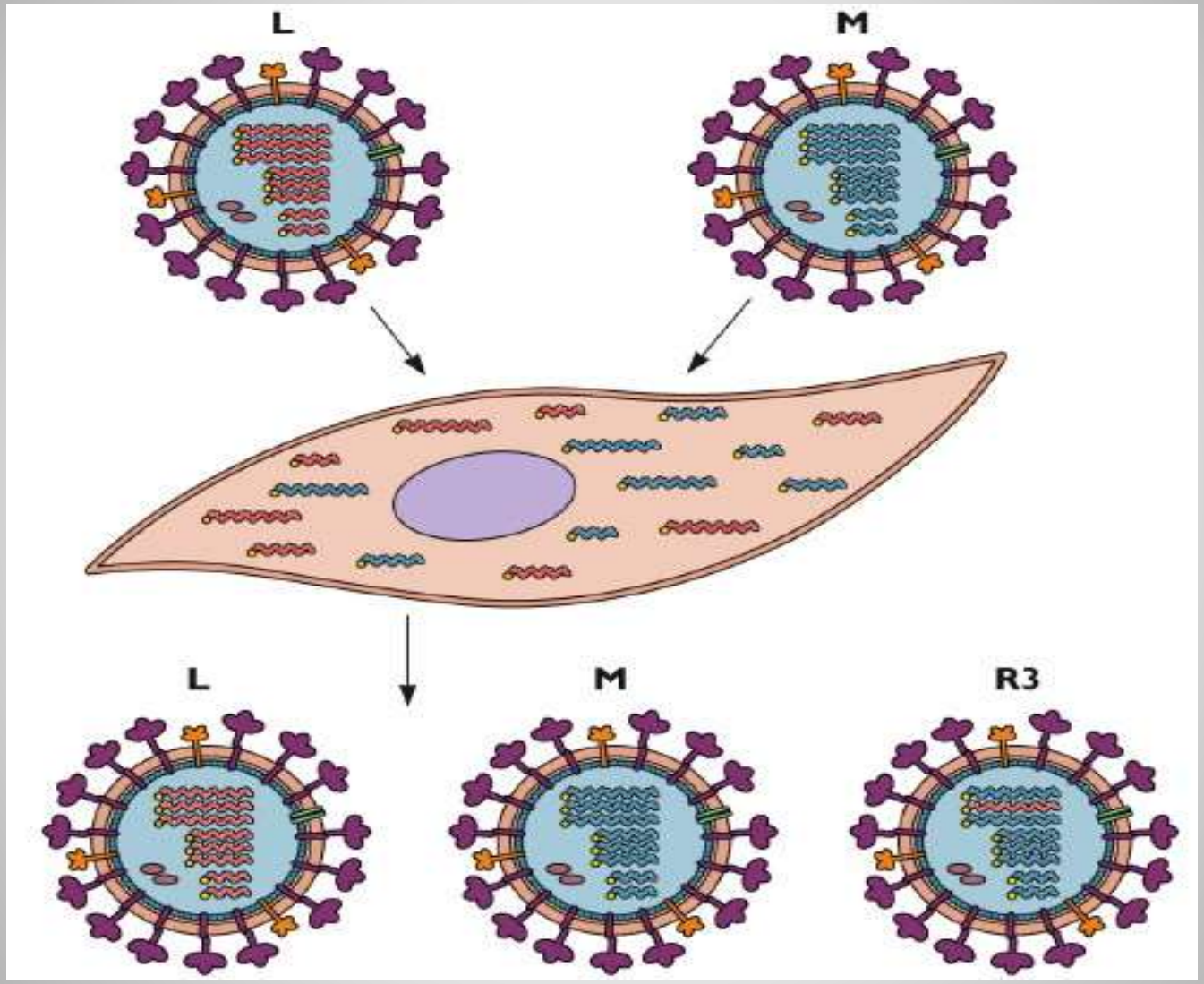
Occur in dsDNA viruses



Reassortment (segmented genomes)

RNA viruses:

influenza virus: Segmented genomes confer evolutionary advantages; different strains of a virus with a segmented genome can shuffle and combine genes and produce progeny viruses or (offspring) that have unique characteristics. This is called reassortment or *viral sex*.


L
M
L
M
R3

Reverse transcribing viruses

❖These have ssRNA (*Retroviridae*, *Metaviridae*, *Pseudoviridae*) or dsDNA (*Hepadnaviridae*) in their particles.

❖Reverse transcribing viruses with RNA genomes (retroviruses), use a DNA intermediate to replicate, whereas those with DNA genomes (pararetroviruses) use an RNA intermediate during genome replication.

❖Both types use a reverse transcriptase, or RNA-dependent DNA polymerase enzyme (**is an enzyme used to generate complementary DNA (cDNA) from an RNA template, a process termed *reverse transcription***), to carry out the nucleic acid conversion.

❖Retroviruses integrate the DNA produced by reverse transcription into the host genome as a provirus as a part of the replication process

- pararetroviruses do not, although integrated genome copies of especially plant pararetroviruses can give rise to infectious virus.
- They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine and lamivudine.
- An example of the first type is HIV, which is a retrovirus. Examples of the second type are the *Hepadnaviridae*, which includes Hepatitis B virus.

Classification of Viruses

Levels of taxonomy

Taxonomic level	Suffix (comment)	Example
Order	-virales (a group of related families)	*Mononegavirales*
Family	-viridae	*Paramyxoviridae*
Subfamily	-virinae	*Paramyxovirinae*
Genus	-virus	*Morbillivirus*
Species	(an individual virus)	*Measles virus*

CLASSIFICATION OF VIRUSES --------basis of classification

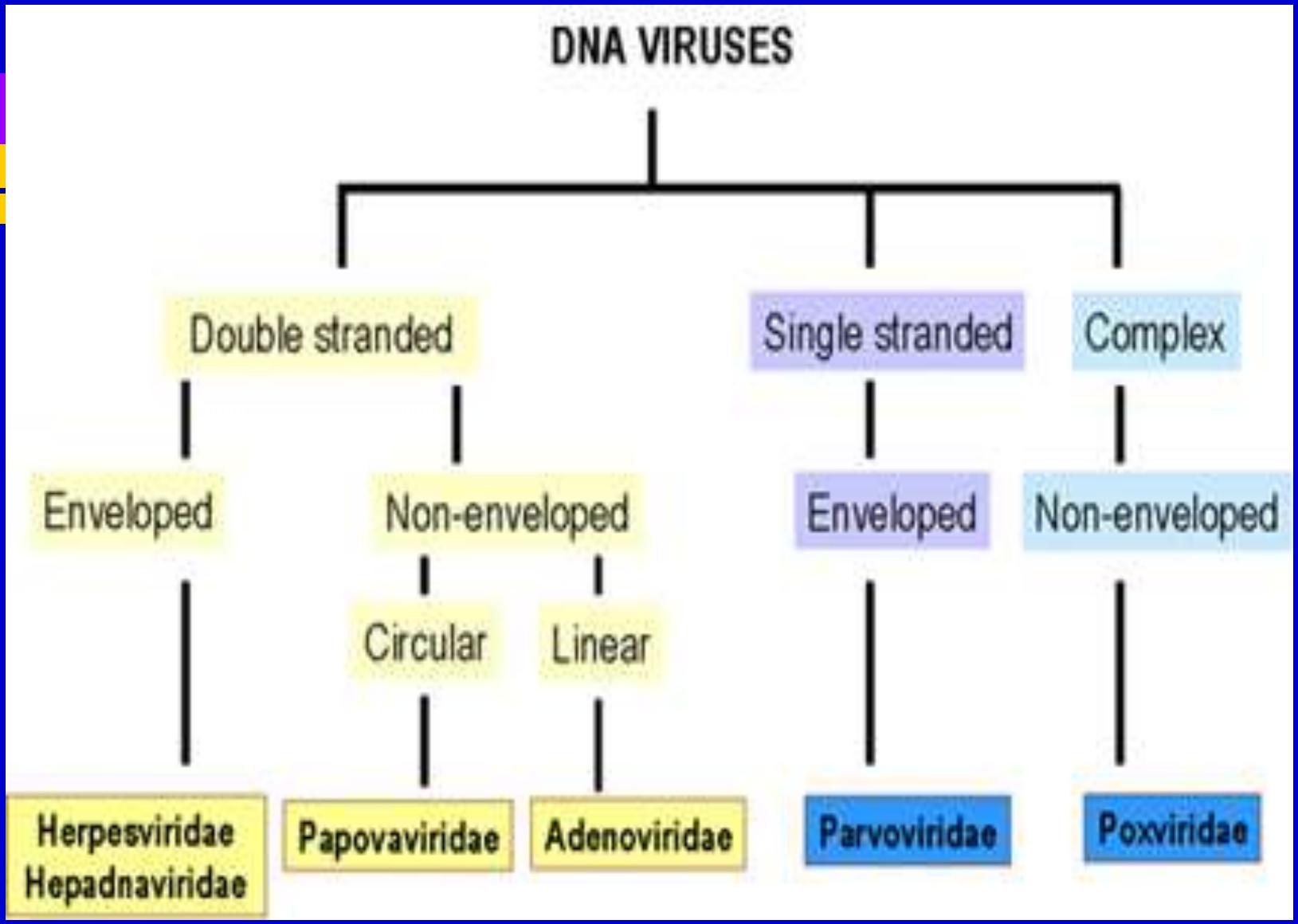
- Virion morphology
- Physicochemical properties of the virion
- Virus genome properties
- Virus protein proteries
- Genome organization and replication
- Antigenic properties
- Biologic properties

CLASSIFICATION OF VIRUSES

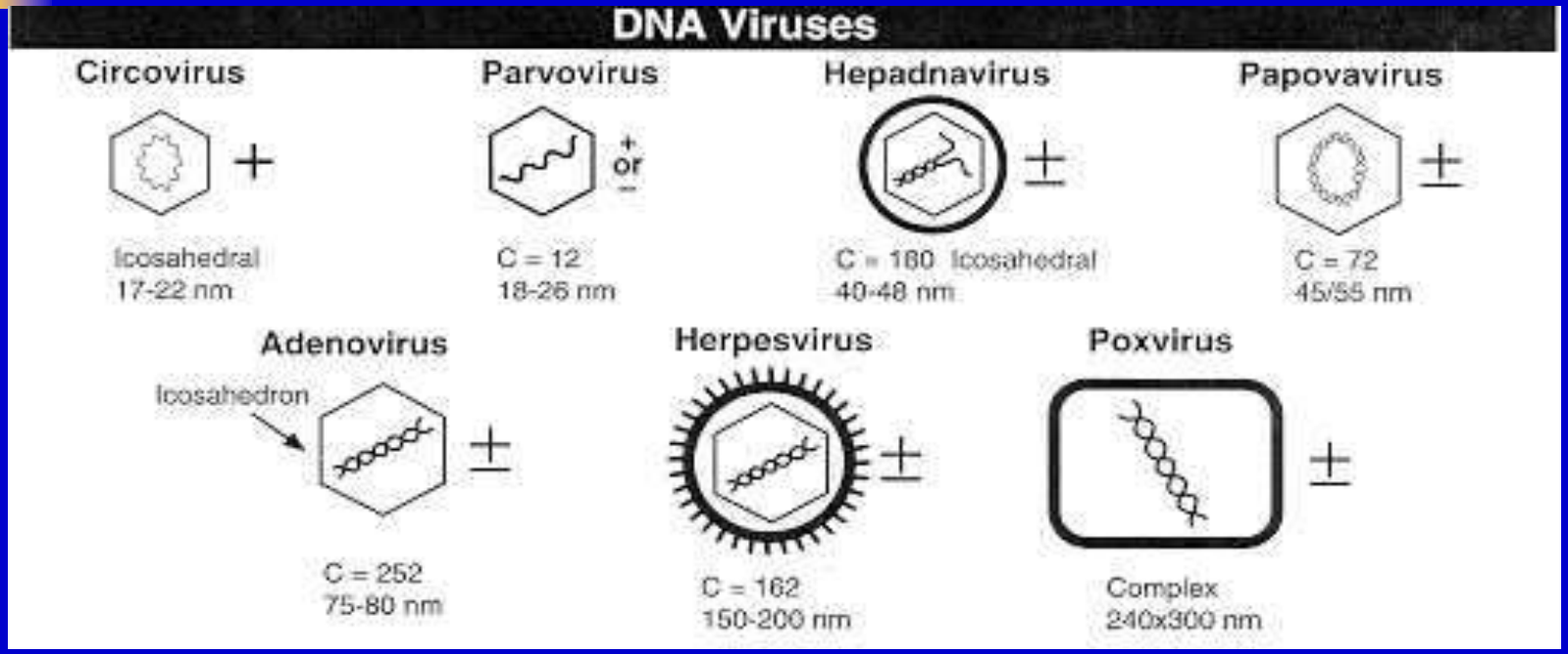
- By 1995
  --71 families, 11 subfamilies
  --164 genera
- For humans and animals
  --24 families,
  --DNA: 7; RNA: 17 for humans

Survey of DNA-containing Viruses

- Parvoviruses: human parvovirus B_{19}
- Papovaviruses: papillomaviruses
- Adenoviruses: 47 types infect humans
- Herpesviruses: human herpesvirus 1-8
- Poxviruses: smallpox; vaccinia
- Hepadnaviruses: HBV


DNA VIRUSES
Double stranded
Single stranded
Complex
Enveloped
Non-enveloped
Enveloped
Non-enveloped
Circular
Linear
Herpesviridae
Hepadnaviridae
Papovaviridae
Adenoviridae
Parvoviridae
Poxviridae

DNA Viruses


Circovirus
+
Icosahedral
17-22 nm
Parvovirus
+ or –
C = 12
18-26 nm
Hepadnavirus
±
C = 160 Icosahedral
40-48 nm
Papovavirus
±
C = 72
45/55 nm
Adenovirus
Icosahedron
±
C = 252
75-80 nm
Herpesvirus
±
C = 162
150-200 nm
Poxvirus
±
Complex
240x300 nm

dsDNA

Herpesviridae

Simplexvirus
Varicellovirus

Cytomegalovirus
Roseolovirus

Lymphocryptovirus
Rhadinovirus

Papovaviridae

Polyomavirus
Papillomavirus

Poxviridae

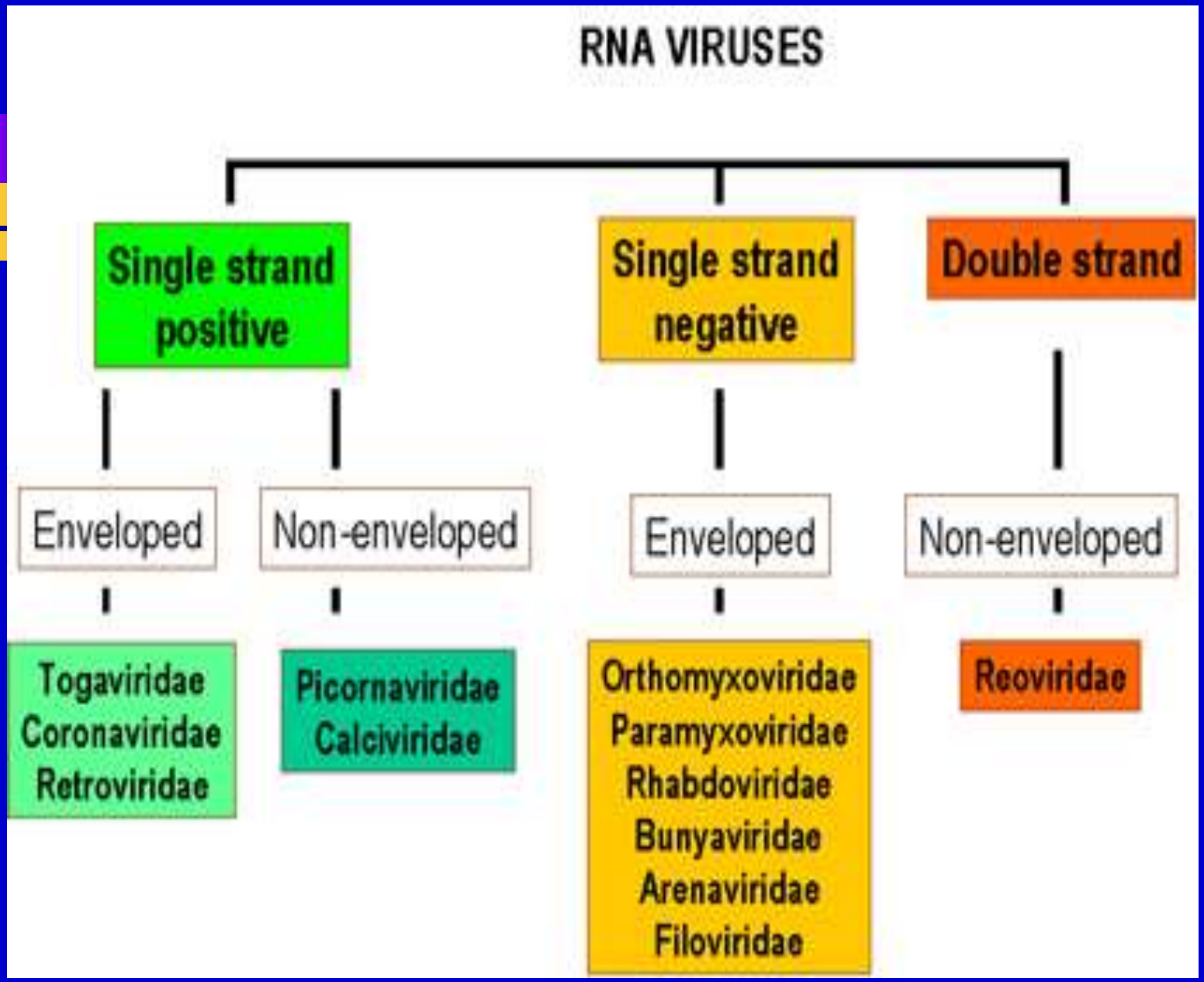
Orthopoxvirus
Parapoxvirus
Avipox
Molluscipoxvirus

Adenoviridae

Mastadenovirus
Aviadenovirus

Survey of RNA-containing Viruses

- Picornaviruses
- Astroviruses
- Caliciviruses
- Reoviruses
- Arboviruses
- Togaviruses
- Flaviviruses
- Arenaviruses
- Coronaviruses: SARS
- Retroviruses
- Bunyaviruses
- Othomyxoviruses
- Paramyxoviruses:
- Rhabdoviruses:rabies virus
- Bornaviruses: BDV
- Filoviruses
- Other viruses
- Viroids


RNA VIRUSES
Single strand positive
Single strand negative
Double strand
Enveloped
Non-enveloped
Enveloped
Non-enveloped
Togaviridae
Coronaviridae
Retroviridae
Picornaviridae
Calciviridae
Orthomyxoviridae
Paramyxoviridae
Rhabdoviridae
Bunyaviridae
Arenaviridae
Filoviridae
Reoviridae

ssDNA

Parvoviridae

- Parvovirus
- Erythrovirus
- Dependovirus

Circoviridae

- Circovirus*

**: TT virus*

Reverse Transcribing

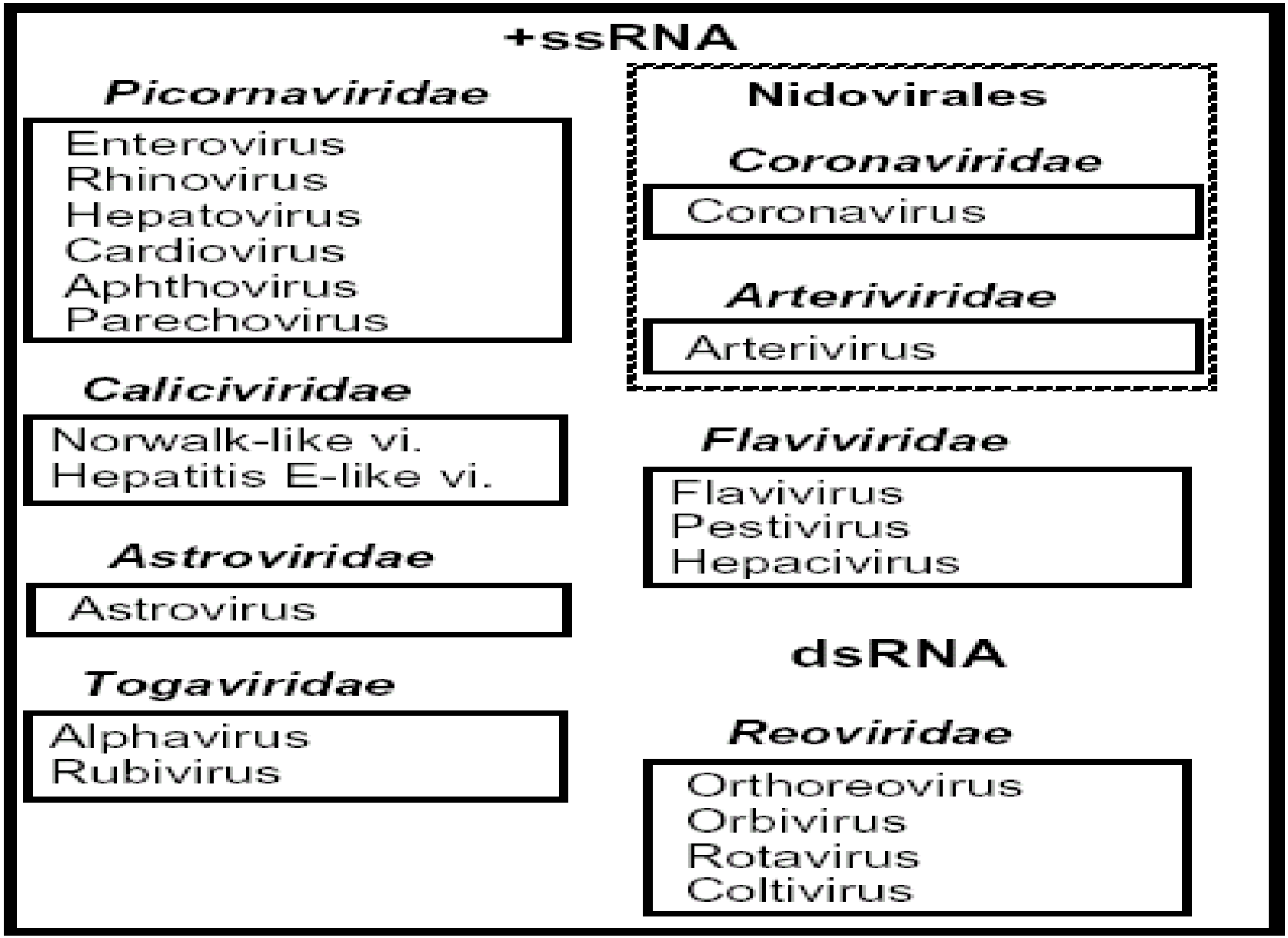
Retroviridae

- Alpharetrovirus
- Betaretrovirus
- Gammaretrovirus
- Deltaretrovirus
- Epsilonretrovirus
- Lentivirus
- Spumavirus

***: Alpha thru epsilon = former oncoretroviruses*

Hepadnaviridae

- Orthohepadnavirus
- Avihepadnavirus


+ssRNA
Picornaviridae
Enterovirus
Rhinovirus
Hepatovirus
Cardiovirus
Aphthovirus
Parechovirus
Caliciviridae
Norwalk-like vi.
Hepatitis E-like vi.
Astroviridae
Astrovirus
Togaviridae
Alphavirus
Rubivirus
Nidovirales
Coronaviridae
Coronavirus
Arteriviridae
Arterivirus
Flaviviridae
Flavivirus
Pestivirus
Hepacivirus
dsRNA
Reoviridae
Orthoreovirus
Orbivirus
Rotavirus
Coltivirus

-ssRNA

Mononegavirales

Paramyxoviridae

Paramyxovirus
Morbillivirus
Rubulavirus

Pneumovirus

Rhabdoviridae

Vesiculovirus
Lyssavirus

Filoviridae

Filovirus

Bornaviridae

Bornavirus

Orthomyxoviridae

Influenzavirus A
Influenzavirus B
Influenzavirus C
Thogotovirus

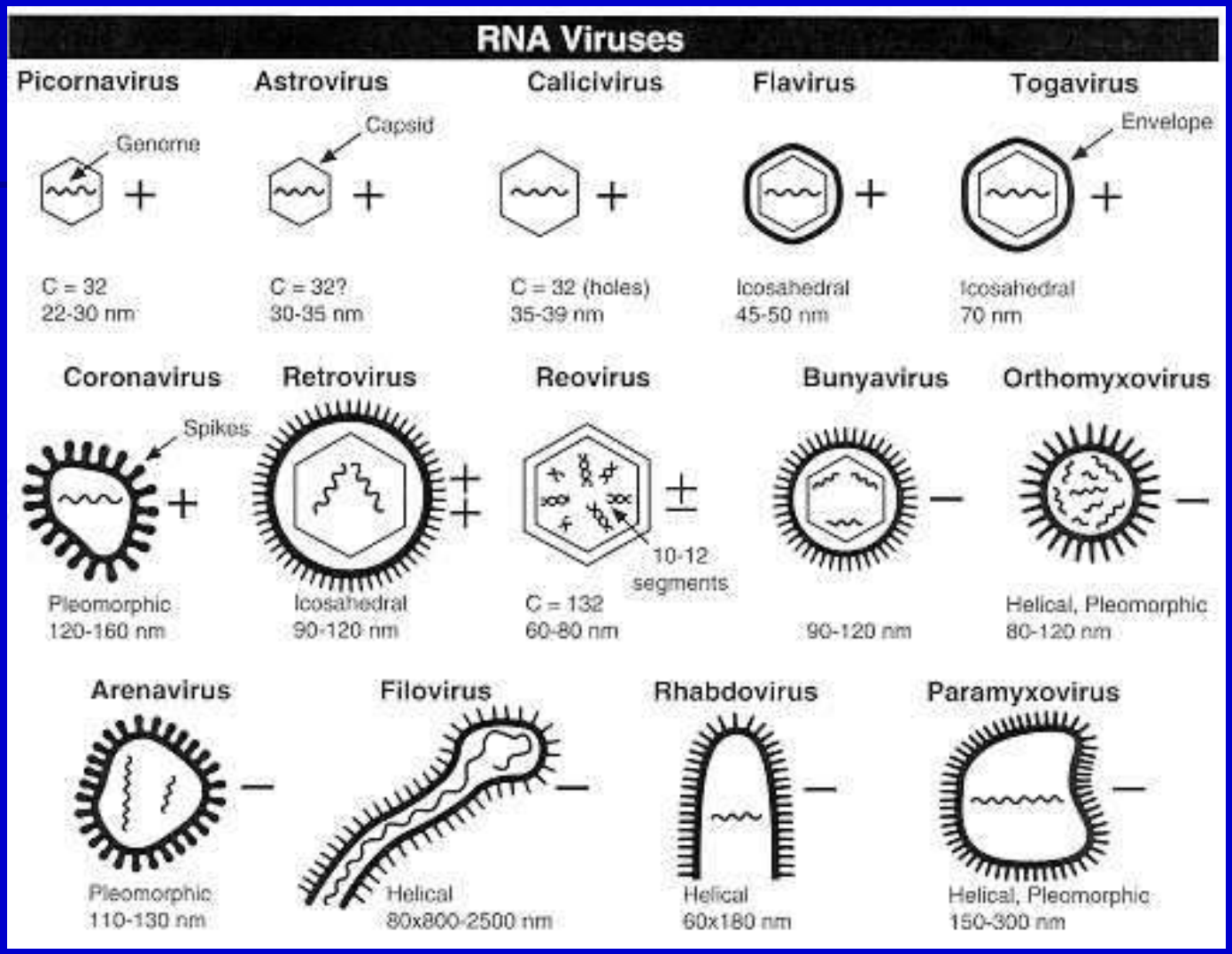
Bunyaviridae

Bunyavirus
Hantavirus
Nairovirus
Phlebovirus

Arenaviridae

Arenavirus

Deltavirus


RNA Viruses
Picornavirus
Genome
C = 32
22-30 nm
Astrovirus
Capsid
C = 32?
30-35 nm
Calicivirus
C = 32 (holes)
35-39 nm
Flavirus
Icosahedral
45-50 nm
Togavirus
Envelope
Icosahedral
70 nm
Coronavirus
Spikes
Pleomorphic
120-160 nm
Retrovirus
Icosahedral
90-120 nm
Reovirus
10-12
segments
C = 132
60-80 nm
Bunyavirus
90-120 nm
Orthomyxovirus
Helical, Pleomorphic
80-120 nm
Arenavirus
Pleomorphic
110-130 nm
Filovirus
Helical
80x800-2500 nm
Rhabdovirus
Helical
60x180 nm
Paramyxovirus
Helical, Pleomorphic
150-300 nm

DNA Viruses

Viral replication implies:

attachment, penetration, and

DNA lytic or lysogenic cycles (what dose it mean)

General Properties: NA

- DNA
  - Single or Double stranded
  - Glycosylated and/or Methylated
    - Cytosine, Uracil, Thymine
  - Circular or Linear
  - Unique purine and/or pyrimidine bases
  - Bound protein molecules

General Properties: Capsid

- Protomers -> Capsomeres -> Capsid
- Protein Coat
- Organization gives the virus form
  - Icosahedral
    - Triangular face with hexon
    - 12 corners with penton
  - Helical
    - Protomers not grouped in capsomeres
    - Bound together to form a ribbon which folds
  - Complex

General Properties: Envelope

- Lies outside the capsid
- Made up of lipids, proteins
- Contains antigens from host & virus
- Enveloped or Nonenveloped (naked)
- +/- Spikes
  - Glycoprotein projections of envelope
  - Functions
    - Enzymatic
    - Adsorption
    - Hemagglutin

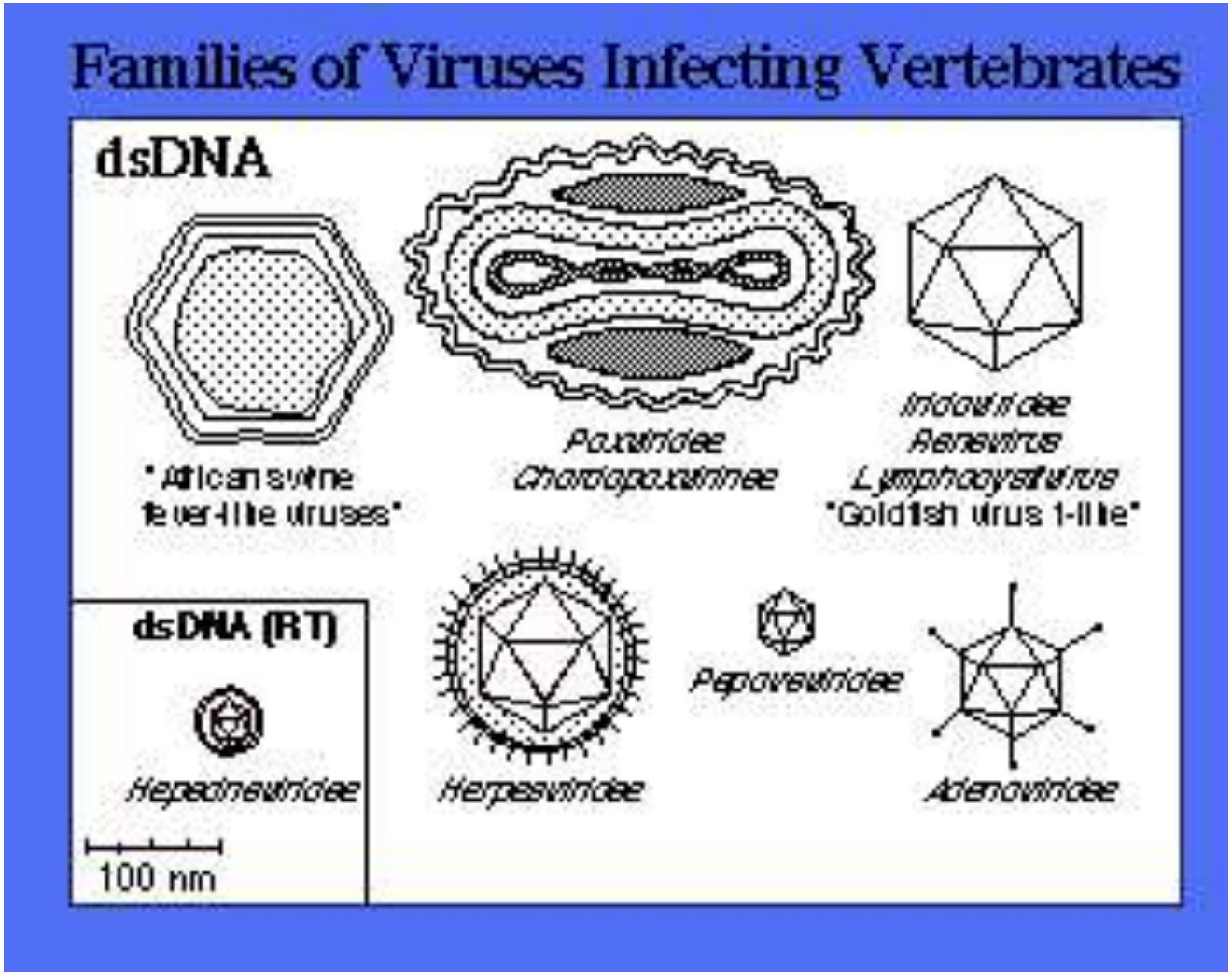
Viral Replication Cycle

- Adsorption (Attachment): viral protein + host cell receptor
- Penetration
- Uncoating: cytoplasm of host using proteolytic enzymes
- Replication of NA (DNA)
  - Early Transcription (ds DNA is needed, ss-> ds)
  - Early Translation (mRNA-> enzymes for viral DNA)
  - Late Transcription (ds DNA used)
  - Late Translation (mRNA-> proteins for capsid)
- Assembly: NA + capsid
- Maturation
  - Enveloped: cell membrane
  - Non-enveloped: naked, accumulated in cell -> inclusions
  - Complex: multilayered membrane
- Release: via cell lysis

Viral Pathogenicity

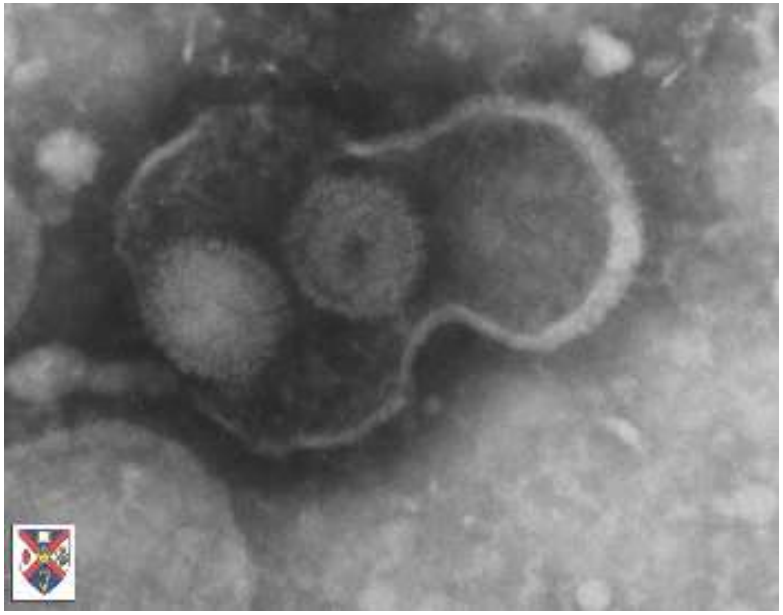
- Contributing Factors
  - Ability to enter cell
  - Ability to grow in cell
  - Ability to combat host defenses
  - Ability to produce damage
    - Cell Lysis via hypersensitivity reactions (II, IV)
    - Production of toxic substances
    - Cell transformation
      - Metabolism and cellular products: Turn “on” genes
      - Structural: Nuclear or Cytoplasmic inclusions

ds DNA Viruses

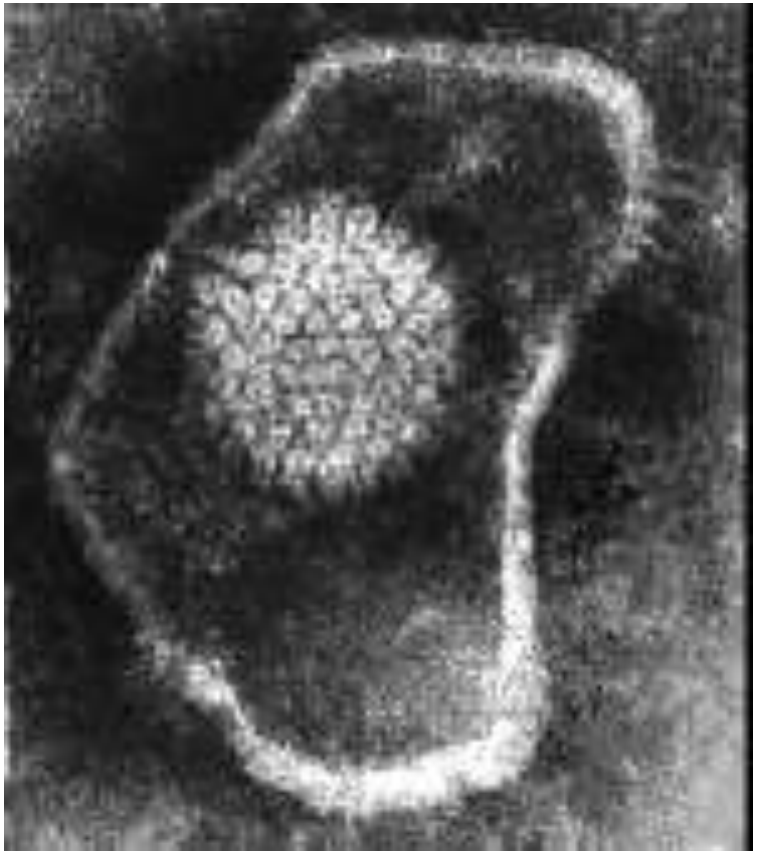


HERPESVIRIDAE

- ds DNA
- Icosahedral
- Asymmetrical tegument between capsid and envelope
- Enveloped
- Glycoprotein spikes
- 8 human serotypes
- Latent, recurring infections



Human Herpesvirus 1 & 2
HSV1,2 or Herpes Simplex



- HSV1: Associated with oro-facial lesions (cold sore)
- HSV2: Associated with genital lesions
- Direct contact
- Subclinical
- Vessicles
- Latency
- DX: Culture, EM
- Reactivation: stress, UV, fever

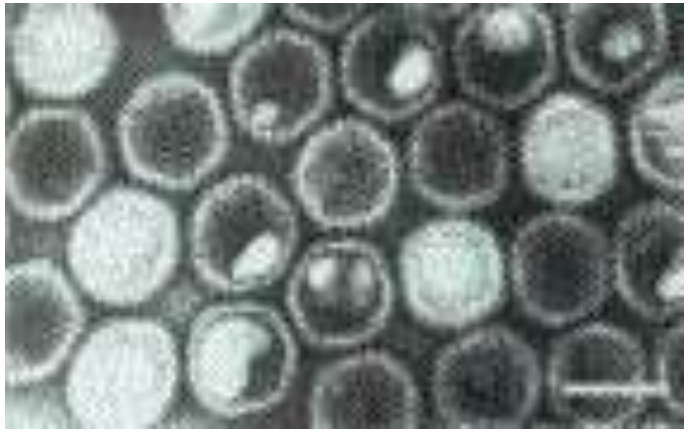
Herpes Simplex Virus

- HSV1
- Gingostomatitis, and KCS (Keratoconjunctivitis sicca)
- Latent infections in trigeminal nerve as an episomal (plasmid) form
- Acute Necrotizing Encephalitis

- HSV 2
- Genital Herpes
- Latent infections in ganglia of sensory nerves that supply the site of primary infection
- Considered STD
- Eruption last 14 days

Herpes Varicella Zoster Virus

- Varicella
  - Chicken pox
  - Primary infection
  - Vesicular rash
  - 21 day incubation
  - Direct or droplet
  - Latent in sensory ganglia
  - Severe complications in adults, perinatal, or immunocompromised individuals



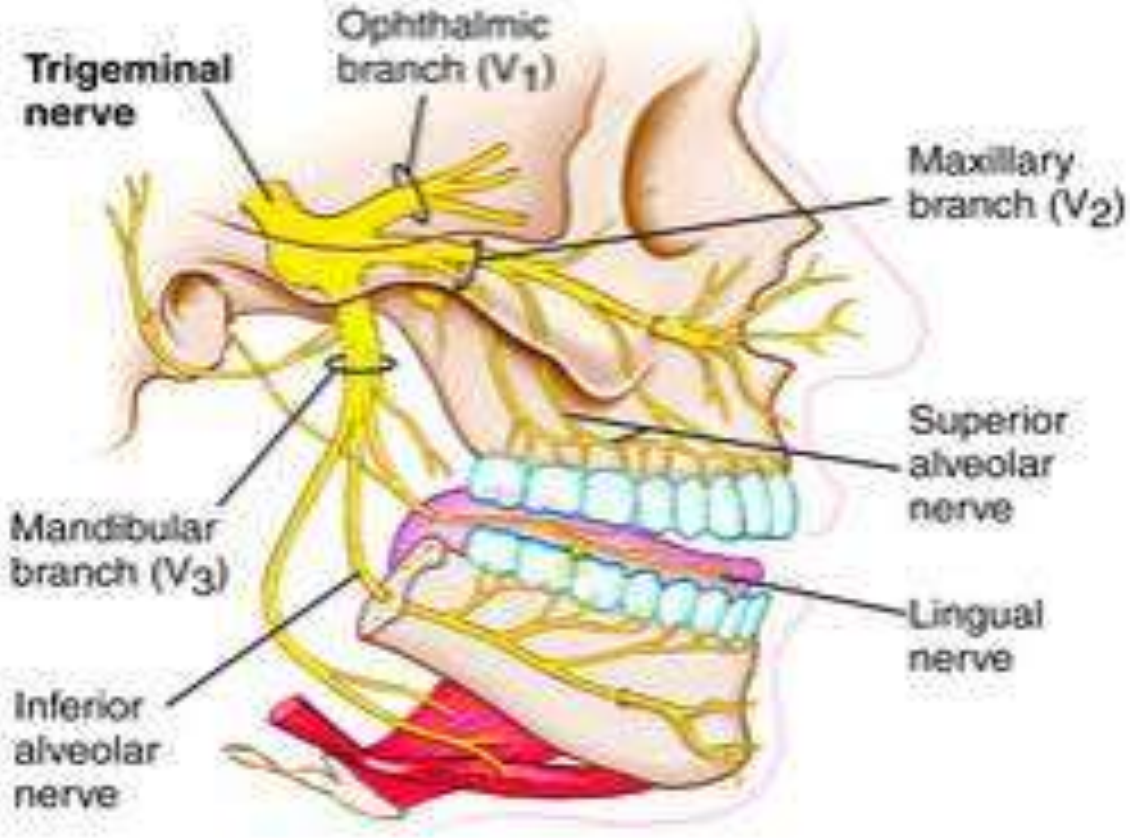
DX: EM, culture, serology for IgM

TX: Acyclovir, nucleoside analog of Guanosine. Binds to DNA polymerase after it is incorporated into host DNA.

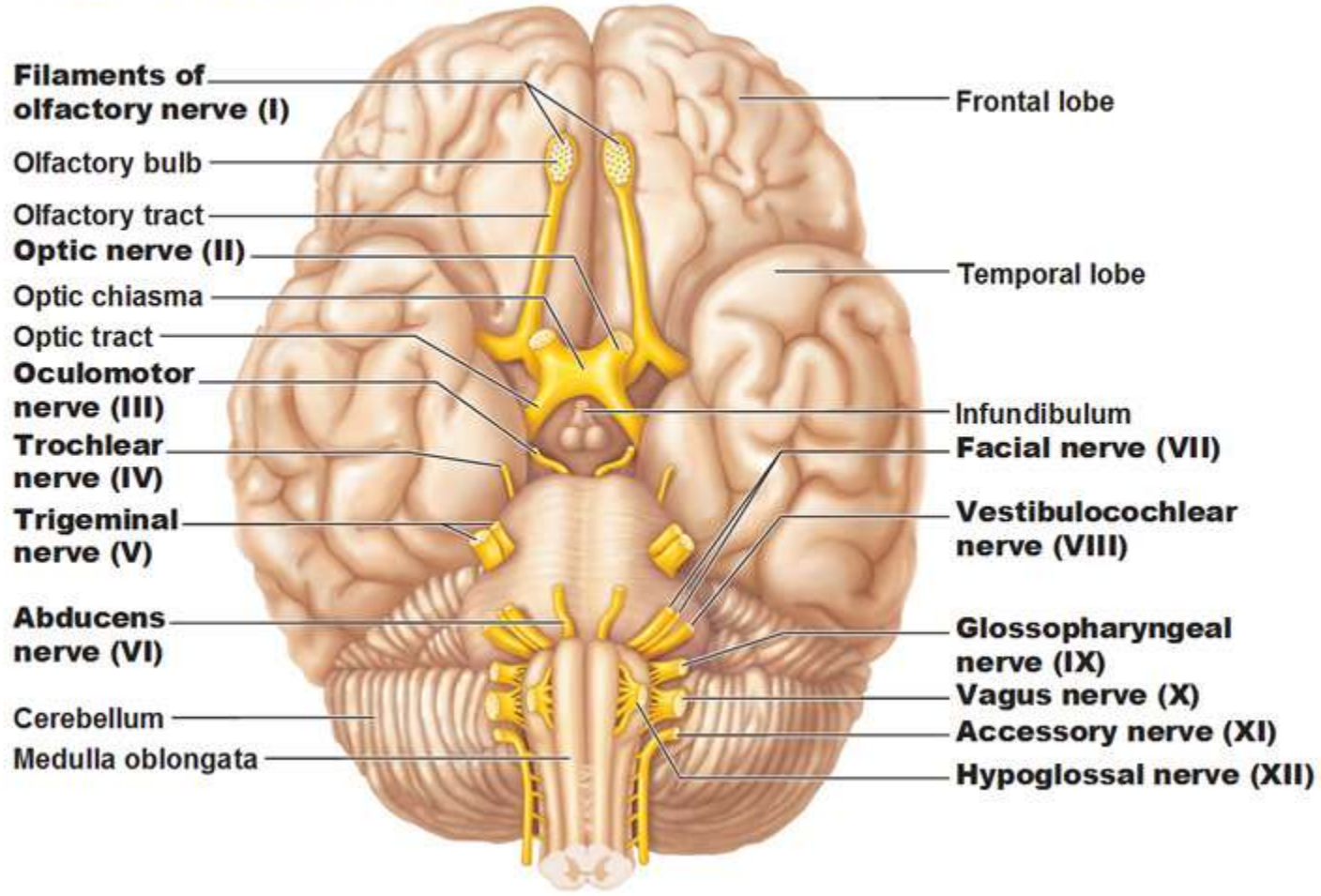
Herpes Varicella Zoster Virus

- Zoster
  - Shingles
  - Reactivation of VZV
  - Associated with immunosuppression
  - Dermatome of sensory ganglion
  - Vesicles
  - DX and TX same as Varicella

- The skin lesions of herpes zoster and chickenpox are histopathologically identical: both contain multinucleated giant cells with eosinophilic intranuclear inclusion bodies.
- The rash of herpes zoster is similar to chickenpox, except that it is restricted to one area of the skin on one side of the body—namely, the dermatome innervated by the ganglion in which the latent virus reactivated.
- Also, the lesions of herpes zoster consist of closely grouped vesicles on an erythromatous base, whereas those of chickenpox are individual and randomly distributed.
- These differences reflect intraneural spread of virus to the skin in herpes zoster, in contrast to viremic spread in chickenpox.


Trigeminal nerve
Ophthalmic branch (V_1)
Maxillary branch (V_2)
Superior alveolar nerve
Lingual nerve
Mandibular branch (V_3)
Inferior alveolar nerve

The Cranial Nerves



Herpes Virus 4 and 5

- Epstein-Barr Virus
  - HV-4
  - Widespread
  - Latent in B cells
  - Direct contact
  - Primary
    - Infectious Mono
  - Reactivation
    - B cell Lymphoma
    - Lymphoproliferative
  - Paul Bunnell Test
    - Agglutination
- Cytomegalovirus
  - HV-5
  - Early life infection
  - syncytia
  - Direct contact, blood (blood transfusion)
  - Congenital
    - Infant
      - Early lymphatic tissue
      - Brain
  - Immunosuppressed
    - Retinitis
    - Enteritis

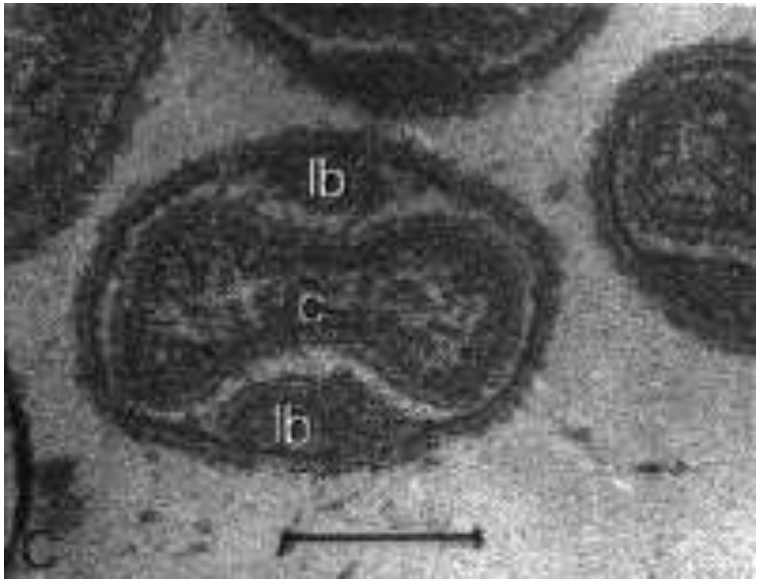
- Paul–Bunnell test: The test is specific for heterophile antibodies produced by the human immune system in response to EBV infection.
- The presence of a heterophile antibody is characterized by broad reactivity with antibodies of other animal species (which are often the source of the assay antibodies).
- The test relies on the agglutination of the sheep RBCs by heterophile antibodies in patient's serum. Heterophile means it reacts with proteins across species lines.
- Heterophile also can mean that it is an antibody that reacts with antigens other than the antigen that stimulated it (an antibody that crossreacts)

Herpes Virus 6, 7, 8

- Human B Lymphotrophic virus (HV-6)
  - Fourth disease
  - Roseola infantum
  - Lymphoproliferative
  - Mononucleosis
- Cryptic Infection of Helper T cells
  - HV-7
  - Fatal encephalitis
- Karposi's Sarcoma
  - HV-8
  - tumor in AIDS patients

POXVIRIDAE

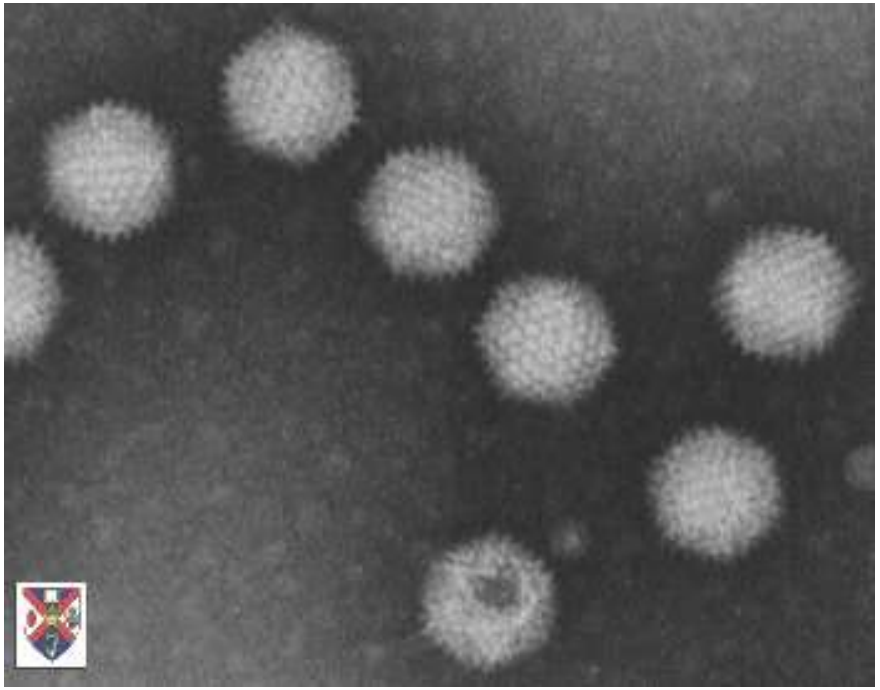
- Largest of all viruses
- Linear ds DNA
- Own RNA polymerase
- Biconcave core
- Two linear or lateral bodies
- Enveloped
- External coat
  - Lipids
  - Tubular proteins



Human Pox Disease Syndromes

- Small Pox
  - Genus Orthopox
  - Variola
  - Direct, droplet
  - 10-12 days incubation in epithelial and endothelial
  - Pustular vesicles that ulcerate, scar
  - Eradicated by global vaccination
  - DX: EM, embryo culture
- Monkey Pox
- Vaccina Virus
  - Used to vaccinate against smallpox
- Cowpox
- Pseudocowpox
- Orf (sheep/goat handlers)
- Molluscum
- Yaba Monkey (tumor virus)
- Tanapox (acute febrile illness accompanied by localized skin lesions)

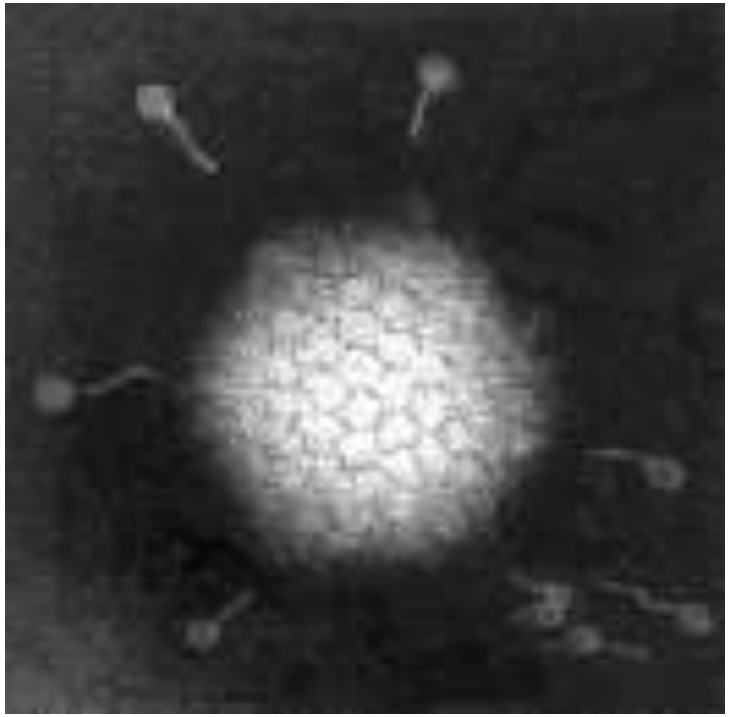
ADENOVIRIDAE



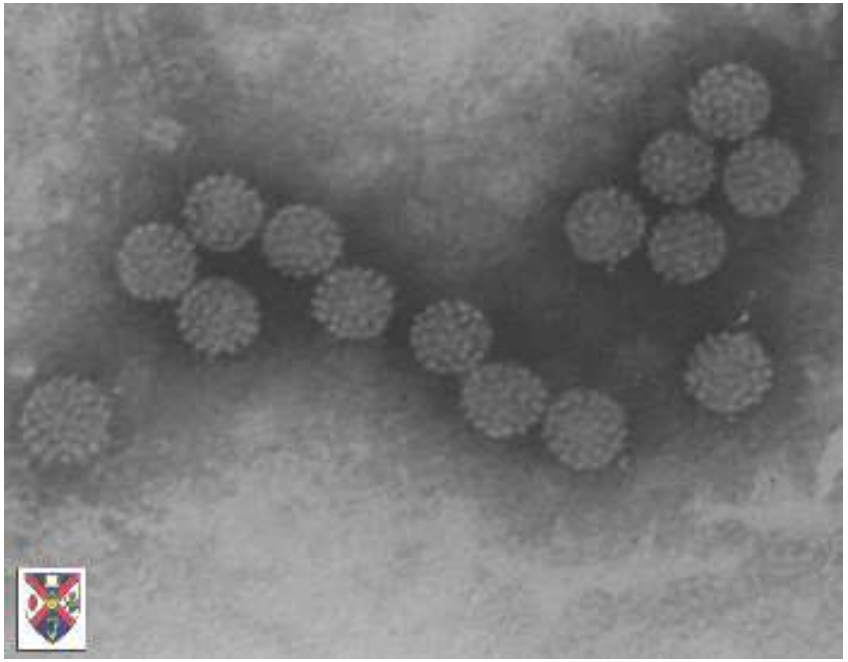
- Linear ds DNA
- Icosahedron
- Nonenveloped
- 12 surface protein fibers project from nucleocapsid
  - Fiber: hemagluttin
- Direct or droplet

Adenovirus Serotype Diseases

- Acute Respiratory Distress (ARD)
- Common cold
- Hemorrhagic Cystitis
- KCS
- Pink-eye
- Gastroenteritis
- Hepatitis

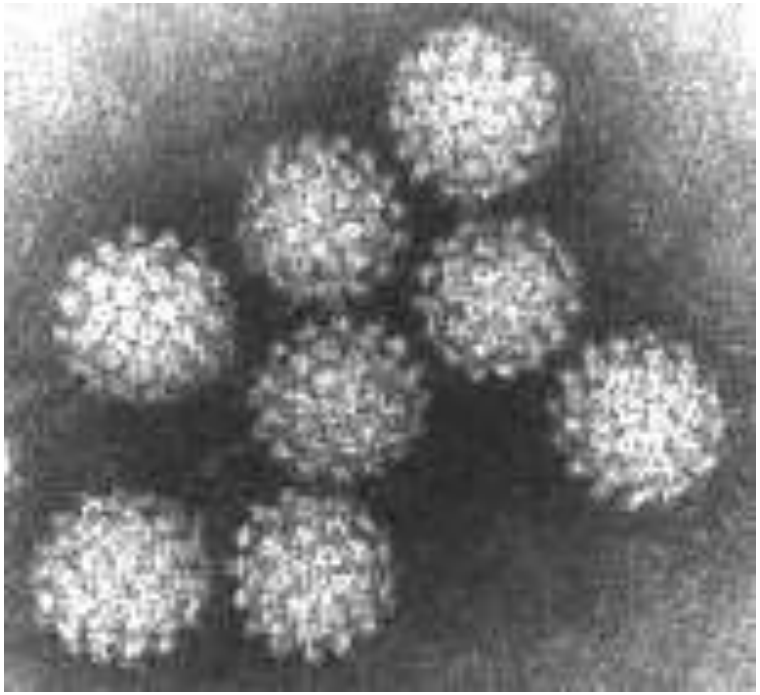


PAPOVIRIDAE



- Circular ds DNA
- Icosahedron
- Nonenveloped
- Mixed capsomeres
  - Pentavalent
  - Hexavalent
- Direct contact

Human Papilloma Virus



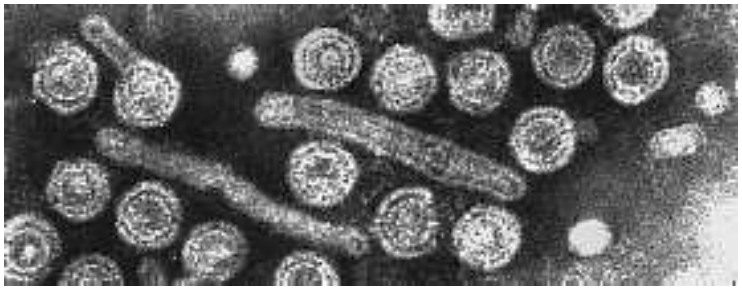
- HPV
- Spread through damaged epithelial cells
- Narrow host range, Humans
- Narrow tissue range, epithelial
- Three major groups

HPV Types

- Cutaneous Warts
  - Benign tumor
  - Regress spontaneously
  - 4 clinical types
    - Verruca vulgaris (common wart, is found at all ages)
    - Deep hyperkeratotic
    - Superficial mosaic
    - Verruca plana(flat warts or plane warts, are 2 to 4 mm in size, smooth, flat-topped papules)
- Epidermodysplasia verruciformis
  - Autosomal recessive
  - Widespread development of warts on body
  - Possible malignancy
- Mucosal HPV
  - STD: genital warts
  - Cervical dysplasia
  - Most are latent

HEPADNAVIRIDAE

- Partially ds DNA with RNA intermediate
- Icosahedral core
- Outer coat extends as sphere or tail
- Surface HBsAg on coat
- Enveloped
- Parentally
  - Direct or Indirect
  - Horizontal or vertical



Hepatitis B or Dane Particle

DX: Serology of HBsAg or AB response

TX: immunoglobulin

Prevention: Immunization using HBsAg, 3 doses q. month for infants and at risk

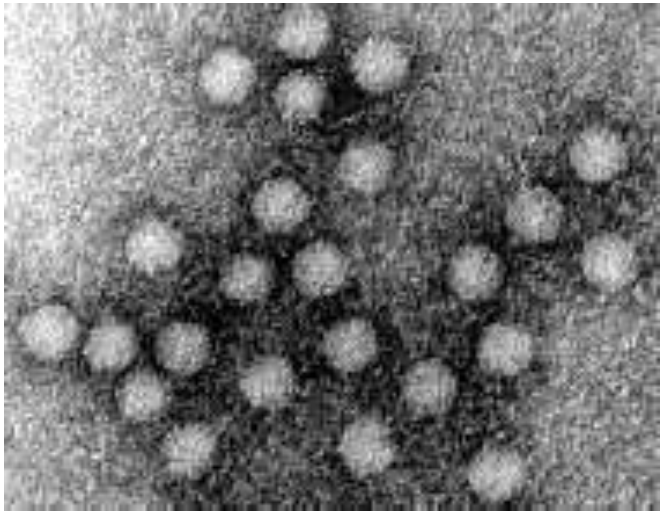
Hepatitis B

- Acute Hepatitis
  - Most individuals eliminate virus
- Serum Hepatitis (long incubation)
  - Failure to eliminate, chronic, active
- Hepatocellular carcinoma
  - Chronic, slow, less aggressive
  - More aggressive = cirrhosis, liver failure

- Virus replicates in the liver over 2-4 months. Surface proteins (HBsAg) shed into blood

ss DNA Viruses

PARVOVIRIDAE



17 day incubation
Hgb drop
Maternal infection during pregnancy → Fetal Anemia
DDx: Rubella
DX: Serum AB

- ss DNA (+ or -)
- Icosahedron
- Nonenveloped
- Smallest DNA virus
- Resp. Droplet spread
- B19 virus
  - Targets erythroid cell line, decreases RBCs
  - Erythemia infectiosum
    - Rash
    - Arthritis

Anti-Viral Therapy

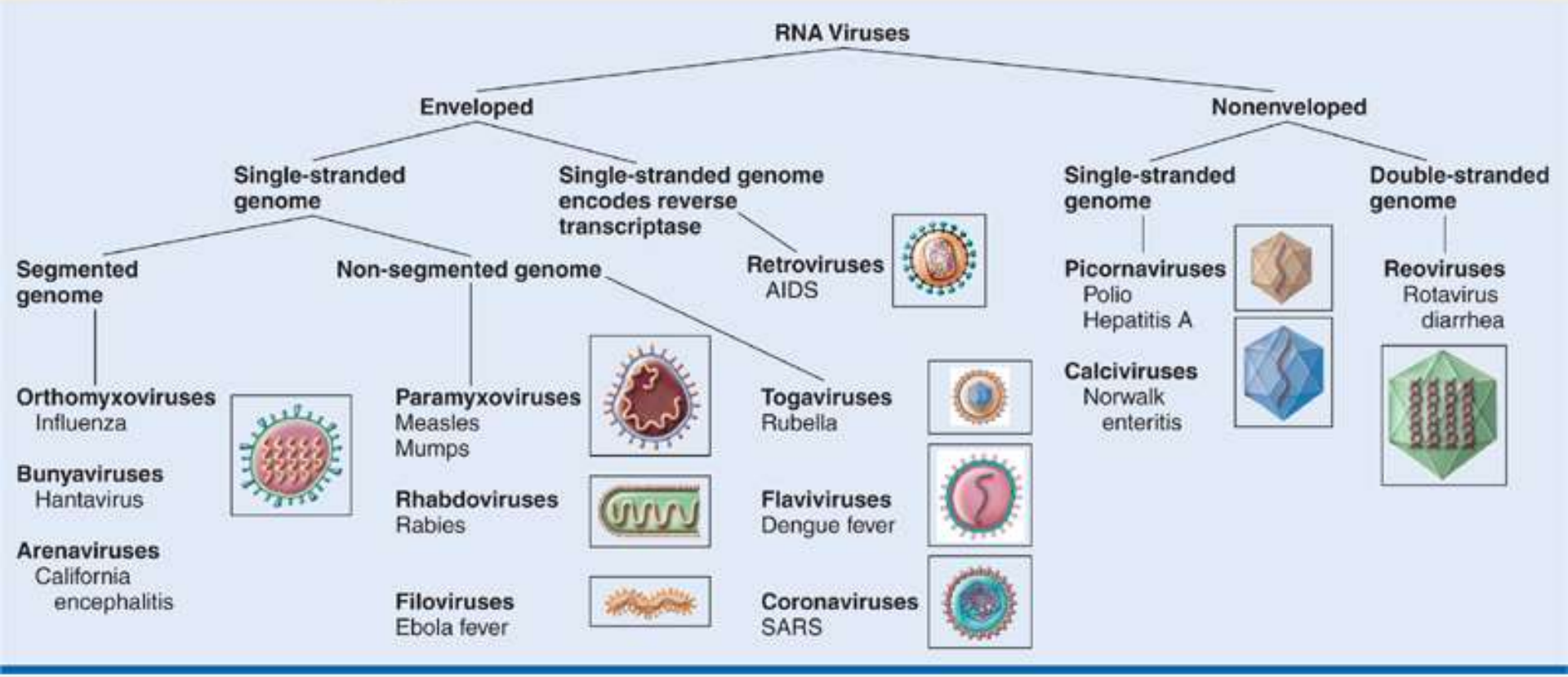
- Nucleotide Analogues
  - Synthetic
  - Incomplete group
    - Deoxy-ribose
    - Ribose
  - Competes with normal nucleotides for incorporation into viral DNA or RNA
  - Associates with viral polymerase, irreversible
  - Causes chain termination
  - Acylovir
    - HSV
    - VZV
  - Gancyclovir
    - Cytomegalovirus
- Immunoglobulins
  - Gamma globulins
  - Binds extracellular virions to prevent attachment /penetration
  - Used for
    - Hep B
    - VZV in neonates
    - Parvovirus
- Interferons
  - Alpha and Beta
  - Antiviral
    - Degrade viral mRNA
    - Inhibit protein synthesis
  - Enhance MHC I, II expression to present viral antigens
  - Used for HepB

RNA Viruses

- Diverse group of microbes
- Assigned to one of 12 families based on envelope, capsid, and nature of RNA genome

TABLE 25.1

RNA Viruses with Examples of Diseases

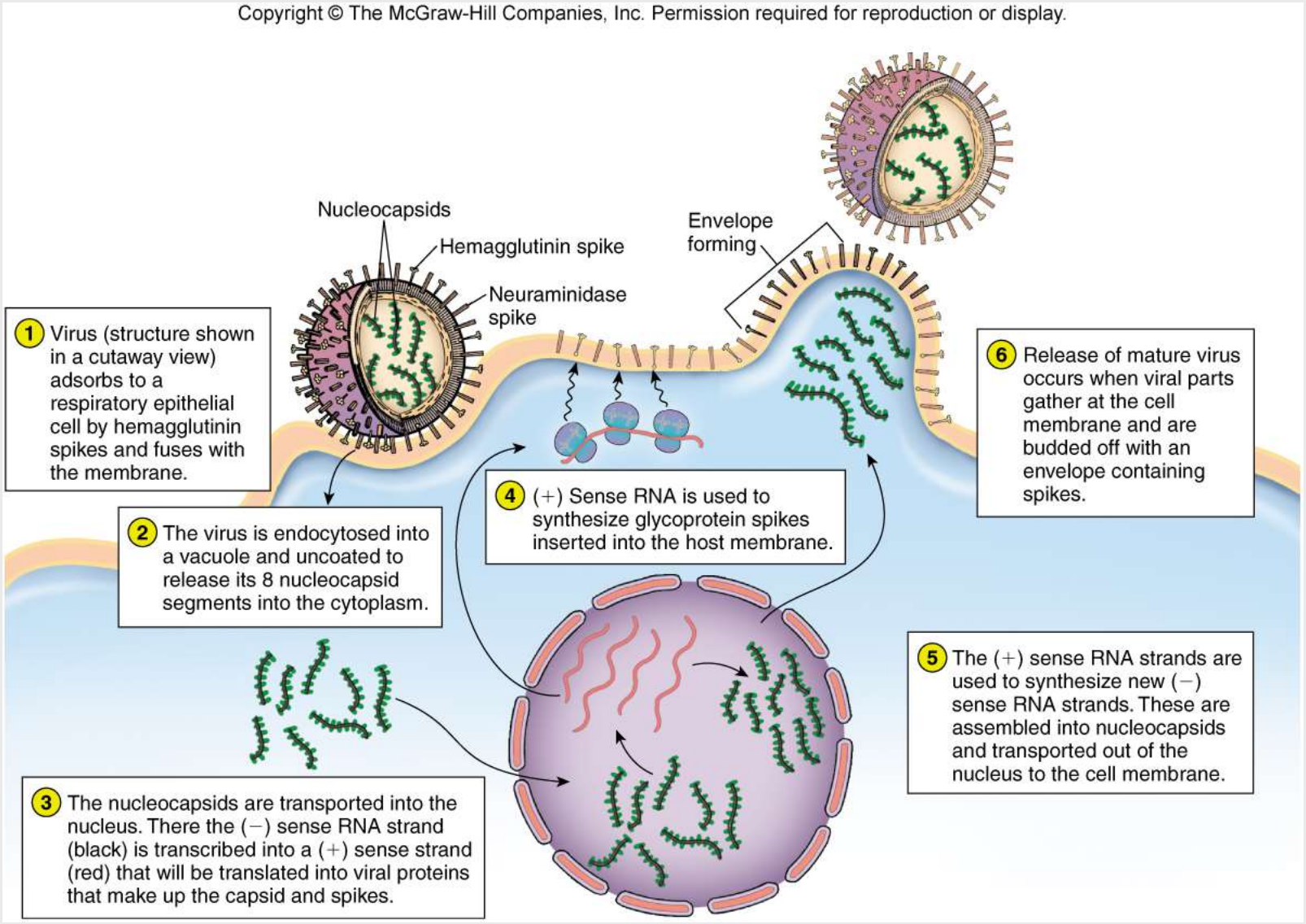


Enveloped Segmented Single-Stranded RNA Viruses

The Biology of Orthomyxoviruses: Influenza

- 3 distinct influenza virus types: A, B, C; Type A causes most infections
- Viral infection
  - Virus attaches to, and multiplies in, the cells of the respiratory tract
  - Segments of RNA genome enter the nucleus (transcribed/translated)
  - Finished viruses are assembled and budded off the cell with an envelope

Influenza virus cycle



- Key to influenza are glycoprotein spikes –
  - **Hemagglutinin** (H) – 15 different subtypes; most important virulence factor; binds to host cells
  - **Neuraminidase** (N) – 9 subtypes – hydrolyzes mucus and assists viral budding and release

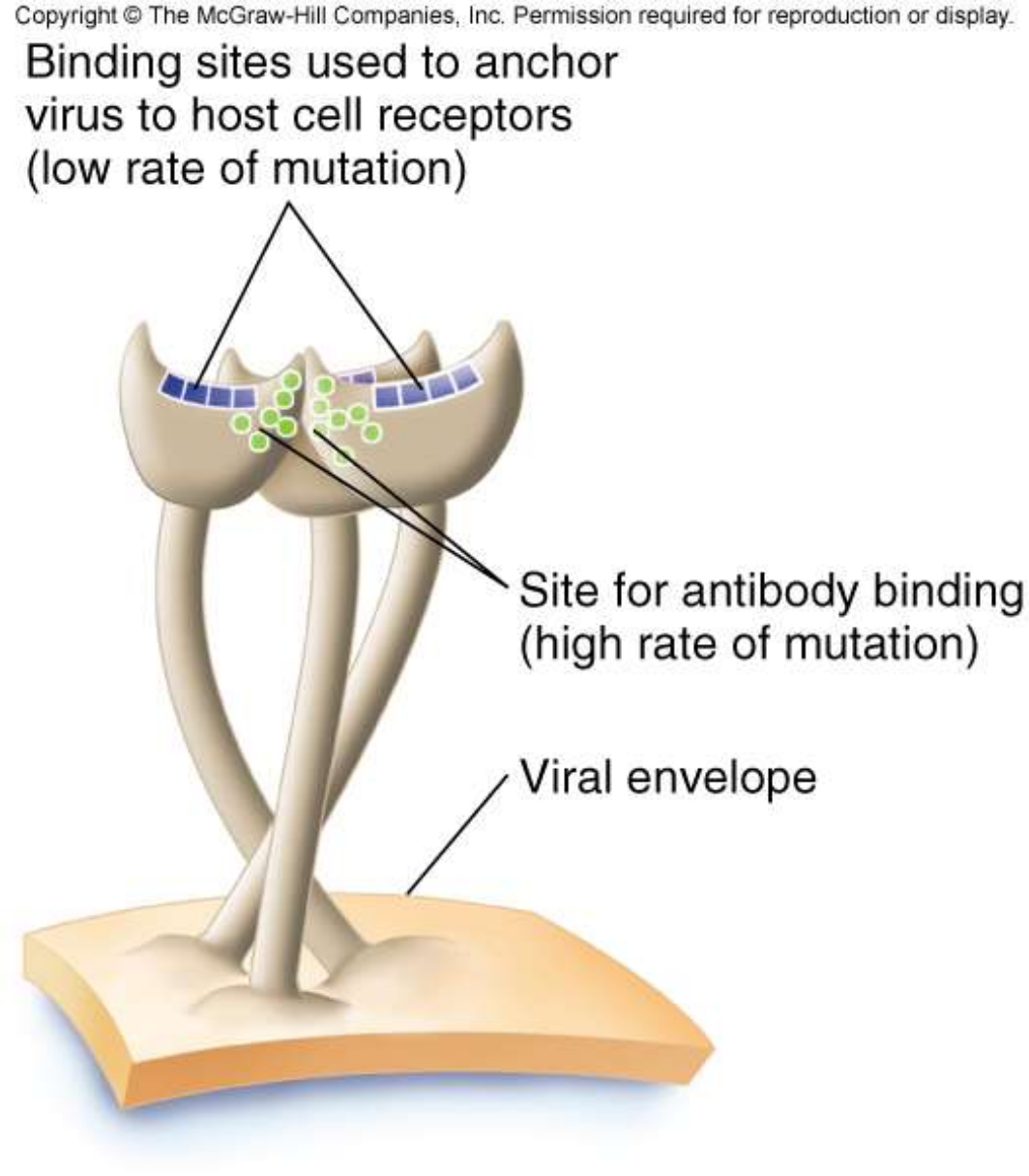
TABLE 25.2 Human Influenza Virus Types and Variant Forms

Type	H/N Subtype	Strain/History
A	H1N1	Spanish flu pandemic of 1918
		A/New Jersey/76* (swine flu outbreak)
		A/USSR/90/77
		A/Texas/36/91
	H2N2	A/Singapore/57 (Asian flu pandemic)
		A/Japan/62
		A/Taiwan/64
	H3N2	A/Hong Kong/68 (Hong Kong flu pandemic)
		A/Johannesburg/33/94
B	None	B/Harbin/07/94
C	None	C/JHB/2/66

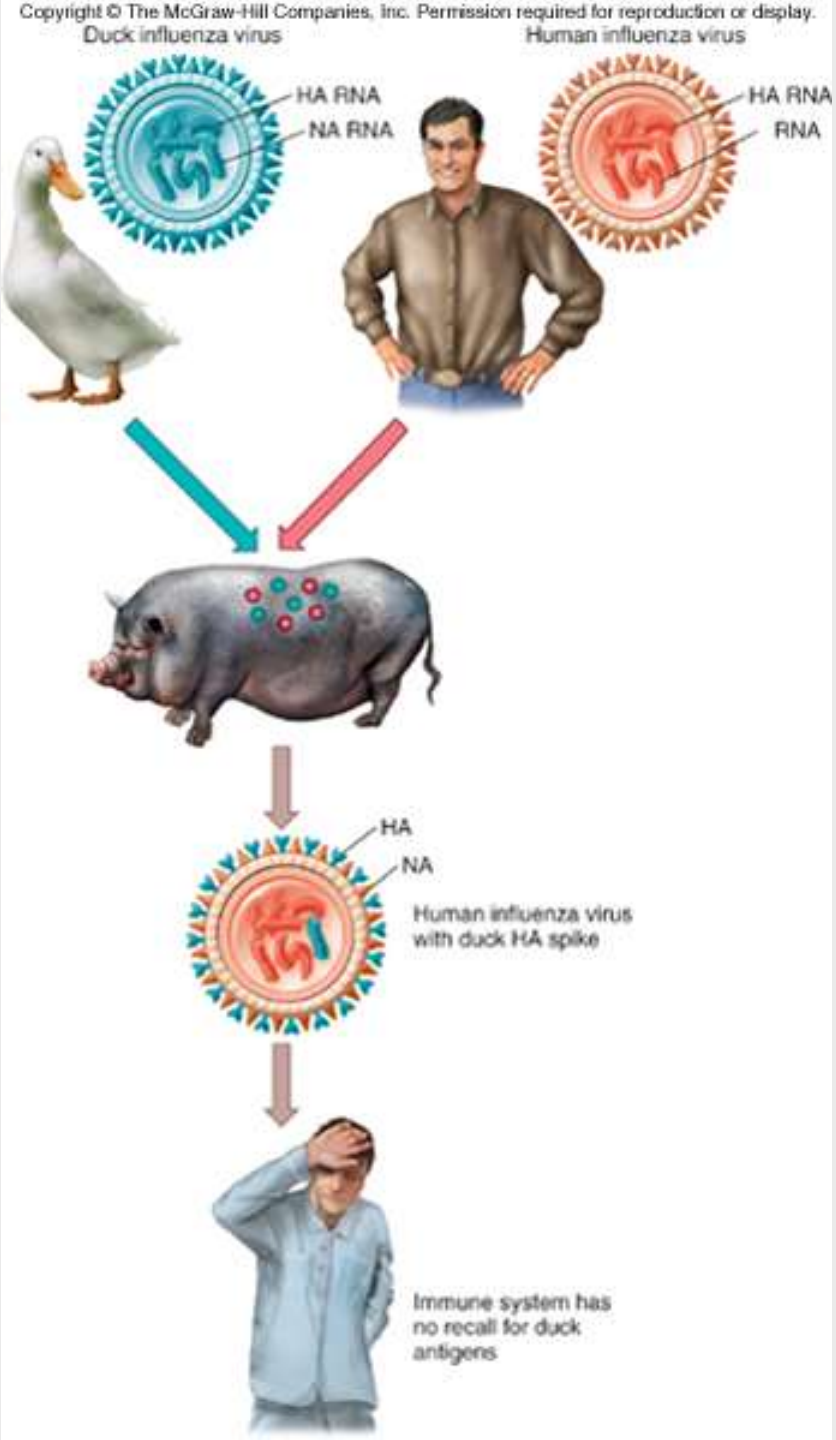
*The last number is the year the virus appeared.

- Both glycoproteins frequently undergo genetic changes decreasing the effectiveness of the host immune response
- Constant mutation is called **antigenic drift** – gradually change their amino acid composition
- **Antigenic shift** – one of the genes or RNA strands is substituted with a gene or strand from another influenza virus from a different animal host
  - Genome of virus consists of 10 genes encoded on 8 separate RNA strands

Hemagglutinin (HA)



Antigenic shift event



Influenza B

- Only undergo antigenic drift
- Not known to undergo antigenic shift

Influenza C

- Known to cause only minor respiratory disease; probably not involved in epidemics

Influenza A

- Acute, highly contagious respiratory illness
- Seasonal, pandemics; among top 10 causes of death in U.S. – most commonly among elderly and small children
- Binds to ciliated cells of respiratory mucosa
- Causes rapid shedding of cells, stripping the respiratory epithelium; severe inflammation
- Fever, headache, myalgia, pharyngeal pain, shortness of breath, coughing
- Weakened host defenses predispose patients to secondary bacterial infections, especially pneumonia

Diagnosis, Treatment, Prevention

- Rapid immunofluorescence tests to detect antigens in a pharyngeal specimen; serological testing to screen for antibody titer
- Treatment: control symptoms; amantadine, rimantadine, zanamivir (Relenza), and oseltamivir (Tamiflu)
- Flu virus has developed high rate of resistance to amantadine and rimantadine
- Annual trivalent vaccine recommended

Enveloped Nonsegmented ssRNA Viruses

Paramyxoviruses

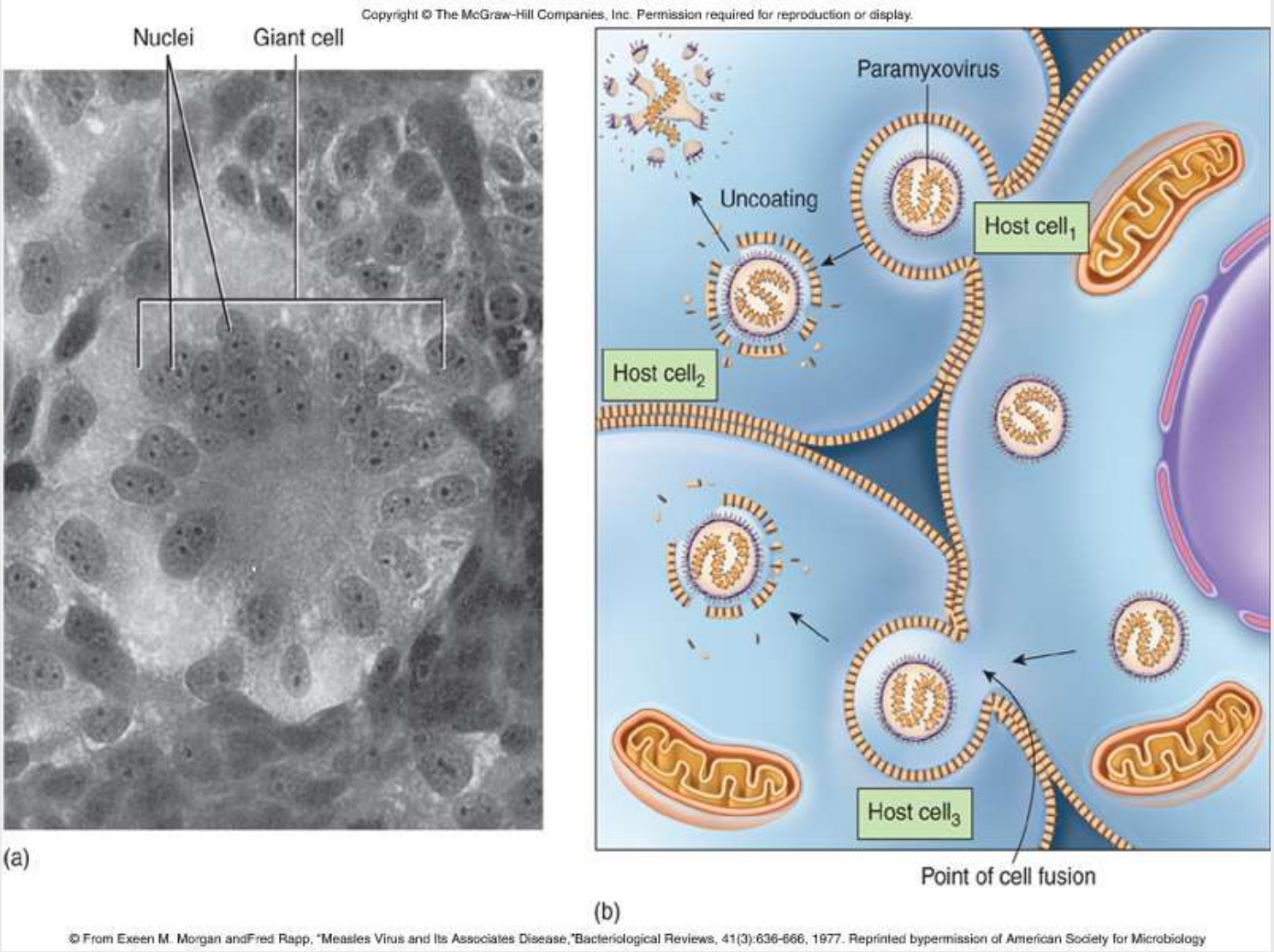
Paramyxoviruses (parainfluenza, mumps virus)

Morbillivirus (measles virus)

Pneumovirus (respiratory syncytia virus)

- Respiratory transmission
- Envelope has glycoprotein and F spikes that initiate cell-to-cell fusion
- Fusion with neighboring cells – syncytium or multinucleate giant cells form

The effects of paramyxoviruses



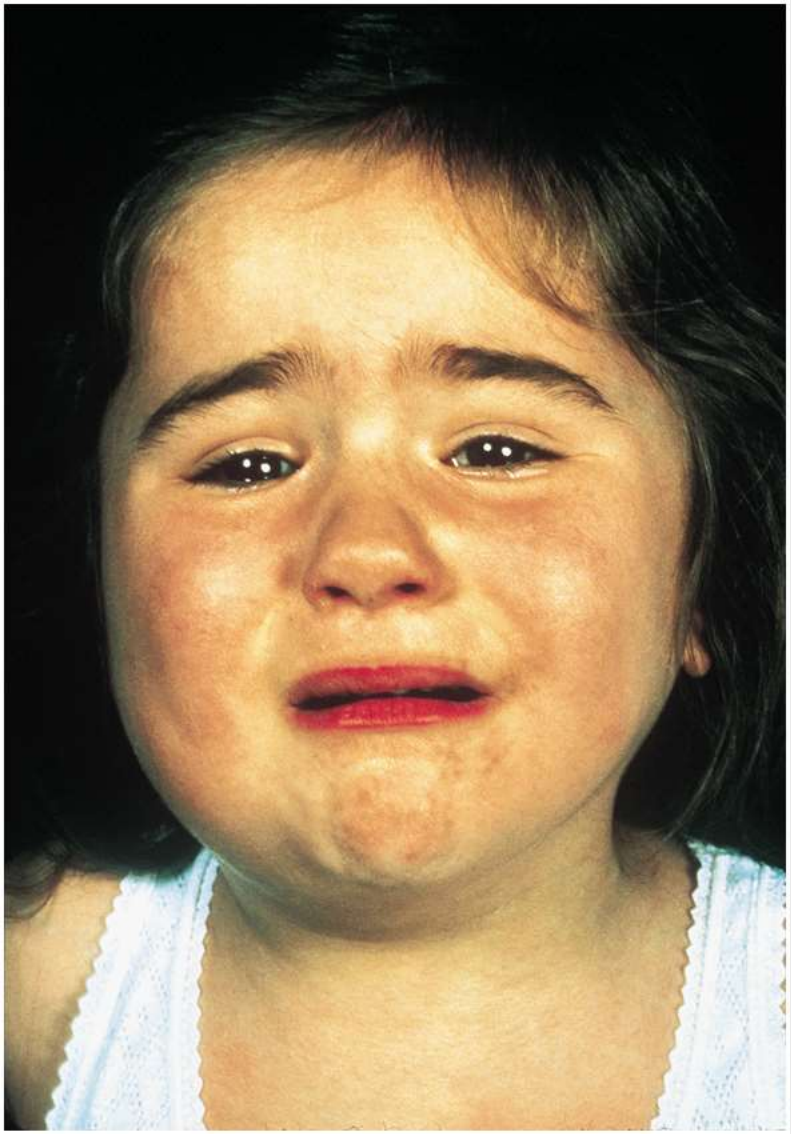
Parainfluenza

- Widespread as influenza but more benign
- Respiratory transmission
- Seen mostly in children
- Minor cold, bronchitis, bronchopneumonia, croup
- No specific treatment available; supportive therapy

Mumps

- Epidemic parotitis; self-limited, associated with painful swelling of parotid salivary glands
- Humans are the only reservoir
- 40% of infections are subclinical; long-term immunity
- 300 cases in U.S./year
- Incubation 2-3 weeks fever, muscle pain and malaise, classic swelling of one or both cheeks
- Usually uncomplicated invasion of other organs; in 20-30% of infected adult males, epididymis and testes become infected; sterility is rare
- Symptomatic treatment
- Live attenuated vaccine MMR

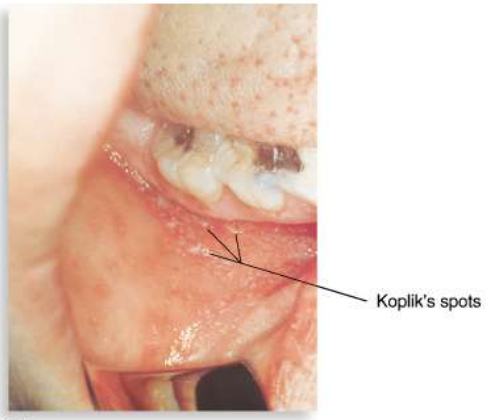
Mumps



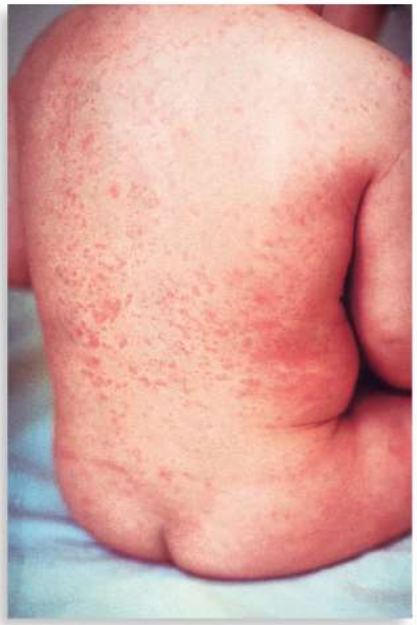
Measles

- Caused by Morbillivirus
- Also known as red measles and rubeola
- Different from German measles
- Very contagious; transmitted by respiratory aerosols
- Humans are the only reservoir
- Less than 100 cases/yr in U.S.; frequent cause of death worldwide
- Virus invades respiratory tract
- Sore throat, dry cough, headache, conjunctivitis, lymphadenitis, fever, Koplik spots – oral lesions
- Exanthem

Signs and symptoms of measles



(a)



(b)

© Centers for Disease Control

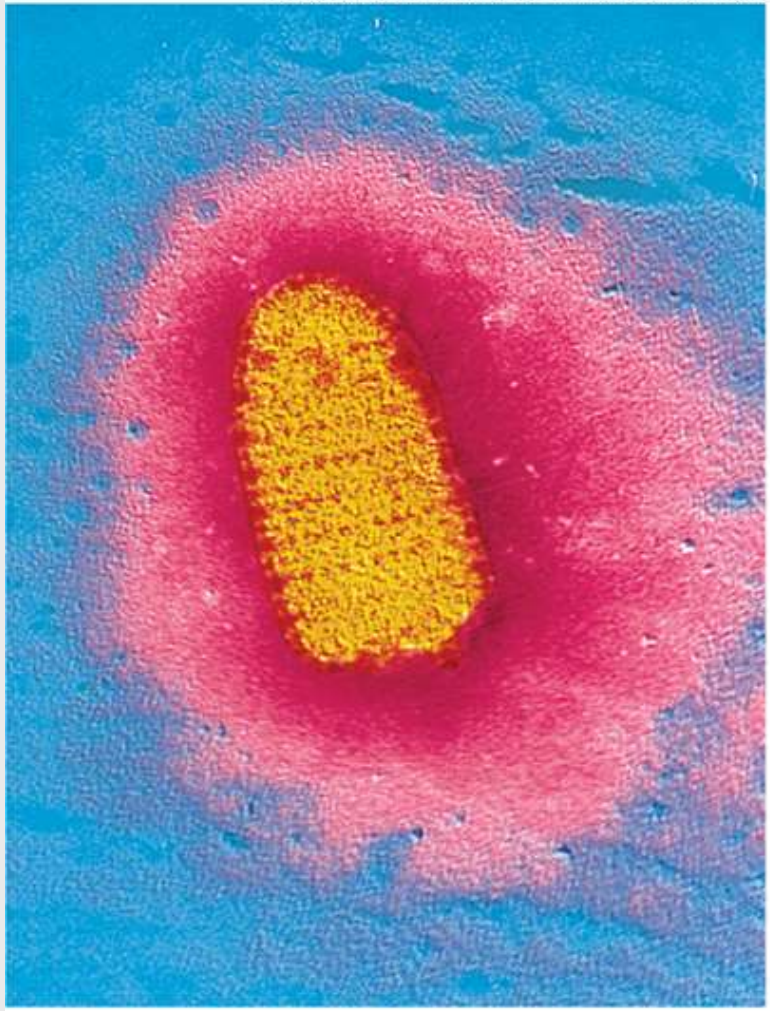
Measles

- Most serious complication is subacute sclerosing panencephalitis (SSPE), a progressive neurological degeneration of the cerebral cortex, white matter, and brain stem
  - 1 case in a million infections
  - Involves a defective virus spreading through the brain by cell fusion and destroys cells
  - Leads to coma and death in months or years
- Attenuated viral vaccine MMR

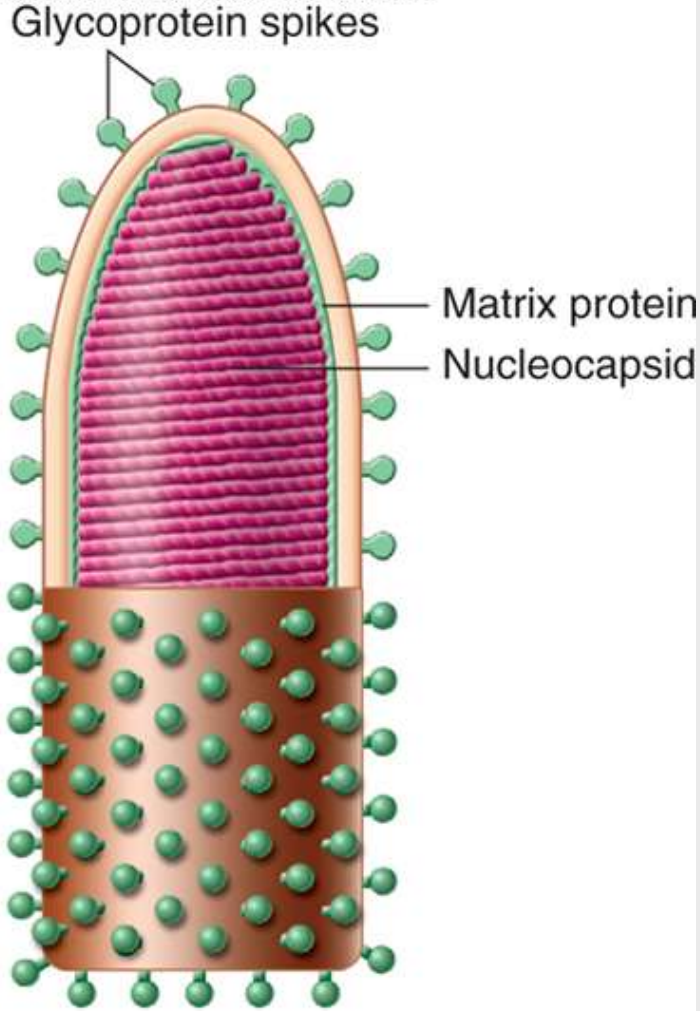
Rabies

- Rhabdovirus family; genus Lyssavirus
- Enveloped, bullet-shaped virions
- Slow, progressive zoonotic disease
- Primary reservoirs are wild mammals; it can be spread by both wild and domestic mammals by bites, scratches, and inhalation of droplets

Structure of the rabies virus

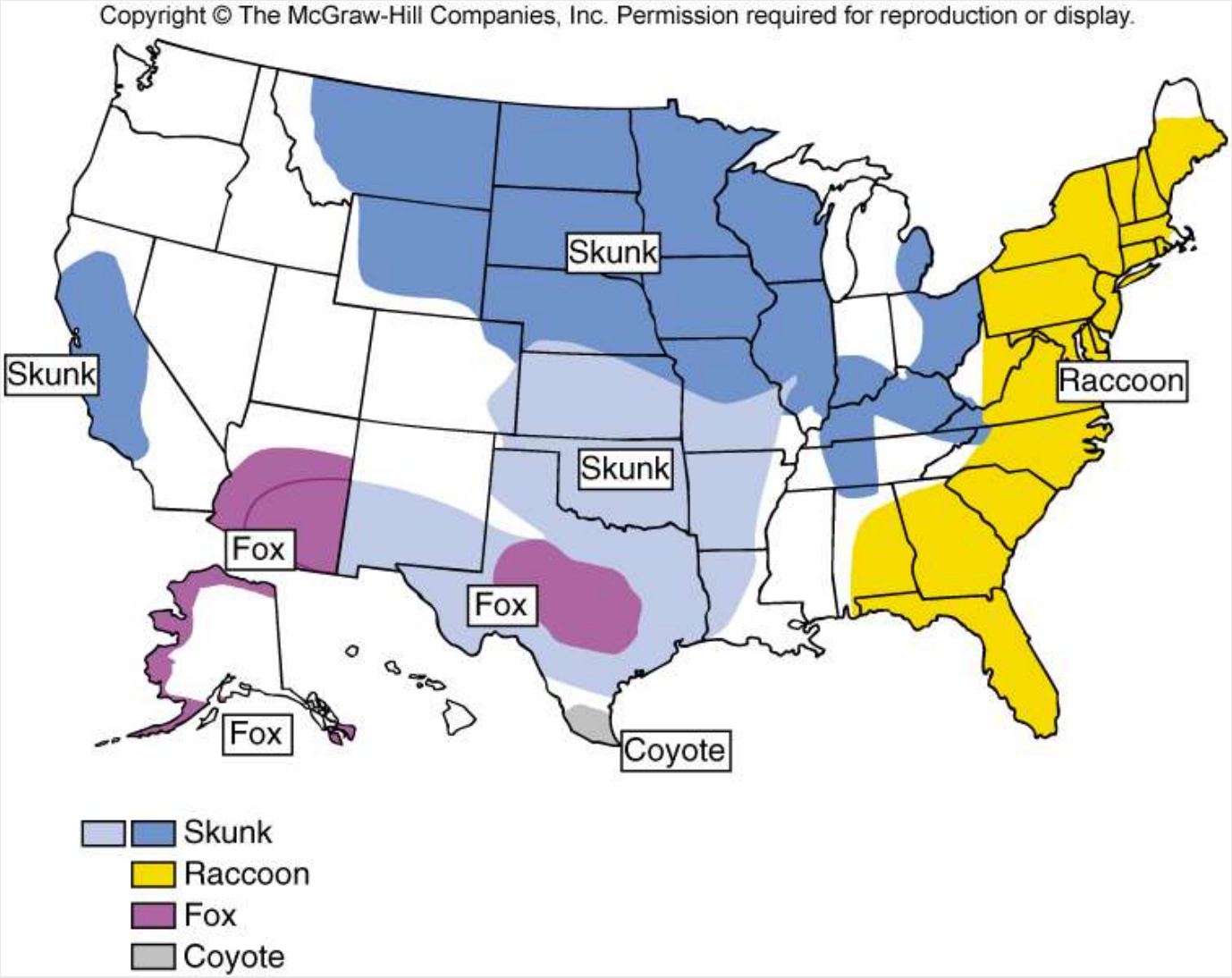


(a)



(b)

Rabies in the United States



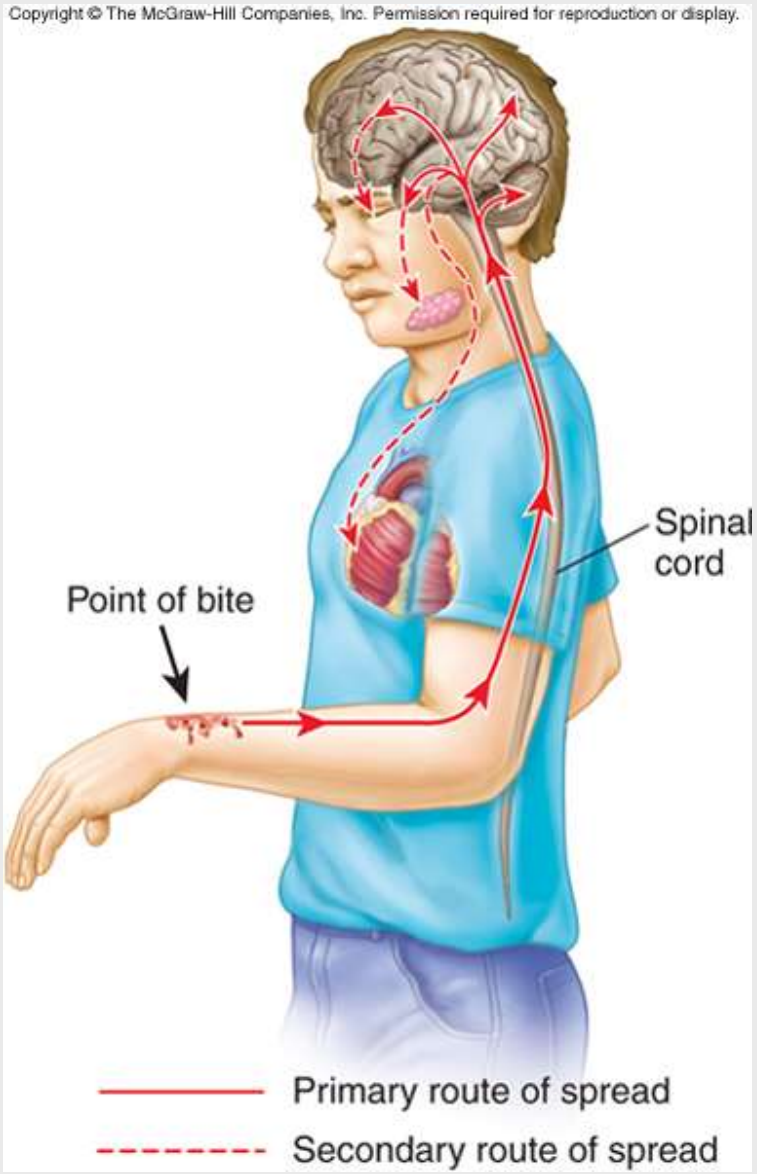
Rabies

- Virus enters through bite, grows at trauma site for a week and multiplies, then enters nerve endings and advances toward the ganglia, spinal cord and brain
- Infection cycle completed when virus replicates in the salivary glands

Clinical phases of rabies:

- Prodromal phase – fever, nausea, vomiting, headache, fatigue; some experience pain, burning, tingling sensations at site of wound
- Furious phase – agitation, disorientation, seizures, twitching, hydrophobia
- Dumb phase – paralyzed, disoriented, stuporous
- Progress to coma phase, resulting in death

Pathologic pictures of rabies



- Often diagnosed at autopsy – intracellular inclusions (Negri bodies) in nervous tissue
- Bite from wild or stray animals demands assessment of the animal, meticulous wound care, and specific treatment
- Preventive therapy initiated if signs of rabies appear
- Treatment – passive and active postexposure immunization
  - Infuse the wound with human rabies immune globulin (HRIG) and globulin; vaccination with human diploid cell vaccine (HDCV), an inactivated vaccine given in 6 doses with 2 boosters
- Control – vaccination of domestic animals, elimination of strays, and strict quarantine practices

Hepatitis C Virus (HCV)

- Flavivirus
- Acquired through blood contact – blood transfusions, needle sharing by drug abusers
- Infections with varying characteristics – 75-85% will remain infected indefinitely; possible to have severe symptoms without permanent liver damage; more common to have chronic liver disease, without overt symptoms
- Cancer may also result from chronic HCV infection
- Treatment with interferon and ribavirin to lessen liver damage; no cure
- No vaccine

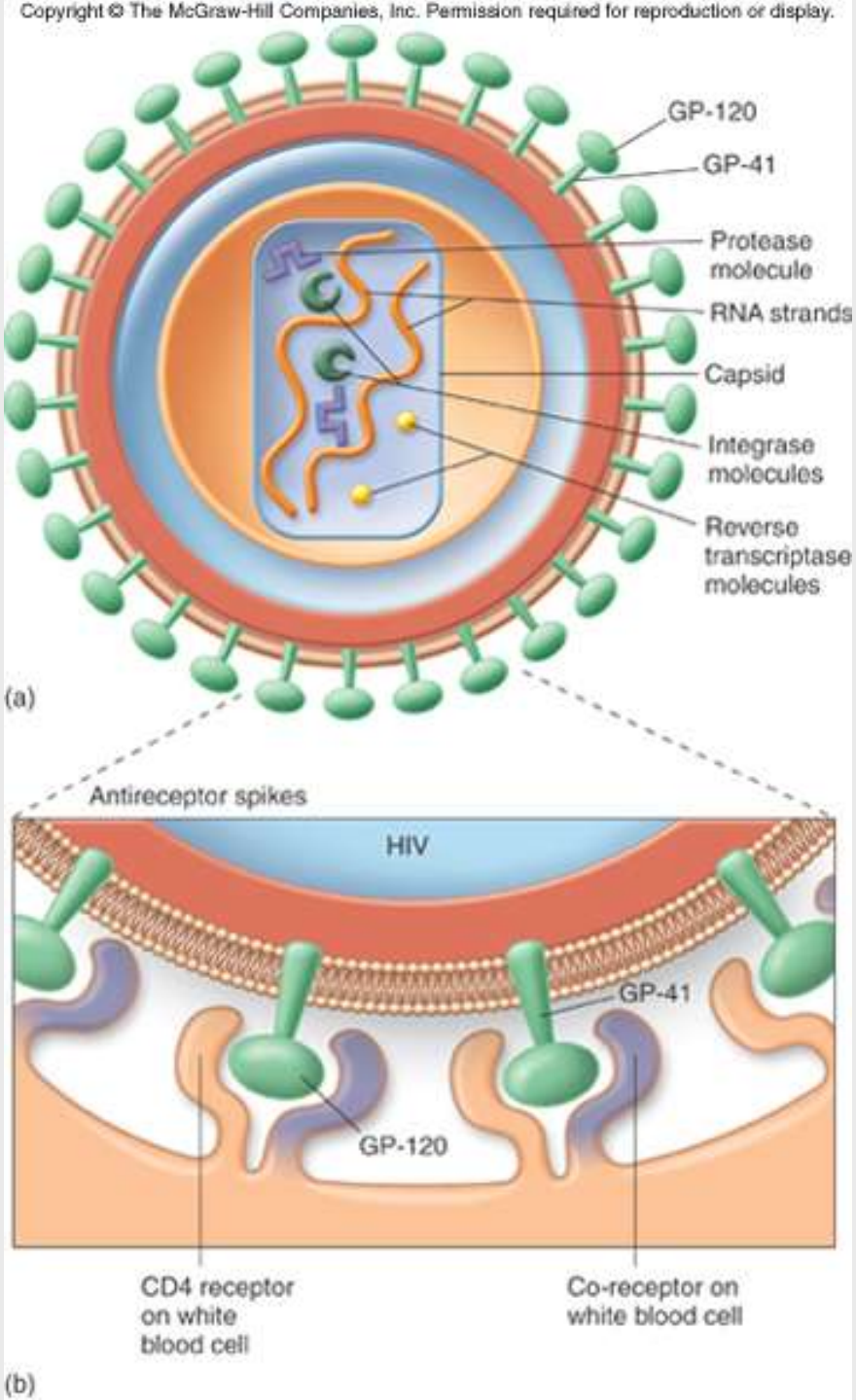
HIV Infections and AIDS

- Human immunodeficiency virus
- Acquired immunodeficiency syndrome
- First emerged in early 1980s
- HIV-1 may have originated from a chimpanzee virus
- 1959 first documented case of AIDS

Causative Agent

- Retrovirus, genus Lentivirus
- Encode reverse transcriptase enzyme which makes a double stranded DNA from the single-stranded RNA genome
- Viral genes permanently integrated into host DNA
- Human Immunodeficiency Virus (HIV) – the cause of Acquired Immunodeficiency Syndrome (AIDS)
- HIV-1 and HIV-2
- T-cell lymphotropic viruses I and II – leukemia and lymphoma
- HIV can only infect host cells that have the required CD4 marker plus a coreceptor

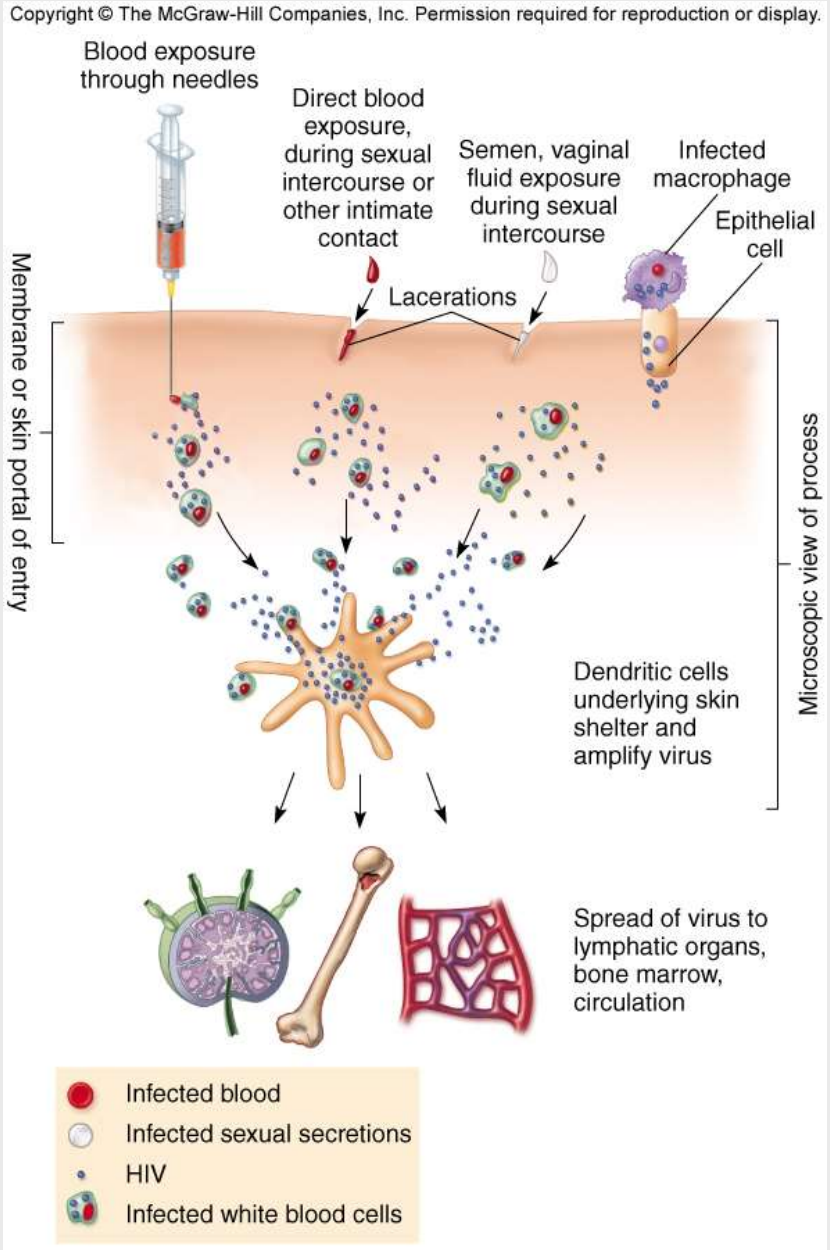
The general structure of HIV



Epidemiology of HIV Infections

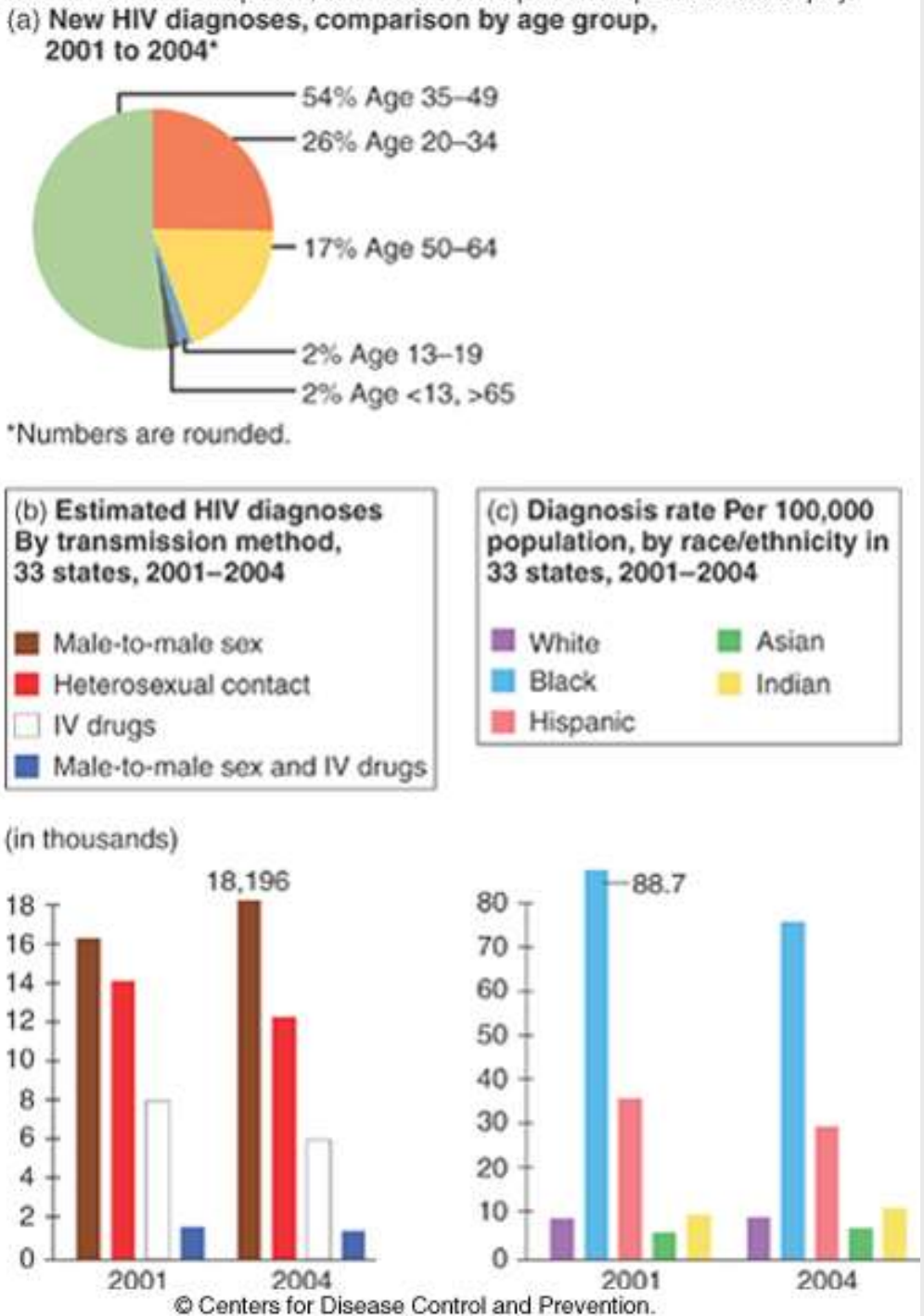
- Transmission occurs by direct and specific routes: mainly through sexual intercourse and transfer of blood or blood products; babies can be infected before or during birth, and from breast feeding
- HIV does not survive long outside of the body

Infection by HIV



- First nationally notifiable in 1984
- 6th most common cause of death among people aged 25-44 years in the U.S.
- Men account for 70% of new infections
- IV drug abusers can be HIV carriers; significant factor in spread to heterosexual population
- In 2006, the number of infected individuals worldwide is estimated to be 33 million with ~1 million in the U.S.

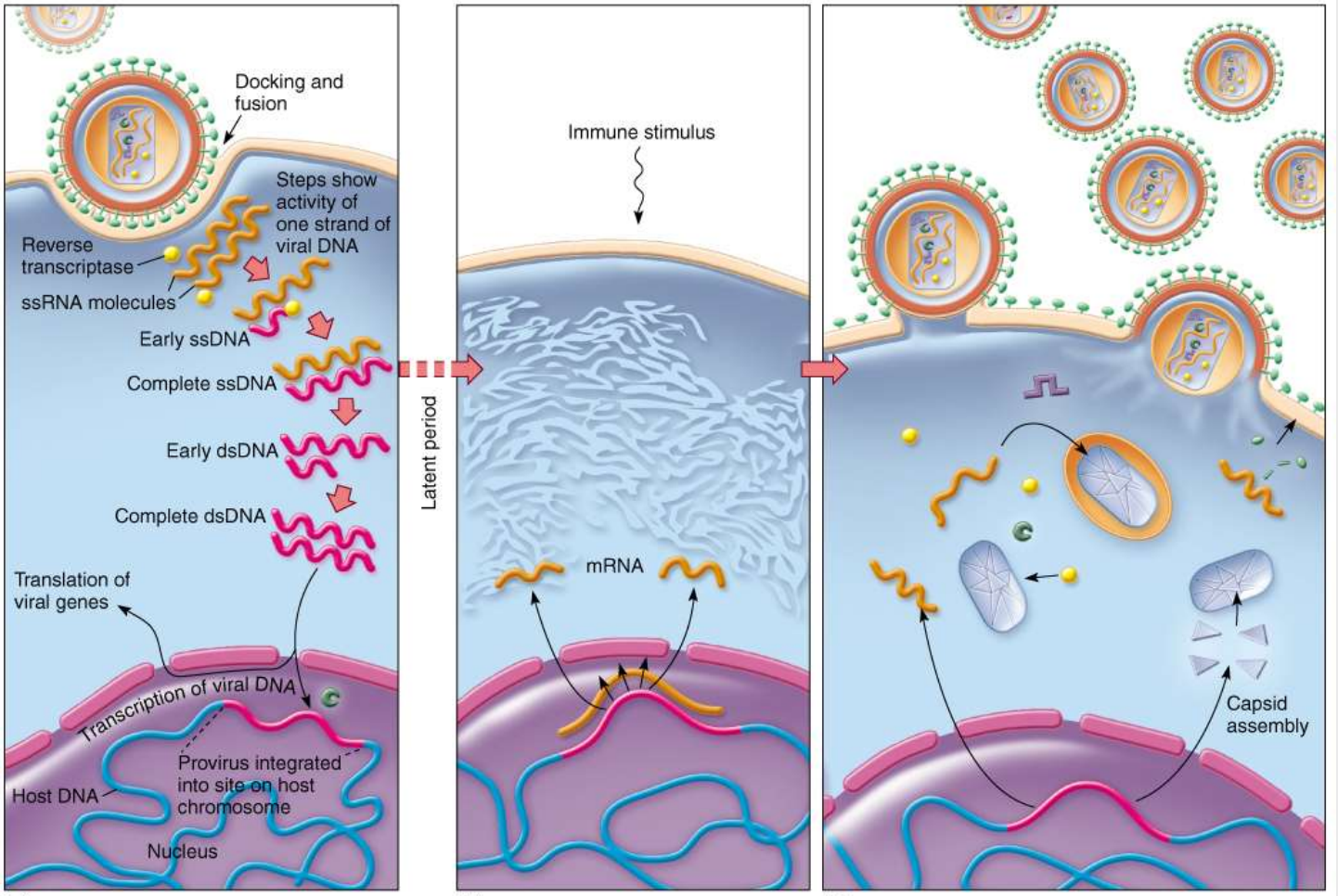
Patterns of HIV infection



Pathogenesis and Virulence Factors of HIV

- HIV enters through mucous membrane or skin and travels to dendritic phagocytes beneath the epithelium, multiplies, and is shed
- Virus is taken up and amplified by macrophages in the skin, lymph organs, bone marrow, and blood
- HIV attaches to CD4 and coreceptor; HIV fuses with cell membrane
- Reverse transcriptase makes a DNA copy of RNA
- Viral DNA is integrated into host chromosome
- Can produce a lytic infection or remain latent

Multiplication cycle of HIV



The virus is adsorbed and fuses with the cell. The twin RNAs are uncoated. Reverse transcriptase catalyzes the synthesis of a single complementary strand of DNA (ssDNA). This single strand serves as a template for synthesis of a double strand (ds) of DNA. In latency, dsDNA is inserted into the host chromosome as a provirus.

After a latent period, various immune activators stimulate the infected cell, causing reactivation of the provirus genes and production of viral mRNA.

HIV mRNA is translated by the cell's synthetic machinery into virus components (capsid, reverse transcriptase, spikes), and the viruses are assembled. Budding of mature viruses lyses the infected cell.

Primary effects of HIV infection:

- Extreme leukopenia – lymphocytes in particular
- Formation of giant T cells and other syncytia allowing the virus to spread directly from cell to cell
- Infected macrophages release the virus in central nervous system, with toxic effect, inflammation

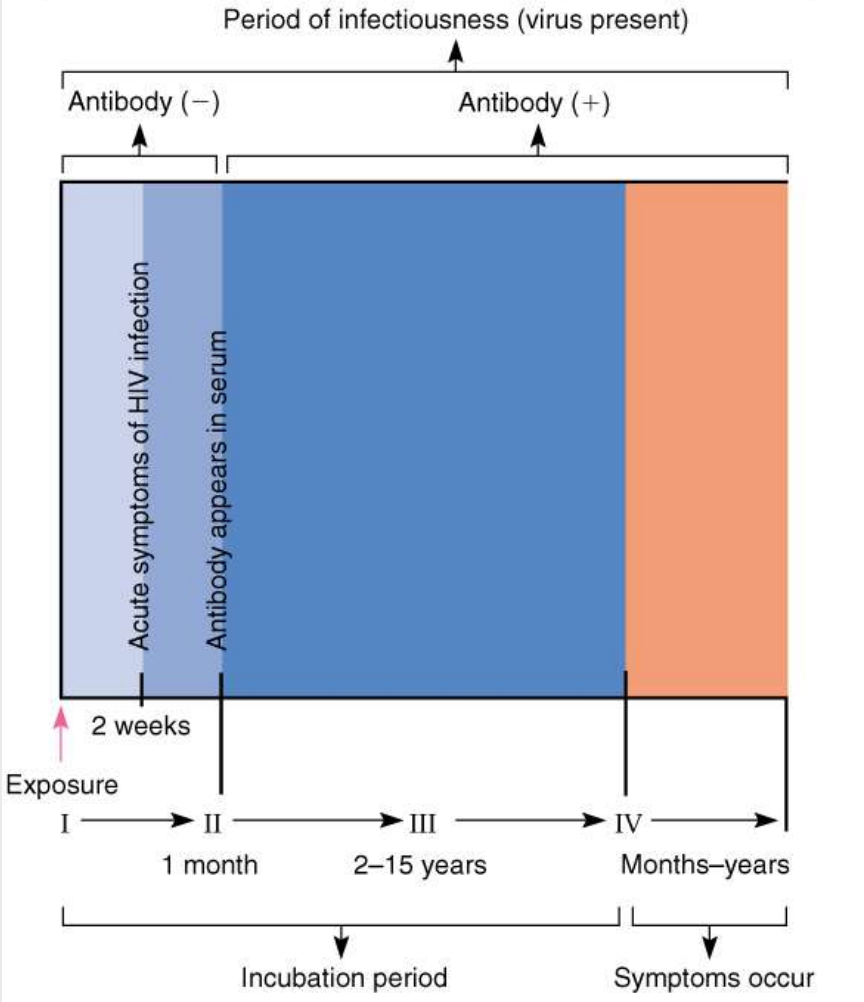
Secondary effects of HIV:

- Destruction on CD4 lymphocytes allows for opportunistic infections and malignancies

Signs and Symptoms of HIV Infections and AIDS

- Symptoms of HIV are directly related to viral blood level and level of T cells
- Initial infection – mononucleosis-like symptoms that soon disappear
- Asymptomatic phase 2-15 years (avg. 10)
- HIV destroys the immune system
- When T4 cell levels fall below 200/μL, AIDS symptoms appear including fever, swollen lymph nodes, diarrhea, weight loss, neurological symptoms, opportunistic infections, and cancers

Timeline in HIV infection



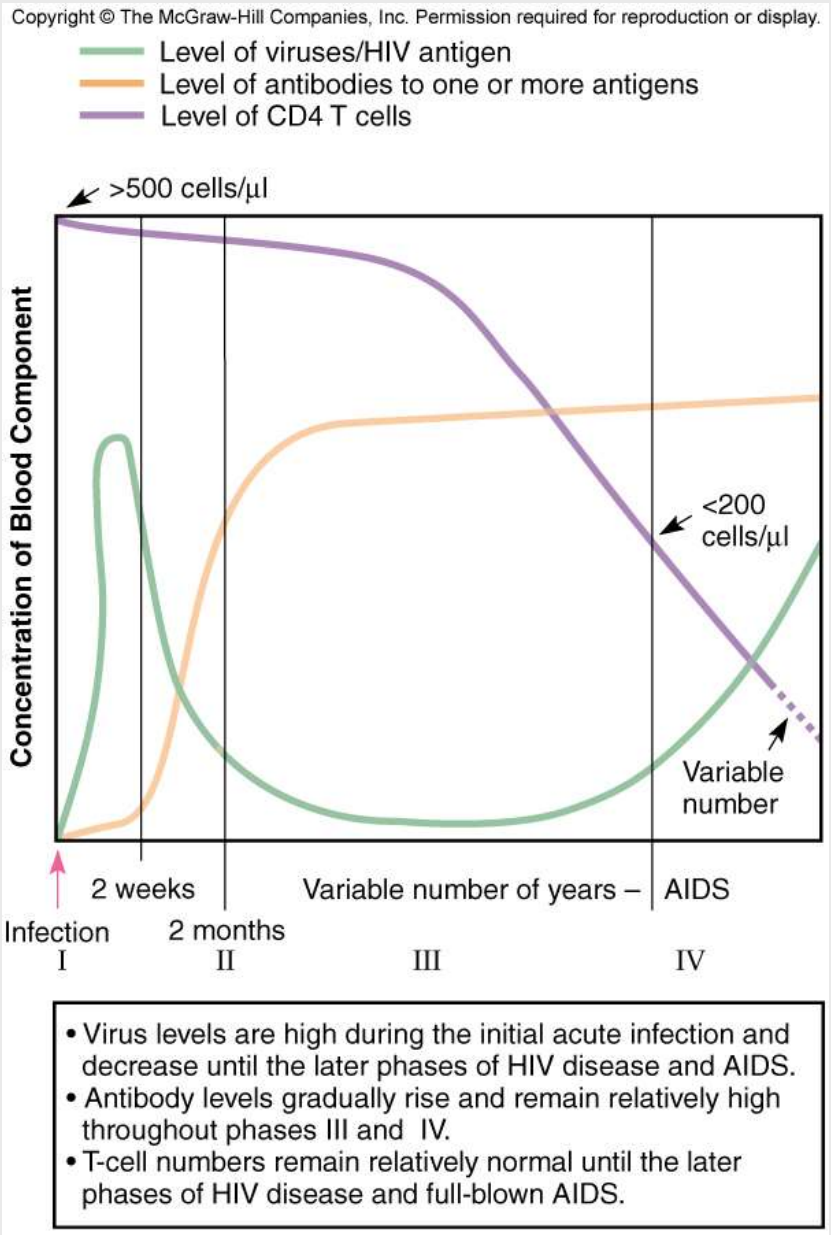
(I) Infection with virus.

(II) Appearance of antibodies in standard HIV tests.

(III) Asymptomatic HIV disease, which can encompass an extensive time period.

(IV) Overt symptoms of AIDS include some combination of opportunistic infections, cancers, and general loss of immune function.

Changes in virus, antibody levels, and T cells



Diagnosis of HIV Infection

- Testing based on detection of antibodies specific to the virus in serum or other fluids; done at 2 levels
- Initial screening
  - ELISA, latex agglutination, and rapid antibody tests
  - Rapid results but may result in false positives
- Follow up with Western blot analysis to rule out false positives
- False negatives can also occur; persons who may have been exposed should be tested a second time 3-6 months later

Diagnosis of AIDS is made when a person meets the criteria:

1. Positive for the virus, and
2. They fulfill one of the additional criteria:
   - They have a CD4 count of fewer than 200 cells/ml of blood
   - Their CD4 cells account for fewer than 14% of all lymphocytes
   - They experience one or more of a CDC-provided list of AIDS-defining illnesses

TABLE 25.A

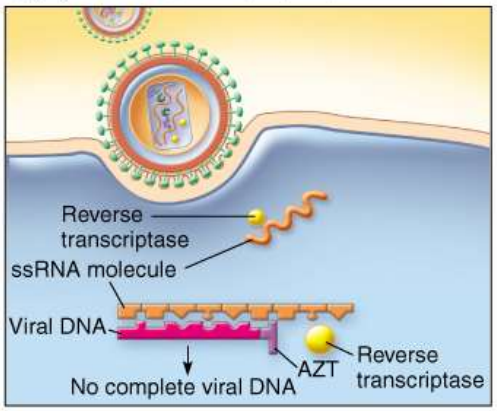
AIDS-Defining Illnesses

Skin and/or Mucous Membranes (includes eyes)	Nervous System	Cardiovascular and Lymphatic System or Multiple Organ Systems	Respiratory Tract	Gastrointestinal Tract	Genitourinary and/or Reproductive Tract
Cytomegalovirus retinitis (with loss of vision) Herpes simplex chronic ulcers (>1 month duration) Kaposi sarcoma	Cryptococcosis, extrapulmonary HIV encephalopathy Lymphoma, primarily in brain Progressive multifocal leukoencephalopathy Toxoplasmosis of the brain	Coccidiomycosis, disseminated or extrapulmonary Cytomegalovirus (other than liver, spleen, nodes) Histoplasmosis, disseminated or extrapulmonary Burkitt lymphoma Immunoblastic lymphoma *Mycobacterium kansasii*, disseminated or extrapulmonary *Mycobacterium tuberculosis*, disseminated or extrapulmonary *Salmonella* septicemia, recurrent Wasting syndrome	Candidiasis of trachea, bronchi, or lungs Herpes simplex bronchitis or pneumonitis *Mycobacterium avium* complex Tuberculosis *(Mycobacterium tuberculosis)* *Pneumocystis (carinii) jiroveci* pneumonia Pneumonia, recurrent in 12-month period	Candidiasis of esophagus, GI tract Herpes simplex chronic ulcers (>1 month duration) or esophagitis Isosporiasis, (diarrhea caused by *Isospora*) chronic intestinal (>1 month duration) Cryptosporidiosis, chronic intestinal (>1 month duration)	Invasive cervical carcinoma Herpes simplex chronic ulcers (>1 month duration)

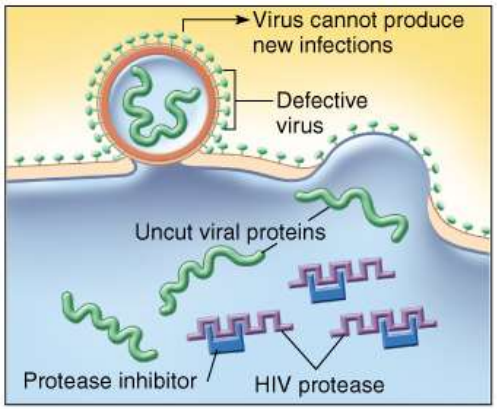
Preventing and Treating HIV

- No vaccine available
  - Monogamous sexual relationships
  - Condoms
  - Universal precautions
- No cure; therapies slow down the progress of the disease or diminish the symptoms
  - Inhibit viral enzymes: reverse transcriptase, protease, integrase
  - Inhibit fusion
  - Inhibit viral integration
  - Highly active anti-retroviral therapy

Mechanisms of action of anti-HIV drugs



(a) **Reverse transcriptase blockers.** A prominent group of drugs (AZT, ddI, 3TC) act as nucleoside analogs to inhibit reverse transcriptase. They are inserted in place of the natural nucleotide by reverse transcriptase but block further action of the enzyme and synthesis of viral DNA.



(b) **Protease inhibitors that cause abnormal viruses to be released.** Protease inhibitors plug into the active sites on HIV protease. This enzyme is necessary to cut elongate HIV protein strands and produce smaller protein units. During budding viruses incorporate this uncut nonfunctioning protein. The resultant viruses are unable to mount an infection.

Nonenveloped Nonsegmented ssRNA Viruses: Picornaviruses and Caliciviruses

- Picornaviruses
  - *Enterovirus* – poliovirus, HAV
  - *Rhinovirus* – rhinovirus
  - *Cardiovirus* – infects heart and brain

Hepatitis A Virus and Infectious Hepatitis

- Cubical picornavirus relatively resistant to heat and acid
- Not carried chronically, principal reservoirs are asymptomatic, short-term carriers or people with clinical disease
- Fecal-oral transmission; multiplies in small intestine and enters the blood and is carried to the liver
- Most infections subclinical or vague, flu-like symptoms occur; jaundice is seldom present

- No specific treatment once the symptoms begin
- Inactivated viral vaccine
- Attenuated viral vaccine
- Pooled immune serum globulin for those entering into endemic areas

Nonenveloped Segmented dsRNA Viruses: Reoviruses

Unusual double-stranded RNA genome

Two best known:

- Rotavirus – oral-fecal transmission; primary viral cause of mortality and morbidity resulting from diarrhea in infants and children
  - Treatment with rehydration and electrolyte replacement
- Reovirus – cold-like upper respiratory infection, enteritis

Prions and Spongiform Encephalopathies

Prions – proteinaceous infectious particles; highly resistant to chemicals, radiation, and heat

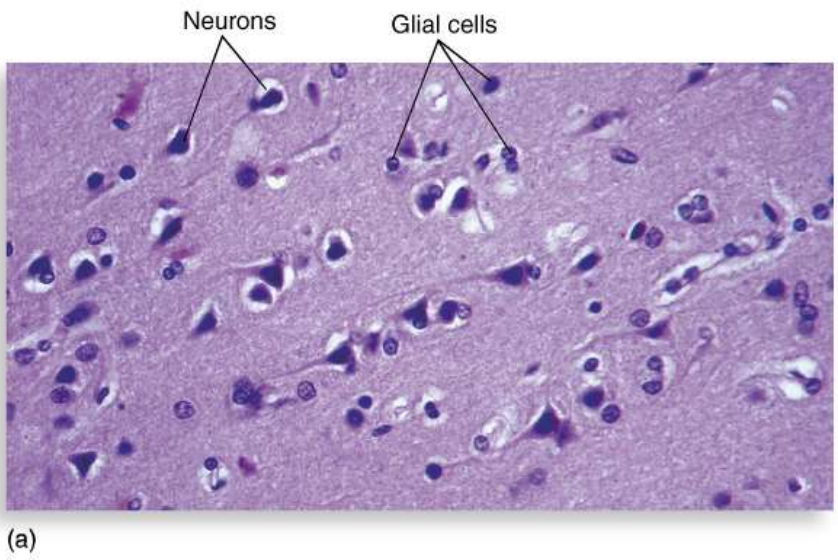
- Cause transmissible spongiform encephalopathies (TSEs) in humans and animals
  - Neurodegenerative diseases with long incubation periods

Human TSE:

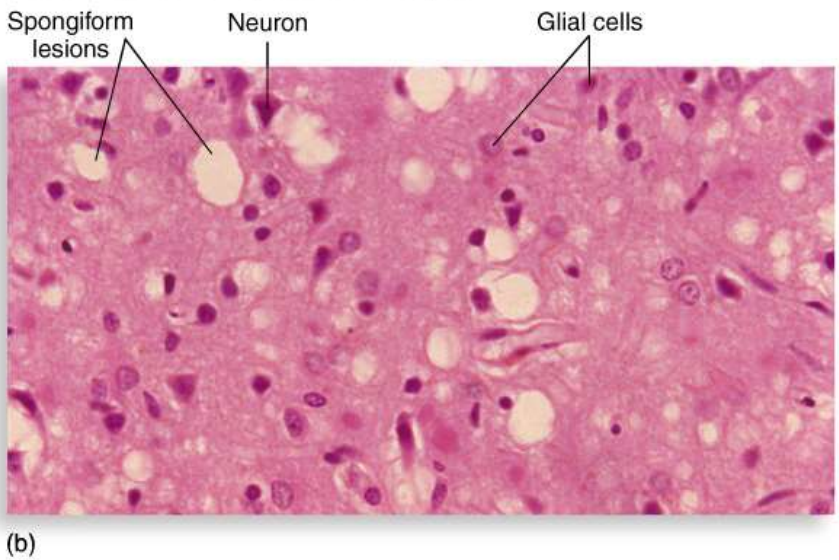
- Creutzfeldt-Jakob Disease (CJD) – alteration in the structure of normal PrP protein found in the brain
  - Abnormal PrP converts normal PrP into abnormal form
- Abnormal PrP results in nerve cell death, spongiform damage, and severe loss of brain function
- Transmission is through direct or indirect contact with infected brain tissue or CSF

- Variant CJD became apparent in the late 1990s after eating meat from cattle afflicted with bovine spongiform encephalopathy
- Difficult to diagnose; requires examination of biopsied brain or nervous tissue
- Prevention relies on avoidance of contaminated tissue
- Treatment focuses on easing symptoms

The microscopic effects of spongiform encephalopathy



(a)



(b)

One step growth curve to study viral replication:

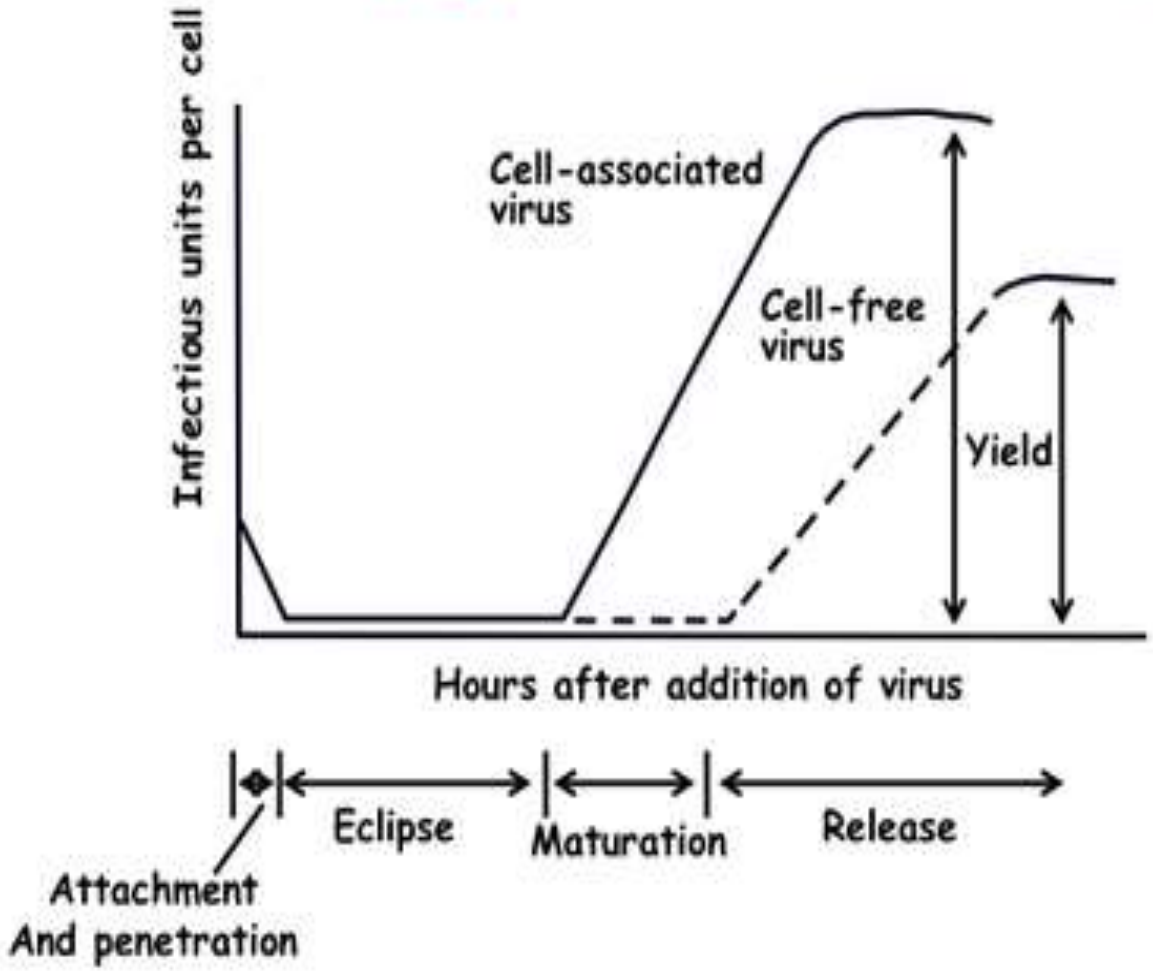
1. Adsorption of virus (initial phase).

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.

One-step growth curve-VIRUSES



Virus latency (or **viral latency**): is the ability of a pathogenic virus to lie dormant (latent) within a cell, denoted as the lysogenic part of the viral life cycle.

- A latent viral infection is a type of persistent viral infection which is distinguished from a chronic viral infection.
- Latency is the phase in certain viruses' life cycles in which, after initial infection, proliferation of virus particles ceases. However, the viral genome is not fully eradicated.
- The result of this is that the virus can reactivate and begin producing large amounts of viral progeny without the host being infected by new outside virus, denoted as the lytic part of the viral life cycle, and stays within the host indefinitely.
- Virus latency is not to be confused with clinical latency during the incubation period when a virus is *not* dormant.

Replication of the genetic material:

DNA viruses

❖The genome replication of most DNA viruses takes place in the cell's nucleus. If the cell has the appropriate receptor on its surface, these viruses enter the cell sometimes by direct fusion with the cell membrane (e.g., herpesviruses) or – more usually – by receptor-mediated endocytosis.

❖Most DNA viruses are entirely dependent on the host cell's DNA and RNA synthesizing machinery, and RNA processing machinery; however, viruses with larger genomes may encode much of this machinery themselves.

❖In eukaryotes the viral genome must cross the cell's nuclear membrane to access this machinery, while in bacteria it need only enter the cell.

RNA viruses

- Replication usually takes place in the cytoplasm.
- RNA viruses can be placed into four different groups depending on their modes of replication.
- The polarity (whether or not it can be used directly by ribosomes to make proteins) of single-stranded RNA viruses largely determines the replicative mechanism; the other major criterion is whether the genetic material is single-stranded or double-stranded.
- All RNA viruses use their own RNA replicase enzymes to create copies of their genomes

Reverse transcribing viruses

❖These have ssRNA (*Retroviridae*, *Metaviridae*, *Pseudoviridae*) or dsDNA (*Hepadnaviridae*) in their particles.

❖Reverse transcribing viruses with RNA genomes (retroviruses), use a DNA intermediate to replicate, whereas those with DNA genomes (pararetroviruses) use an RNA intermediate during genome replication.

❖Both types use a reverse transcriptase, or RNA-dependent DNA polymerase enzyme (**is an enzyme used to generate complementary DNA (cDNA) from an RNA template, a process termed *reverse transcription***), to carry out the nucleic acid conversion.

❖Retroviruses integrate the DNA produced by reverse transcription into the host genome as a provirus as a part of the replication process

- pararetroviruses do not, although integrated genome copies of especially plant pararetroviruses can give rise to infectious virus.
- They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine and lamivudine.
- An example of the first type is HIV, which is a retrovirus. Examples of the second type are the *Hepadnaviridae*, which includes Hepatitis B virus.

Classification of Viruses

Levels of taxonomy

Taxonomic level	Suffix (comment)	Example
Order	-virales (a group of related families)	*Mononegavirales*
Family	-viridae	*Paramyxoviridae*
Subfamily	-virinae	*Paramyxovirinae*
Genus	-virus	*Morbillivirus*
Species	(an individual virus)	*Measles virus*

CLASSIFICATION OF VIRUSES
-------basis of classification

- Virion morphology
- Physicochemical properties of the virion
- Virus genome properties
- Virus protein proteries
- Genome organization and replication
- Antigenic properties
- Biologic properties

CLASSIFICATION OF VIRUSES

- By 1995

  --71 families, 11 subfamilies

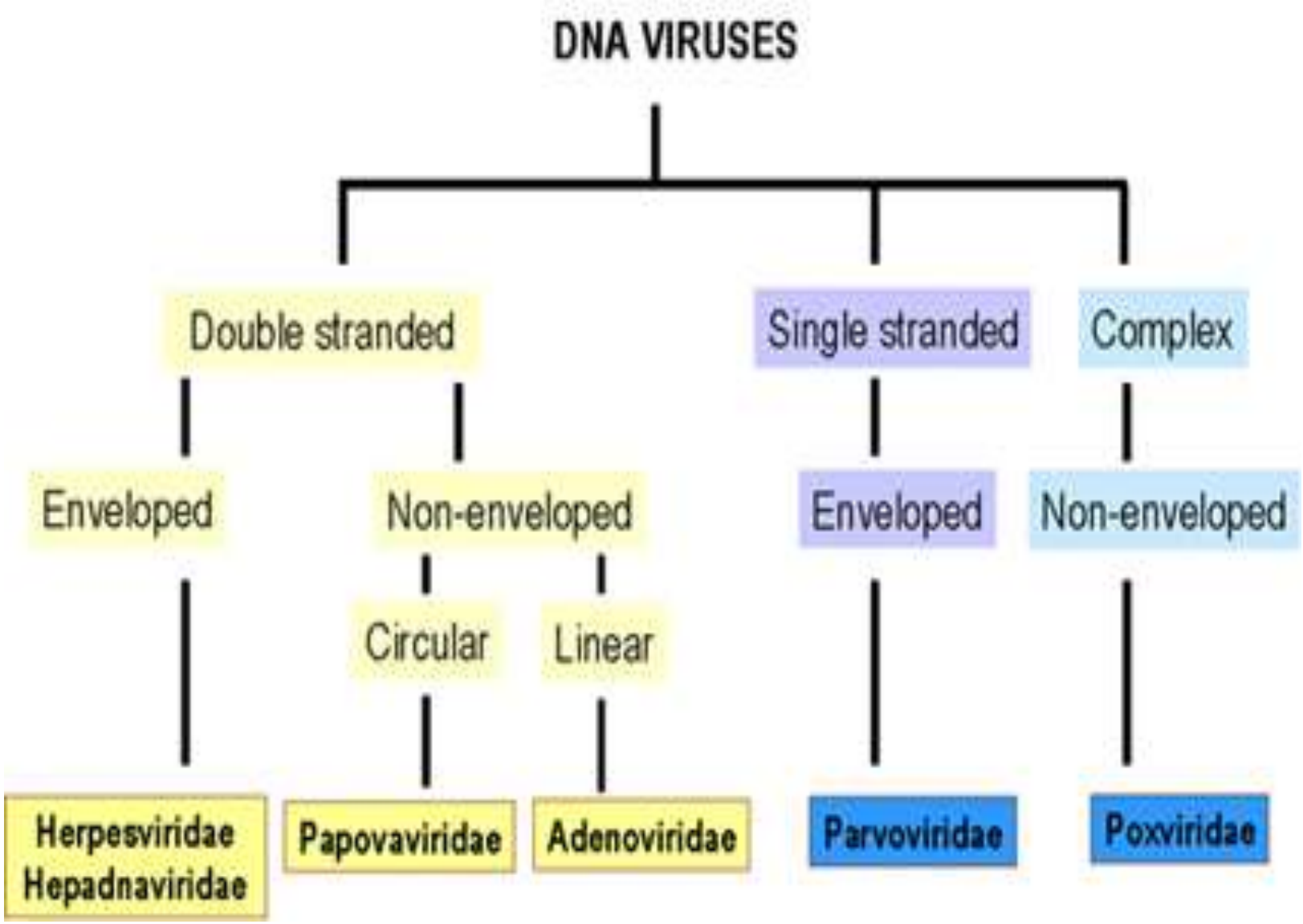
  --164 genera
- For humans and animals

  --24 families,

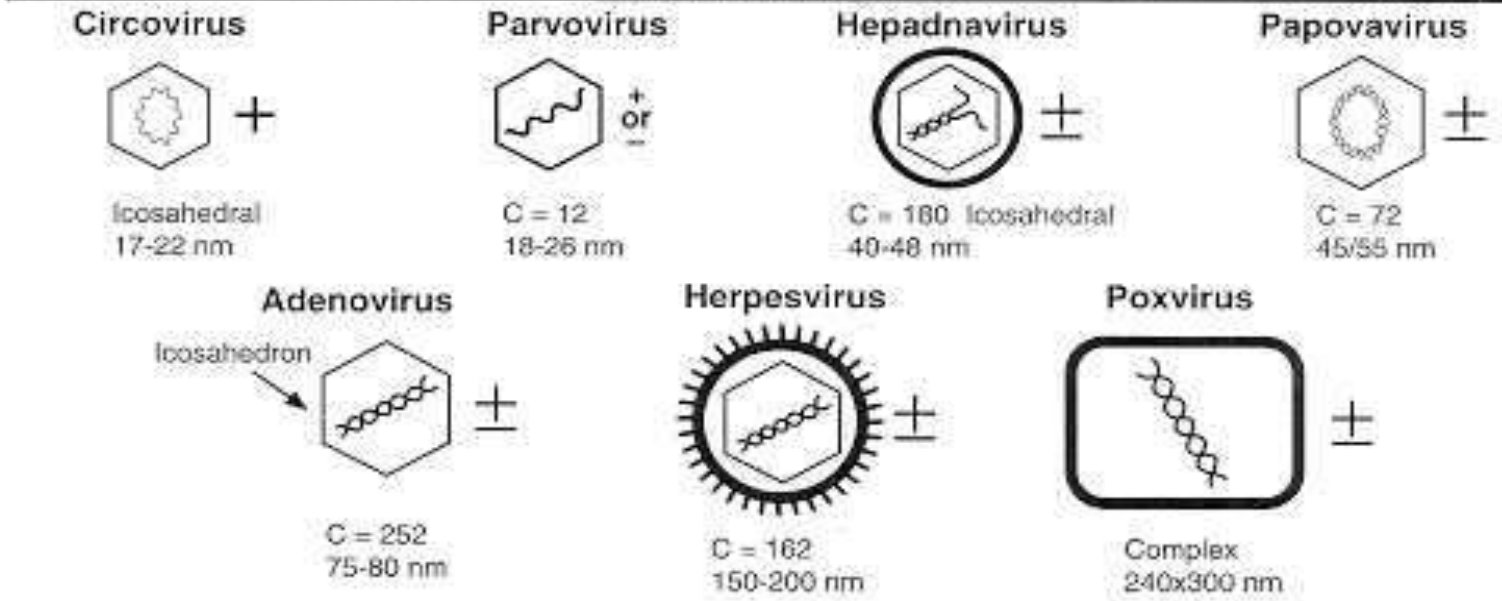
  --DNA: 7; RNA: 17 for humans

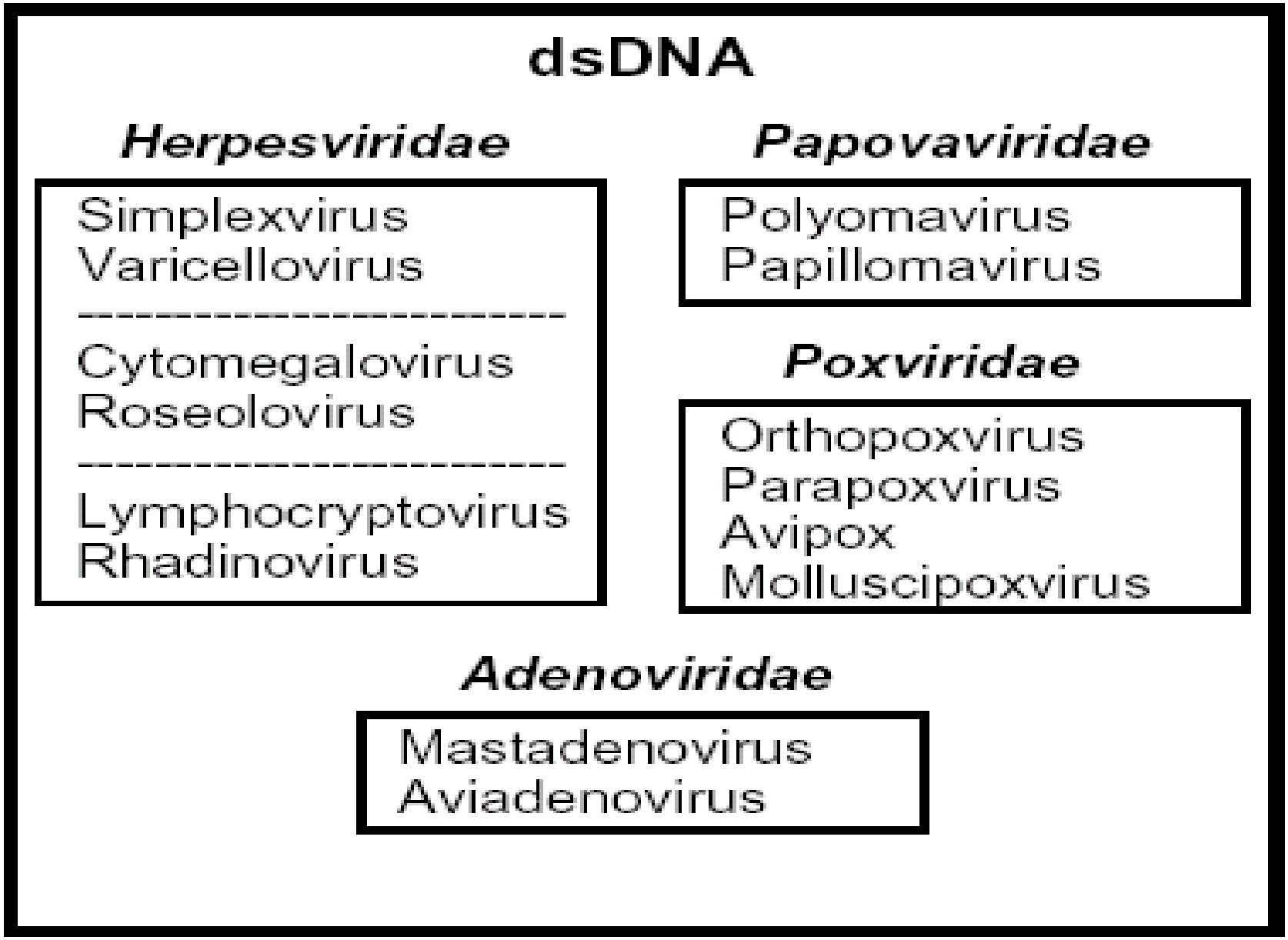
Survey of DNA-containing Viruses

- Parvoviruses: human parvovirus B_{19}
- Papovaviruses: papillomaviruses
- Adenoviruses: 47 types infect humans
- Herpesviruses: human herpesvirus 1-8
- Poxviruses: smallpox; vaccinia
- Hepadnaviruses: HBV


DNA VIRUSES
Double stranded
Single stranded
Complex
Enveloped
Non-enveloped
Enveloped
Non-enveloped
Circular
Linear
Herpesviridae
Hepadnaviridae
Papovaviridae
Adenoviridae
Parvoviridae
Poxviridae

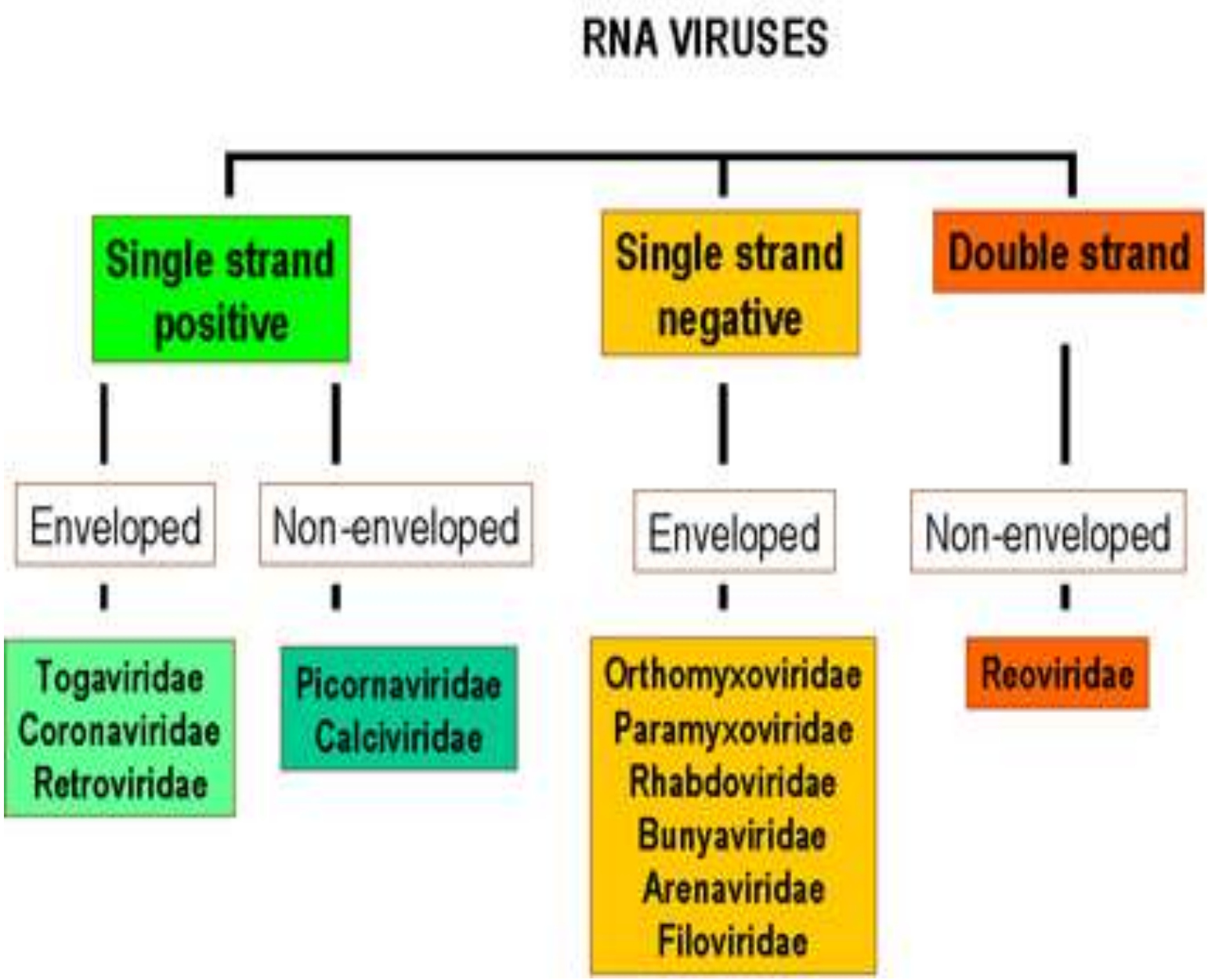
DNA Viruses


Circovirus
+
Icosahedral
17-22 nm
Parvovirus
+
or
−
C = 12
18-26 nm
Hepadnavirus
±
C = 160 Icosahedral
40-48 nm
Papovavirus
±
C = 72
45/55 nm
Adenovirus
Icosahedron
±
C = 252
75-80 nm
Herpesvirus
±
C = 162
150-200 nm
Poxvirus
±
Complex
240x300 nm


dsDNA
Herpesviridae
Simplexvirus
Varicellovirus
Cytomegalovirus
Roseolovirus
Lymphocryptovirus
Rhadinovirus
Papovaviridae
Polyomavirus
Papillomavirus
Poxviridae
Orthopoxvirus
Parapoxvirus
Avipox
Molluscipoxvirus
Adenoviridae
Mastadenovirus
Aviadenovirus

Survey of RNA-containing Viruses

- Picornaviruses
- Astroviruses
- Caliciviruses
- Reoviruses
- Arboviruses
- Togaviruses
- Flaviviruses
- Arenaviruses
- Coronaviruses: SARS
- Retroviruses
- Bunyaviruses
- Othomyxoviruses
- Paramyxoviruses:
- Rhabdoviruses:rabies virus
- Bornaviruses: BDV
- Filoviruses
- Other viruses
- Viroids


RNA VIRUSES
Single strand positive
Single strand negative
Double strand
Enveloped
Non-enveloped
Enveloped
Non-enveloped
Togaviridae
Coronaviridae
Retroviridae
Picornaviridae
Calciviridae
Orthomyxoviridae
Paramyxoviridae
Rhabdoviridae
Bunyaviridae
Arenaviridae
Filoviridae
Reoviridae

ssDNA

Parvoviridae

- Parvovirus
- Erythrovirus
- Dependovirus

Circoviridae

- Circovirus*

**: TT virus*

Reverse Transcribing

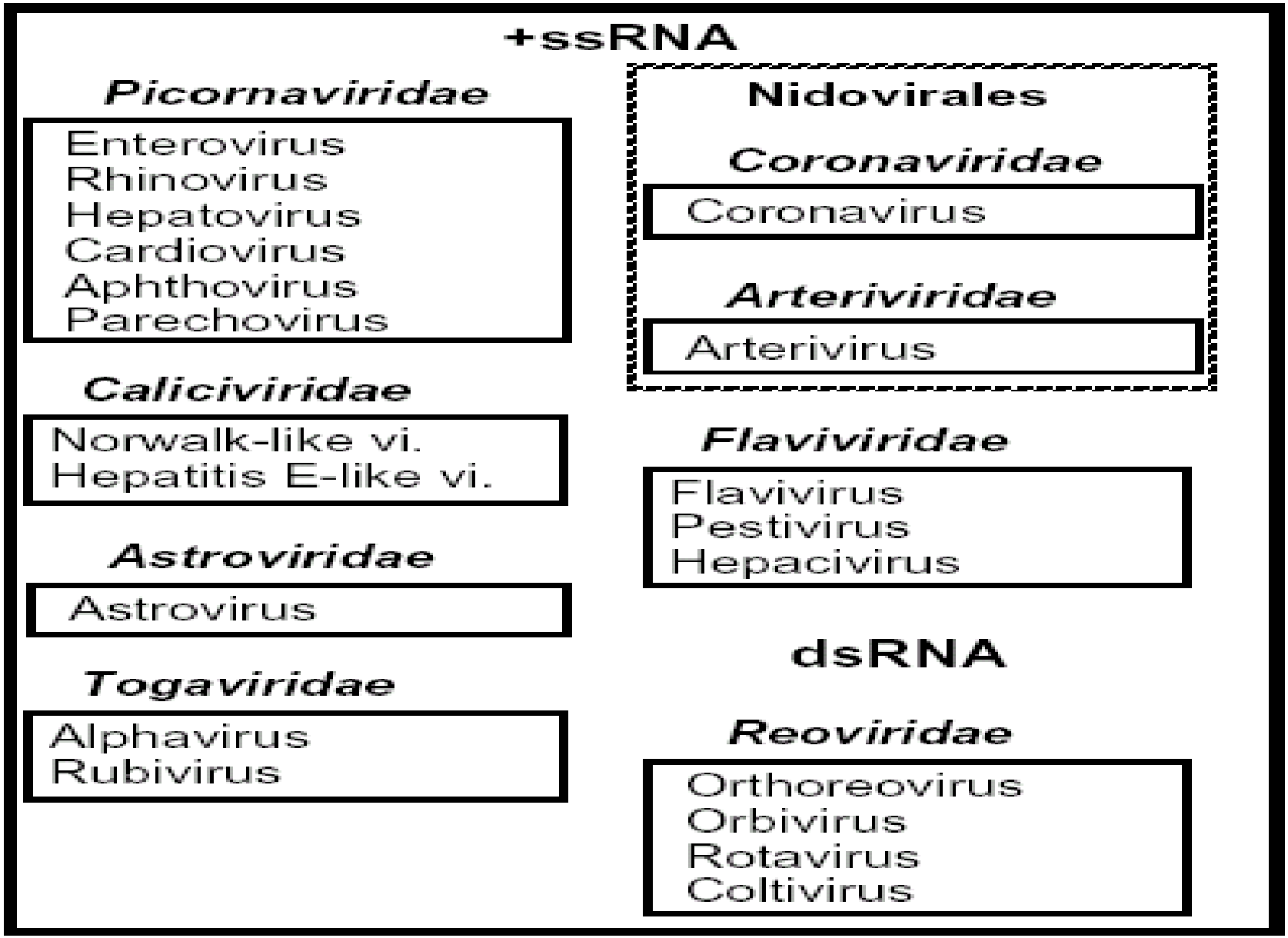
Retroviridae

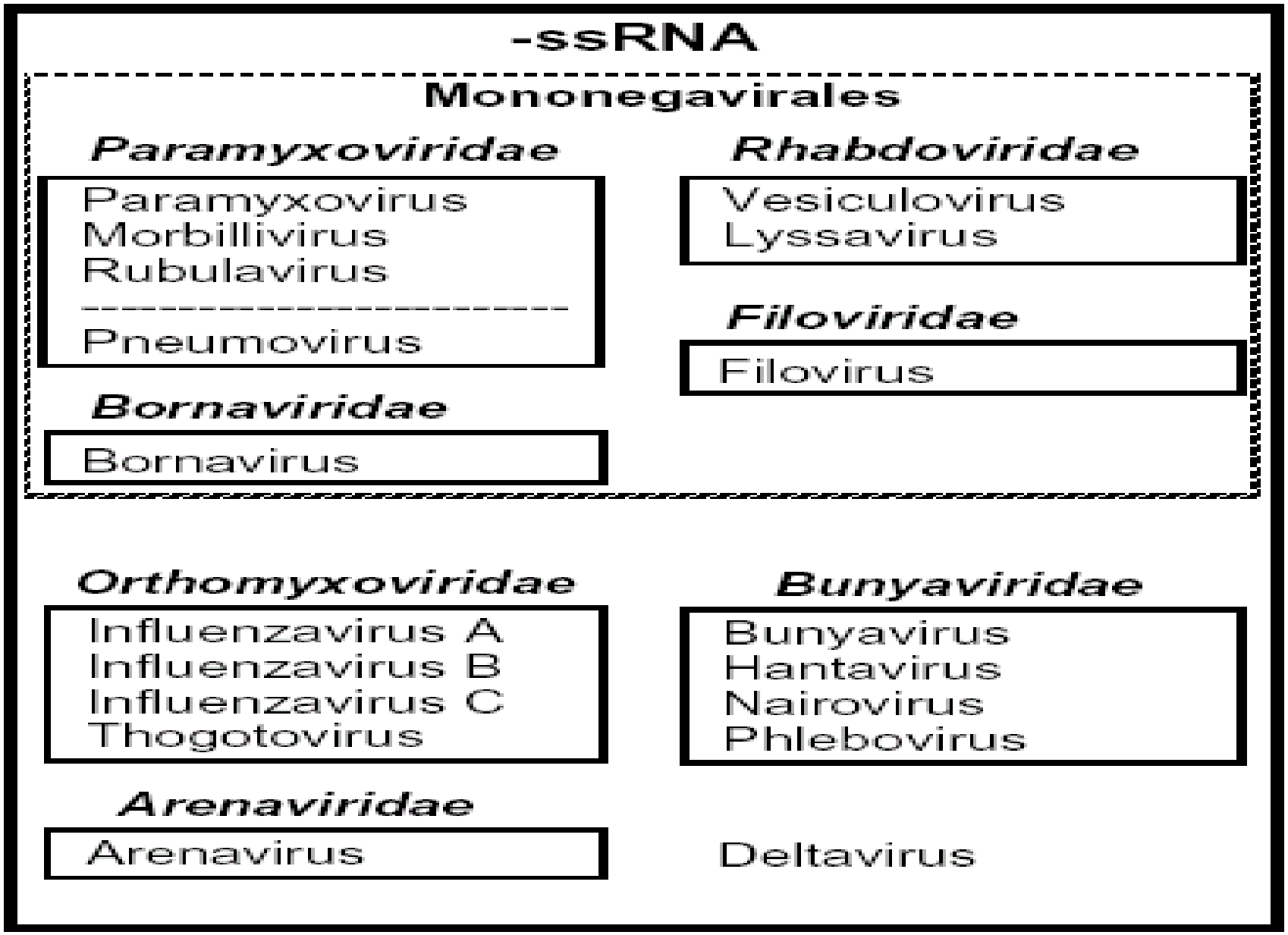
- Alpharetrovirus
- Betaretrovirus
- Gammaretrovirus
- Deltaretrovirus
- Epsilonretrovirus
- Lentivirus
- Spumavirus

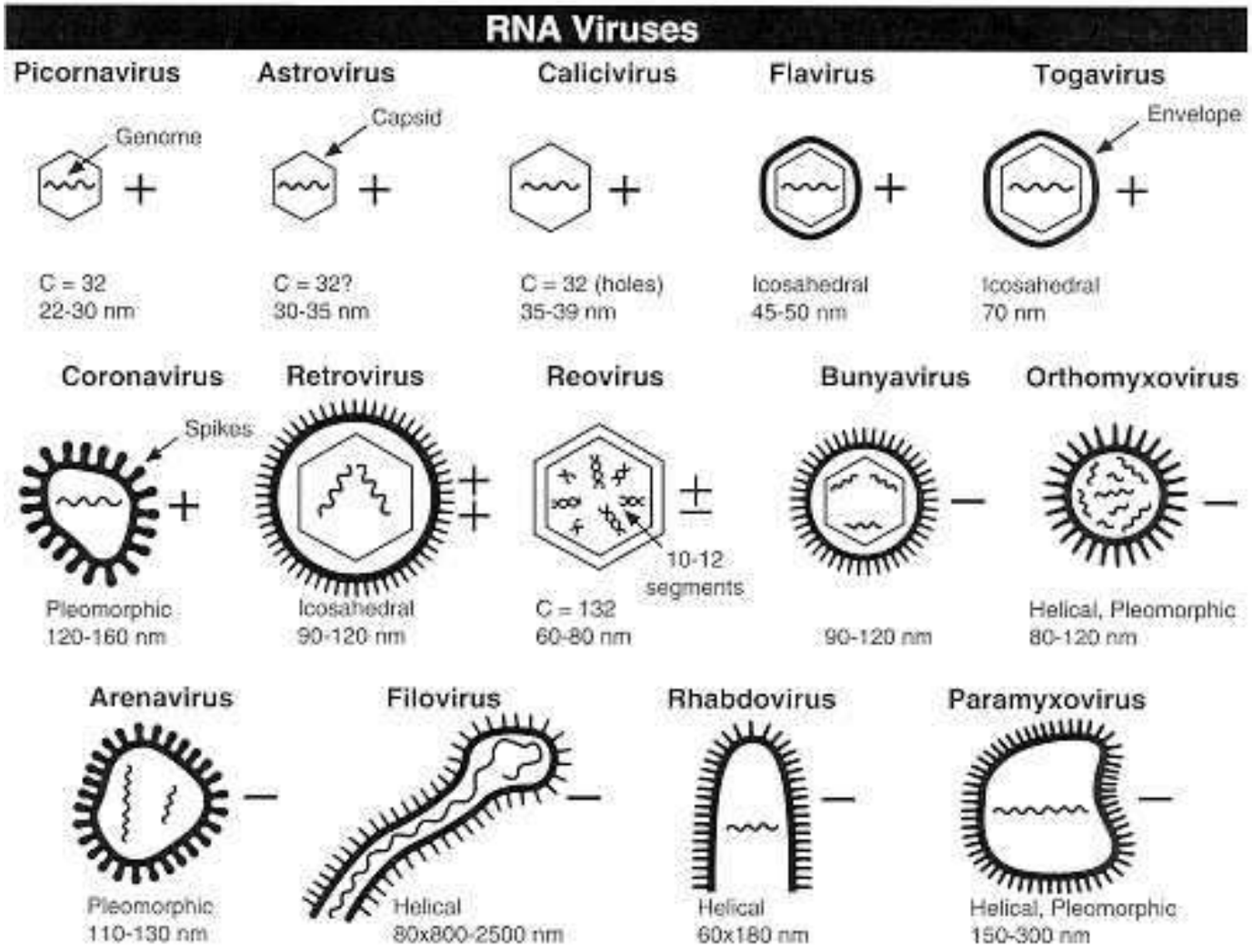
***: Alpha thru epsilon = former oncoretroviruses*

Hepadnaviridae

- Orthohepadnavirus
- Avihepadnavirus


+ssRNA
Picornaviridae
Enterovirus
Rhinovirus
Hepatovirus
Cardiovirus
Aphthovirus
Parechovirus
Caliciviridae
Norwalk-like vi.
Hepatitis E-like vi.
Astroviridae
Astrovirus
Togaviridae
Alphavirus
Rubivirus
Nidovirales
Coronaviridae
Coronavirus
Arteriviridae
Arterivirus
Flaviviridae
Flavivirus
Pestivirus
Hepacivirus
dsRNA
Reoviridae
Orthoreovirus
Orbivirus
Rotavirus
Coltivirus


-ssRNA
Mononegavirales
Paramyxoviridae
Paramyxovirus
Morbillivirus
Rubulavirus
Pneumovirus
Rhabdoviridae
Vesiculovirus
Lyssavirus
Filoviridae
Filovirus
Bornaviridae
Bornavirus
Orthomyxoviridae
Influenzavirus A
Influenzavirus B
Influenzavirus C
Thogotovirus
Bunyaviridae
Bunyavirus
Hantavirus
Nairovirus
Phlebovirus
Arenaviridae
Arenavirus
Deltavirus


RNA Viruses
Picornavirus
Genome
+
C = 32
22-30 nm
Astrovirus
Capsid
+
C = 32?
30-35 nm
Calicivirus
+
C = 32 (holes)
35-39 nm
Flavirus
+
Icosahedral
45-50 nm
Togavirus
Envelope
+
Icosahedral
70 nm
Coronavirus
Spikes
+
Pleomorphic
120-160 nm
Retrovirus
+
+
Icosahedral
90-120 nm
Reovirus
±
10-12
segments
C = 132
60-80 nm
Bunyavirus
−
90-120 nm
Orthomyxovirus
−
Helical, Pleomorphic
80-120 nm
Arenavirus
−
Pleomorphic
110-130 nm
Filovirus
−
Helical
80x800-2500 nm
Rhabdovirus
−
Helical
60x180 nm
Paramyxovirus
−
Helical, Pleomorphic
150-300 nm