An Introduction to Viruses

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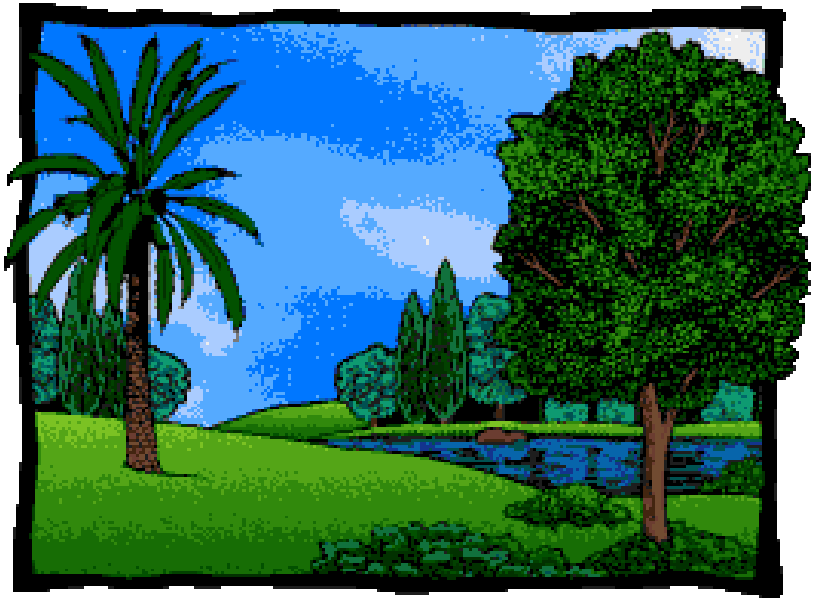
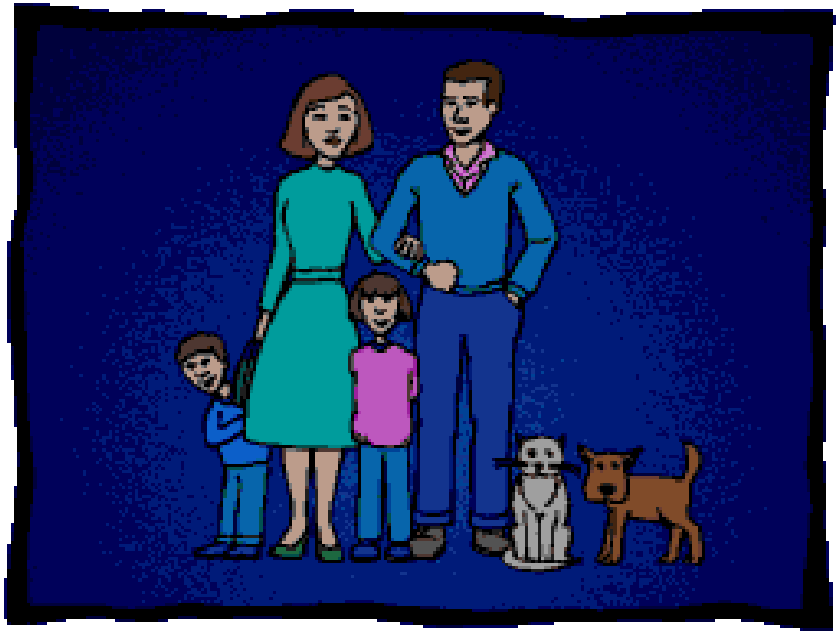
Virus infections are Universal …….





Introduction to Virology

- A virus is an obligate intracellular parasite containing genetic material surrounded by protein
- Virus particles can only be observed by an **electron microscope**

Introduction to Virology

- Recognizing the shape, size, and structure of different viruses is critical to the study of disease
  - Viruses have an inner core of nucleic acid surrounded by protein coat known as an envelope
  - Most viruses range in sizes from 20 – 450 nanometers

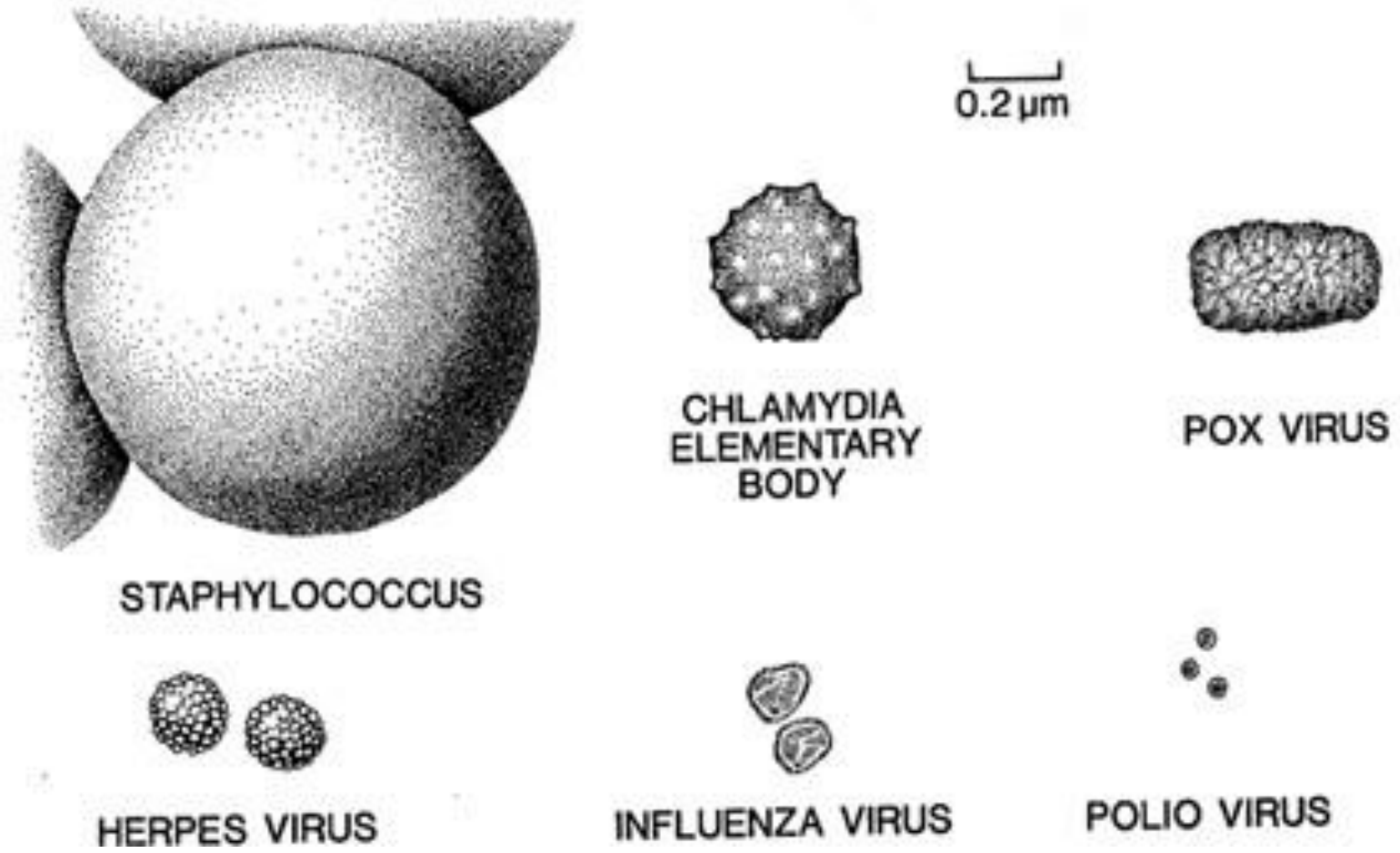
Viral Properties

- **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**

Virus vs. cells

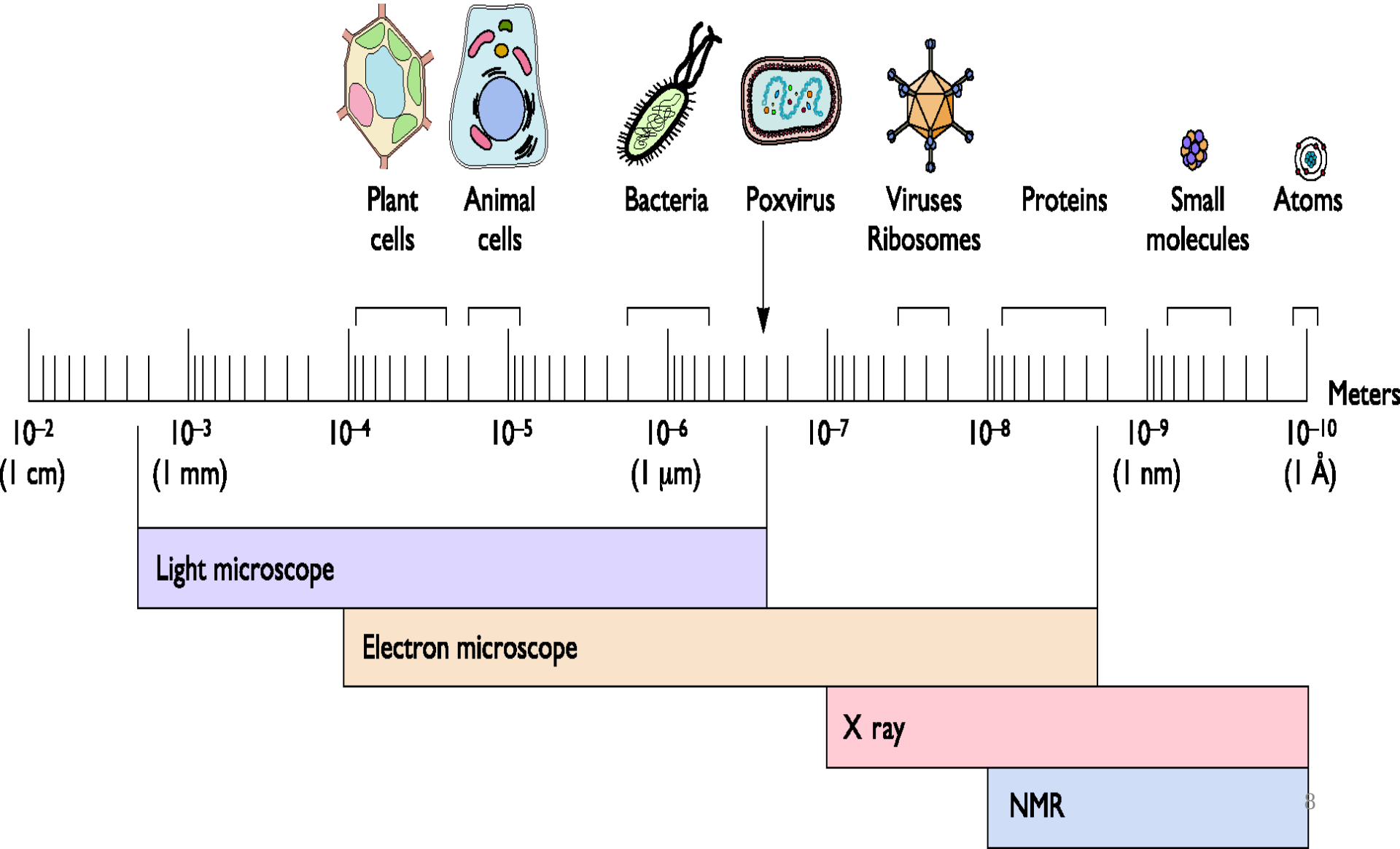
Property	Viruses	Cells
Type of nucleic acid	DNA or RNA	DNA and RNA
Proteins	Few	Many
Lipoprotein membrane	Enveloped present in some viruses	Cell membrane present in all cells
Ribosomes	Absent	Present
Mitochondria	Absent	Present in eukaryotic cells
Enzymes	None or few	Many
Multiplication by binary fission	No	Yes (most cells)

Viruses are Ultramicroscopic



Koneman et al. Color Atlas and Textbook of Microbiology 5th Ed. 1997

The size of viruses

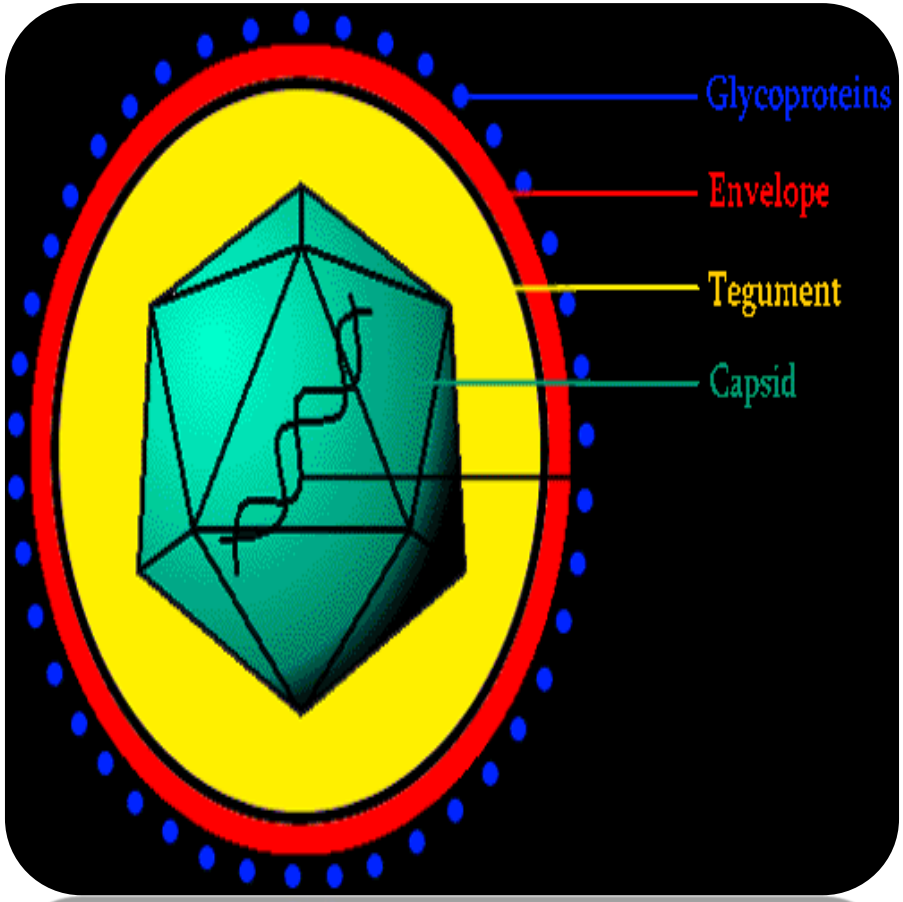


VIRAL STRUCTURE – SOME TERMINOLOGY

- virus particle = virion
- protein which coats the genome = capsid
- capsid usually symmetrical
- capsid + genome = nucleocapsid
- may have an envelope

Virion

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



Viral Structure - Overview

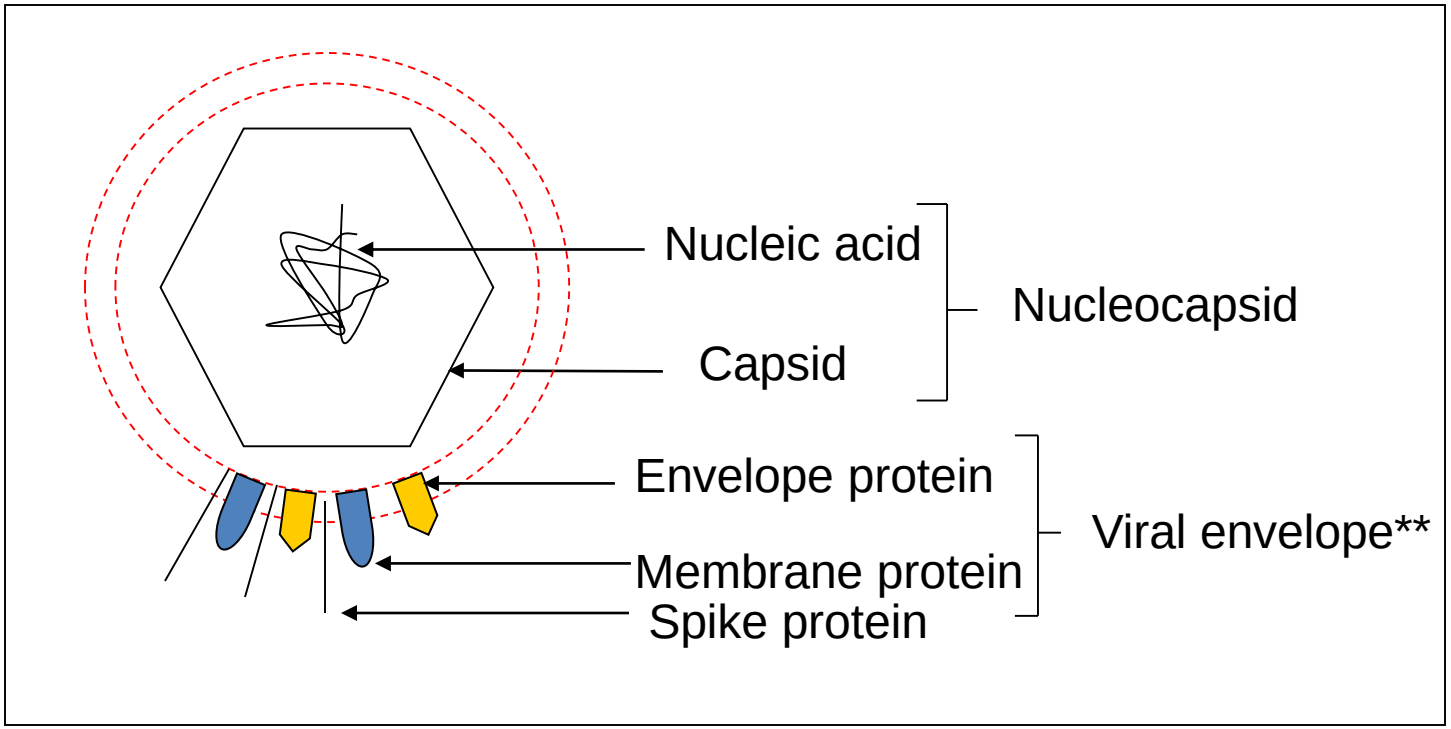


Fig 1. Schematic overview of the structure of animal viruses

** does not exist in all viruses

Distinguishing characteristics of viruses

- Obligate intracellular parasites
- Extreme genetic simplicity
- Contain DNA or RNA
- Replication involves disassembly and reassembly
- Replicate by "one-step growth”

Naming viruses

- No taxa above Family (no kingdom, phylum, etc)
- Classified based on structures, size, nucleic acids, host species, target cells.
- 19 families of animal viruses (6 DNA, 13 RNA)
- Family name ends in – viridae
- Subfamily ends in — virinae
- Genus name ends in – virus
- Species
  - ➢ Example
  - – Family – Herpesviridae
  - – Subfamily - Herpesvirinae
  - – Genus – Simplex virus
  - – Common name – herpes virus (Herpes simplex virus I (HSV-I)
  - – Disease – fever blisters, cold sores

How are viruses named?

- Based on:
  - the disease they cause

    poliovirus, rabies virus
  - the type of disease

    murine leukemia virus
  - geographic locations

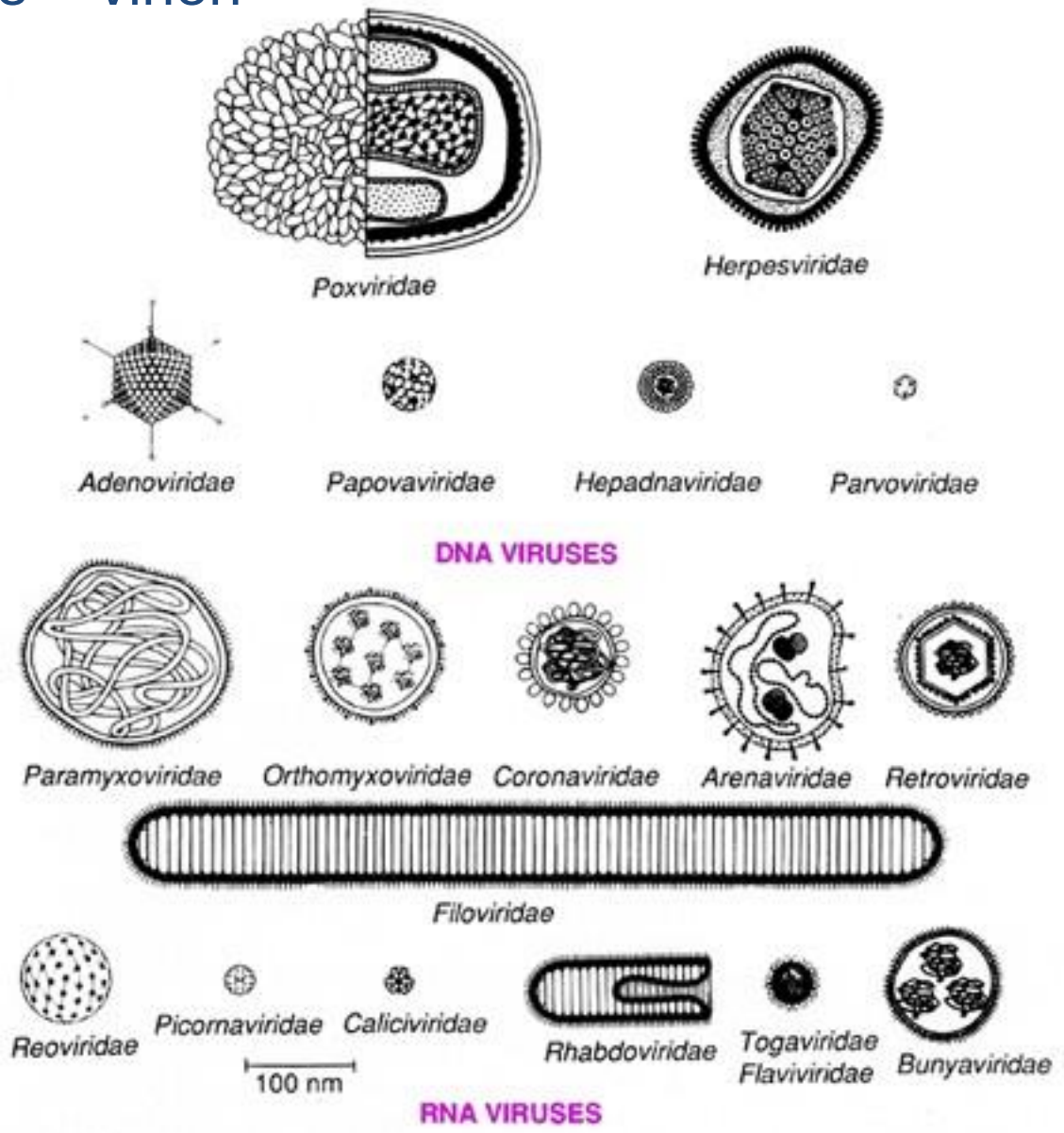
    Sendai virus, Coxsackie virus
  - their discovers

    Epstein-Barr virus
  - how they were originally thought to be contracted

    dengue virus (“evil spirit”), influenza virus (the “influence” of bad air)
  - combinations of the above

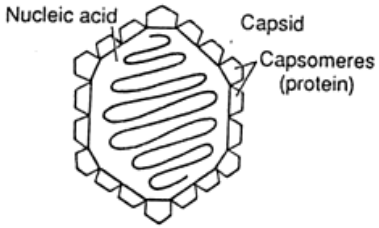
    Rous Sarcoma virus

Virus particle = virion

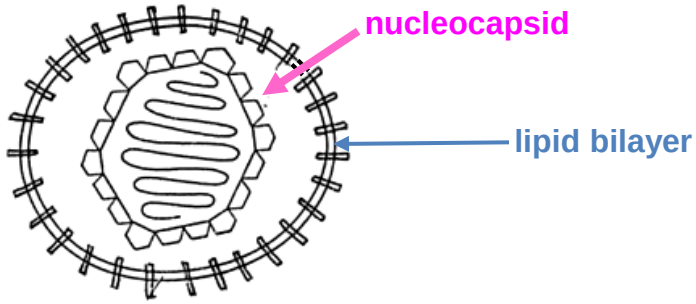


5 BASIC TYPES OF VIRAL STRUCTURE

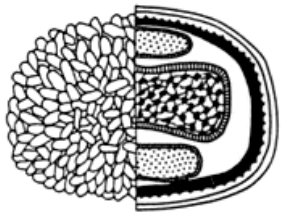
icosahedral nucleocapsid



ICOSAHEDRAL

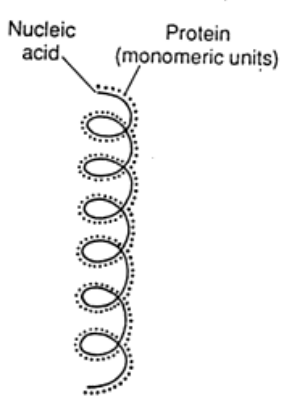


ENVELOPED ICOSAHEDRAL

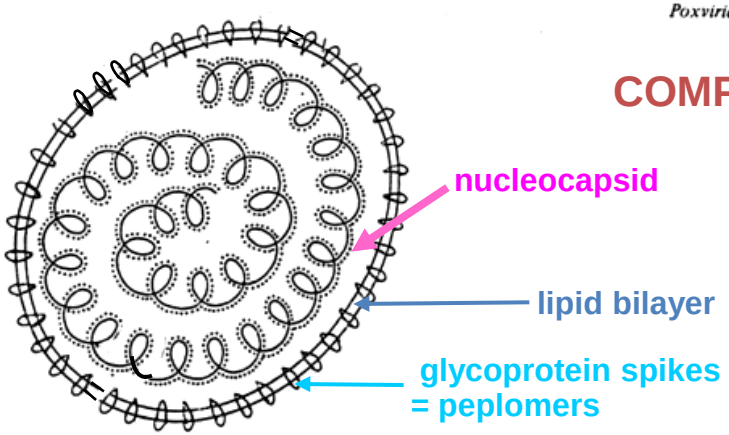


COMPLEX

helical nucleocapsid



HELICAL



ENVELOPED HELICAL

Viral Structure

- Varies in size, shape and symmetry
- 3 types of capsid symmetry:
  - Cubic (icosahedral)
    - Has 20 faces, each an equilateral triangle. Eg. adenovirus
  - Helical
    - Protein binds around DNA/RNA in a helical fashion eg. Coronavirus
  - Complex
    - Is neither cubic nor helical eg. poxvirus

VIRAL STRUCTURE (virion)

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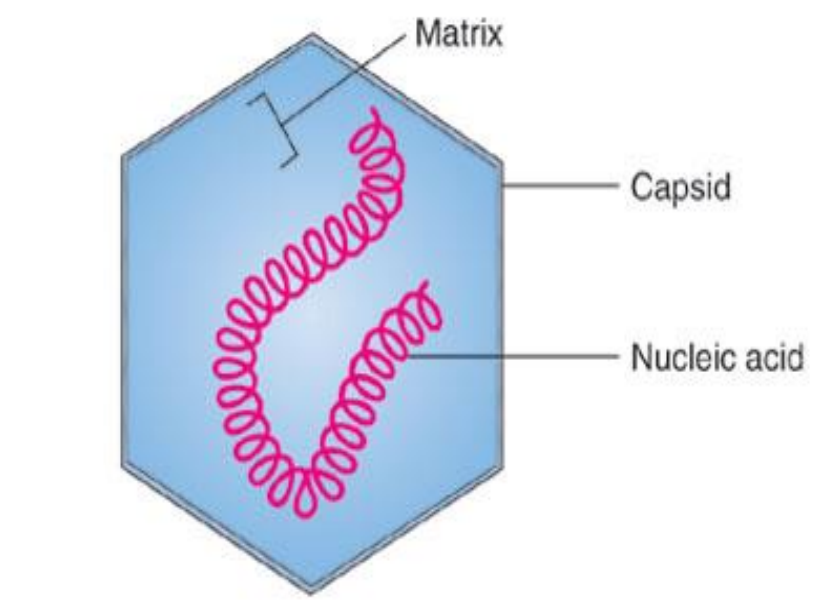
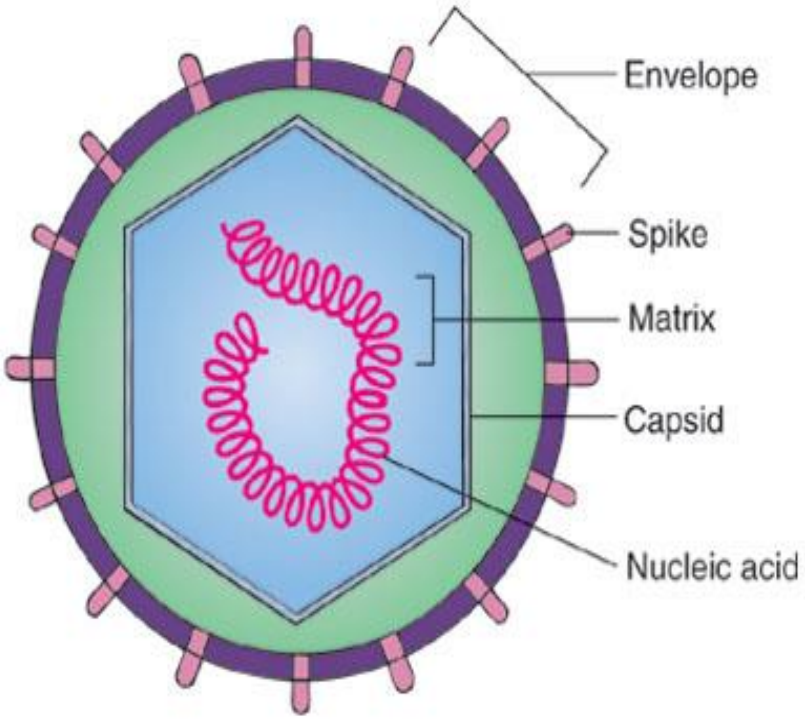


(a) **Naked Nucleocapsid Virus**



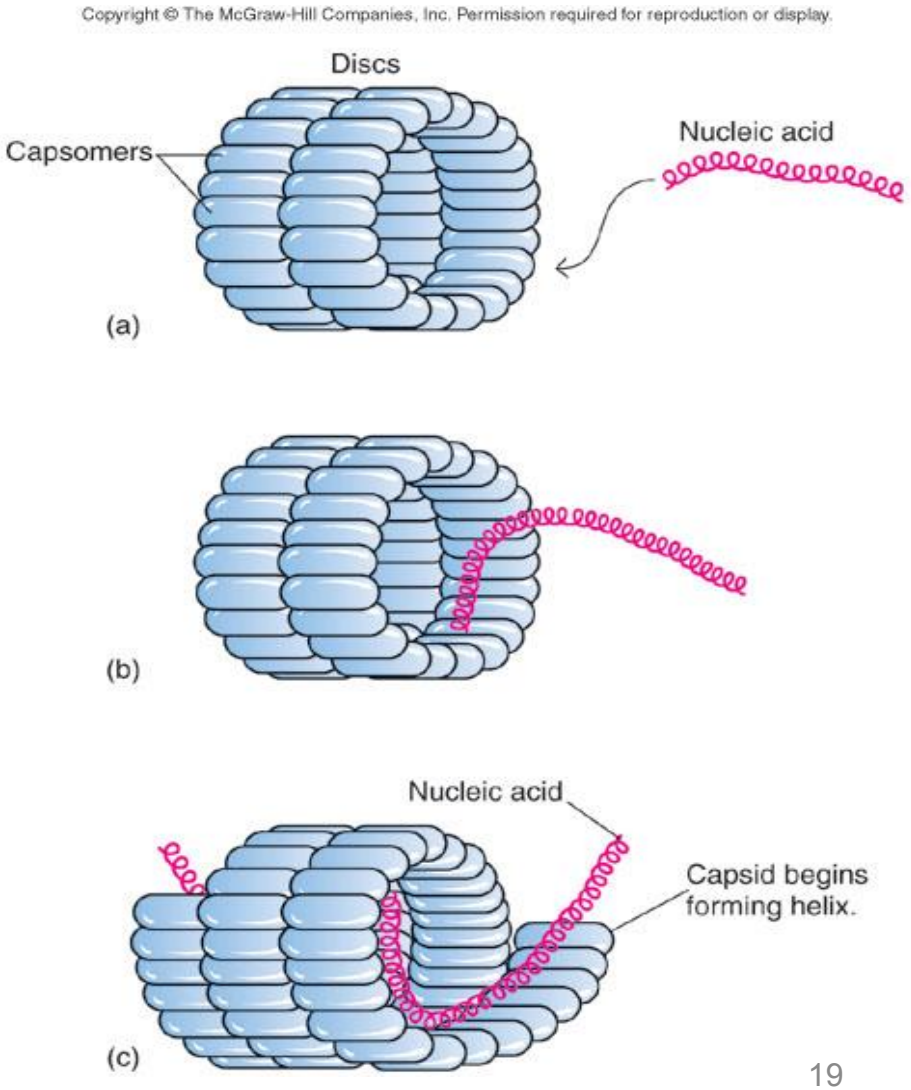
(b) **Enveloped Virus**

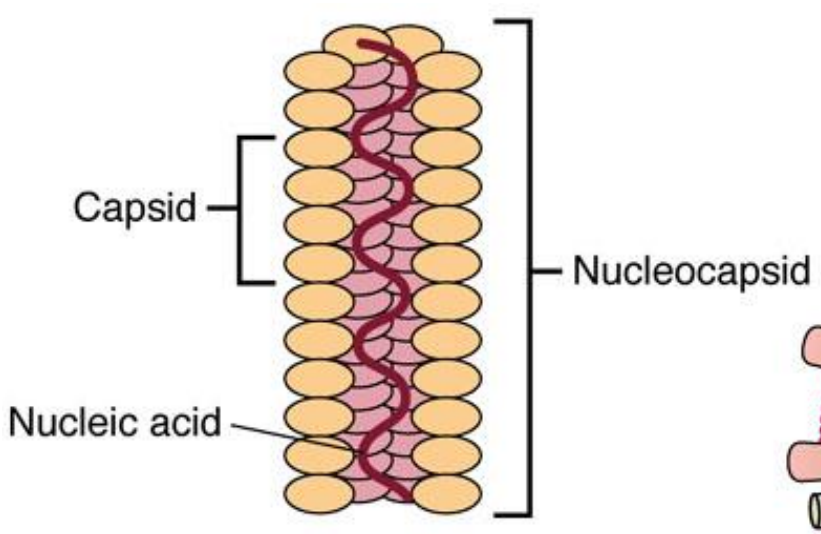
1. Protect genome during passage from one cell to another
2. Aid in entry process
3. Package enzymes for early steps of infection

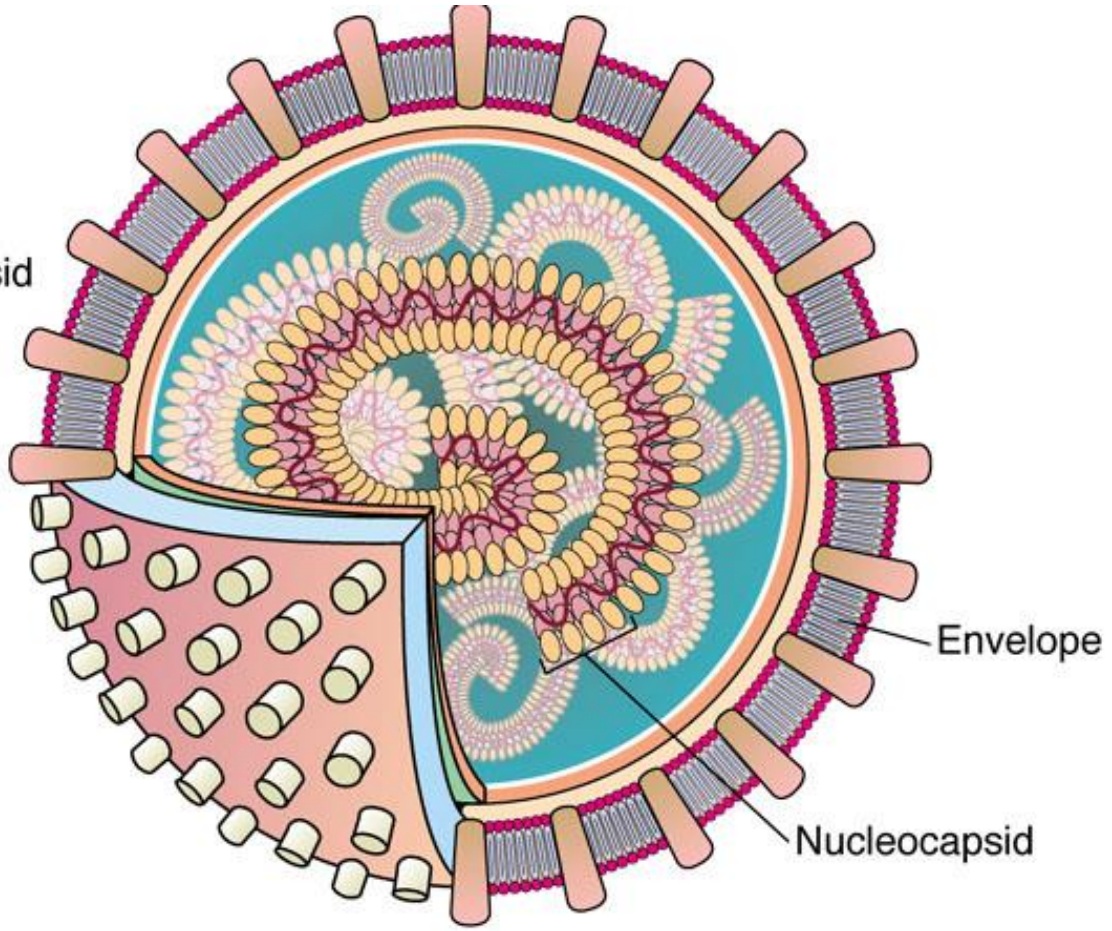
CAPSID STRUCTURE

1. Helical capsid

- Rod-shaped capsomers
- Coil around hollow center
- Nucleic acid is kept inside – wound-up within tube (Helix)



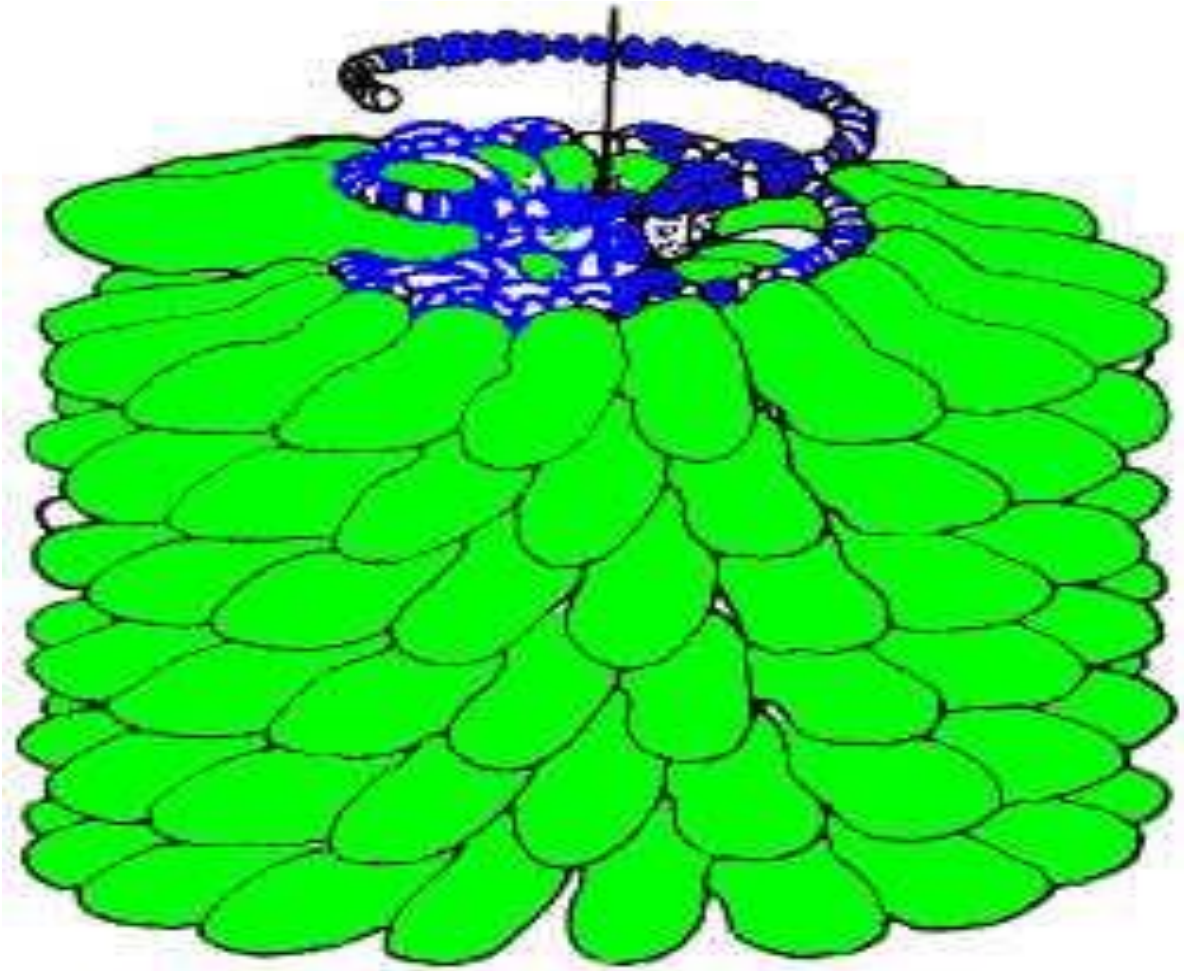




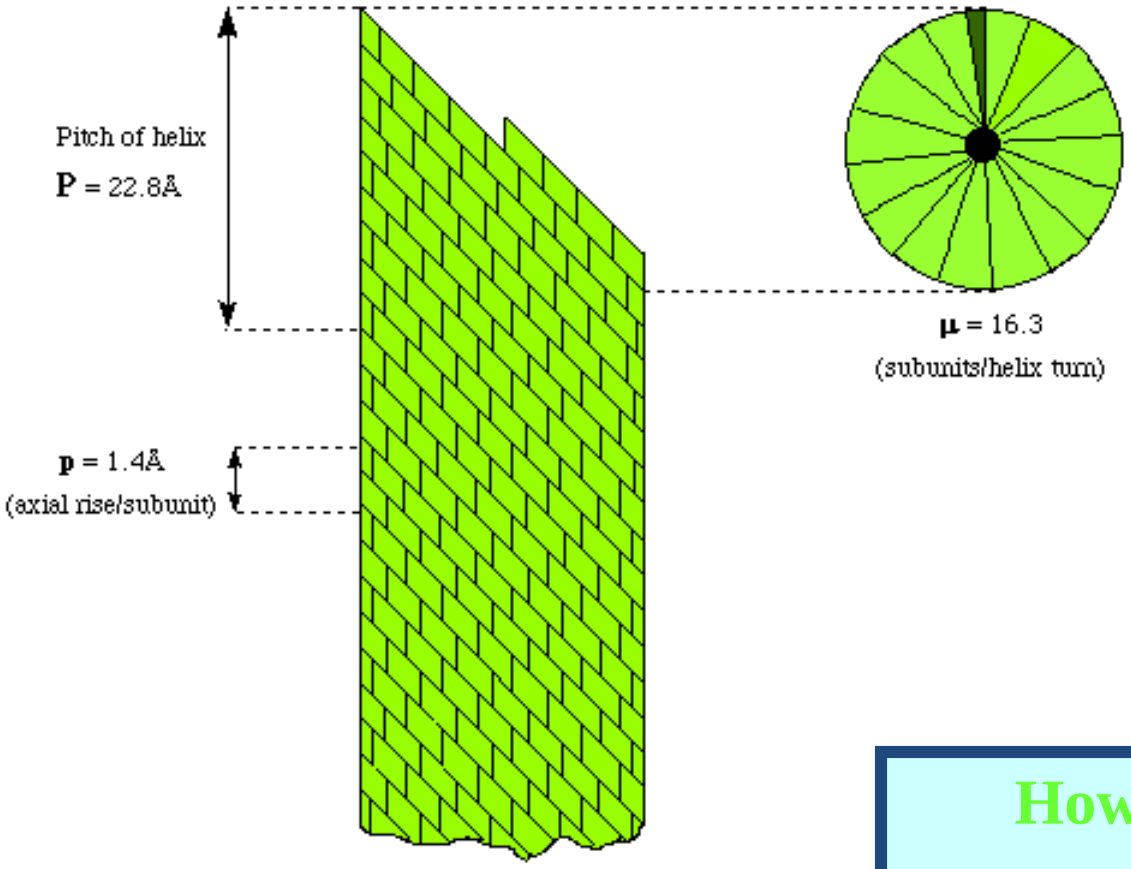
Helical – capsid surrounds DNA like hollow tube

Ex: Influenza , measles, rabies (enveloped)

Helical symmetry



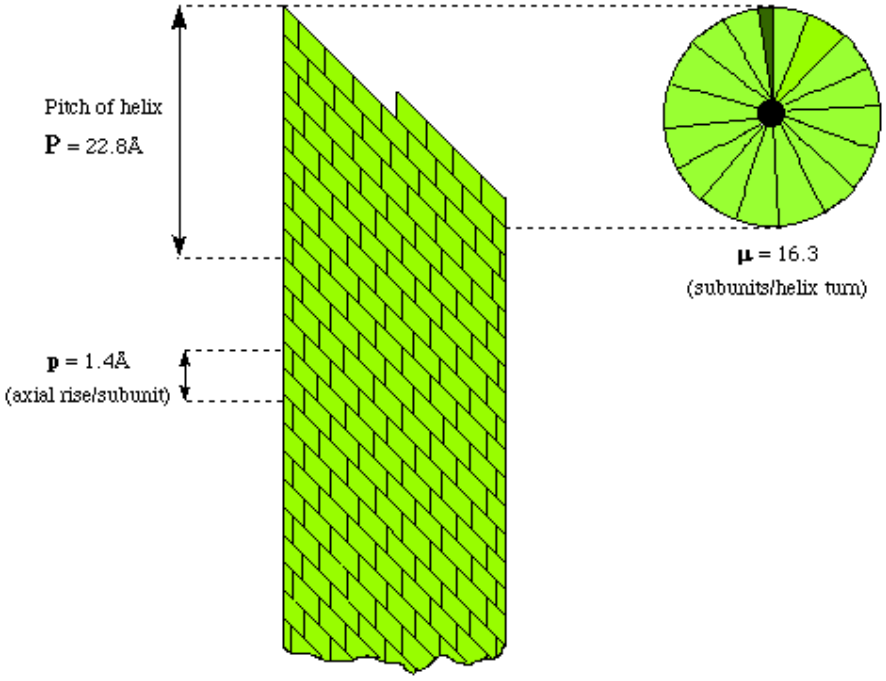
Helical symmetry



How to assemble

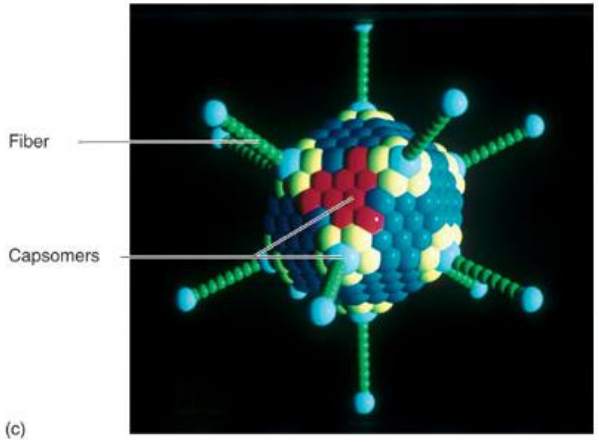
Helical symmetry

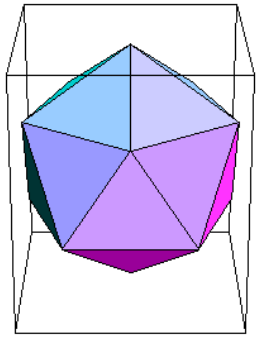
In 1955, Fraenkel, Conrat, and Williams demonstrated that tobacco mosaic virus (TMV) spontaneously formed when mixtures of purified coat protein and its genomic RNA were incubated together.



TMV, a filamentous virus

2. icosahedral





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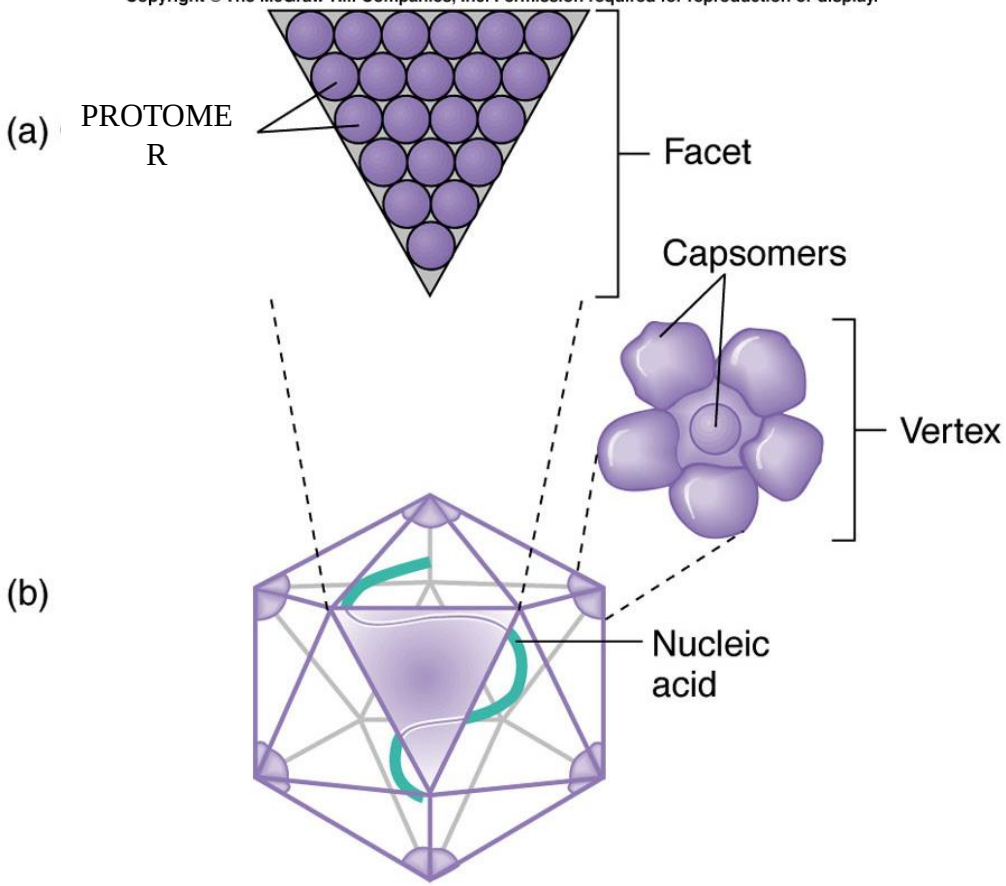
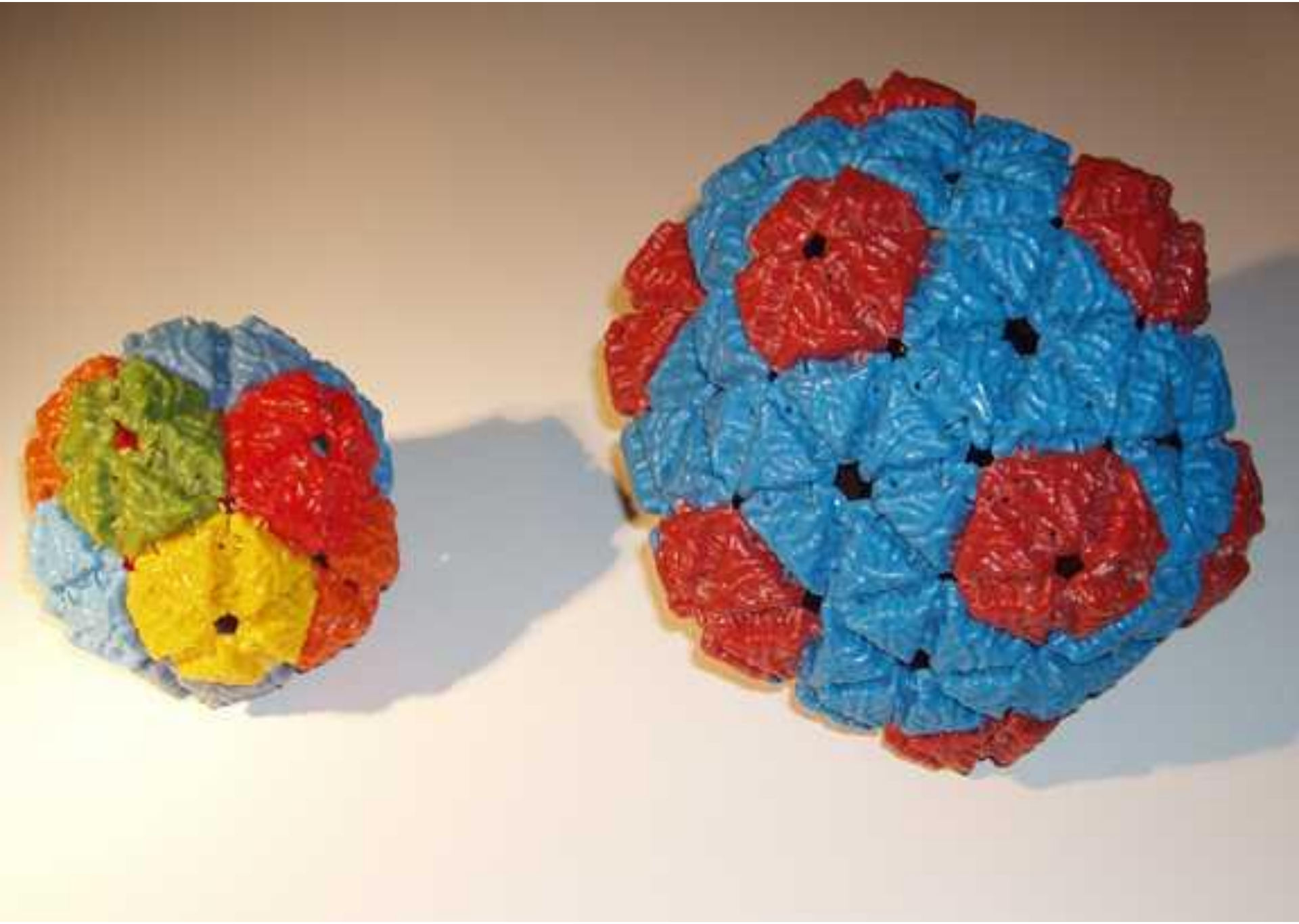
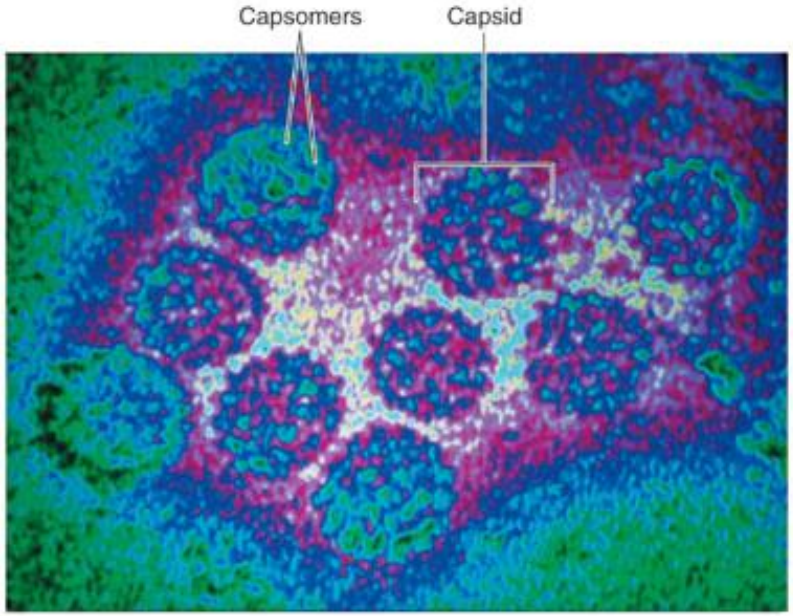


- 20-sided with 12 corners
- Vary in the number of capsomers
- Each capsomer may be made of 1 or several proteins
- Some are enveloped





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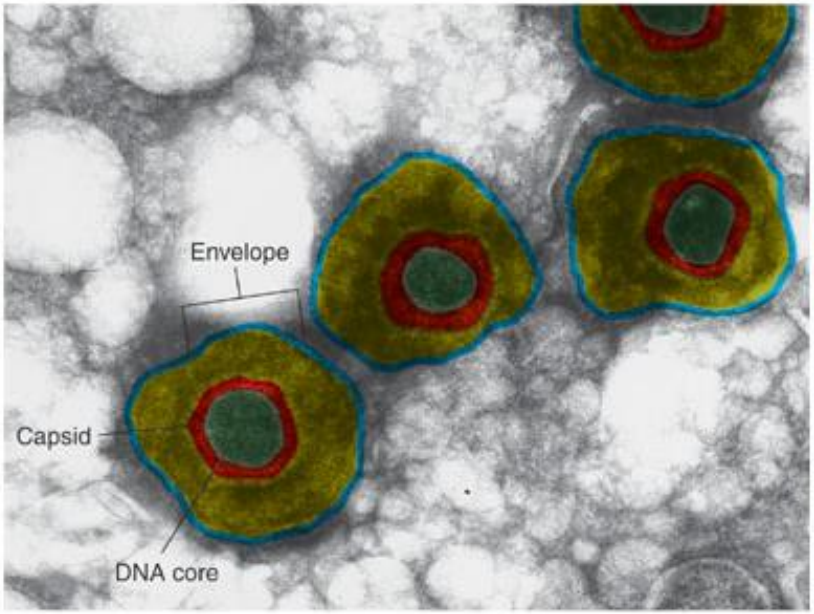

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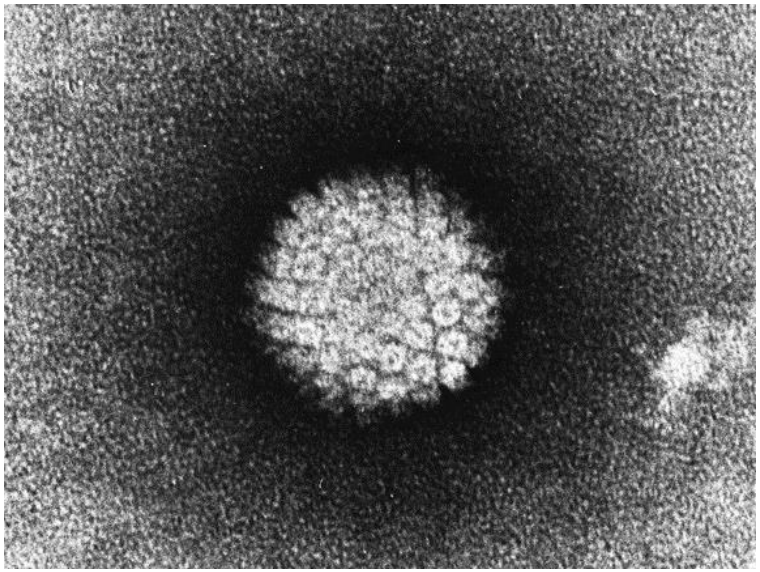
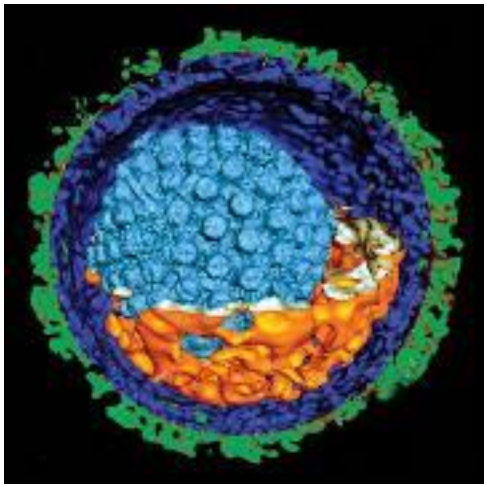
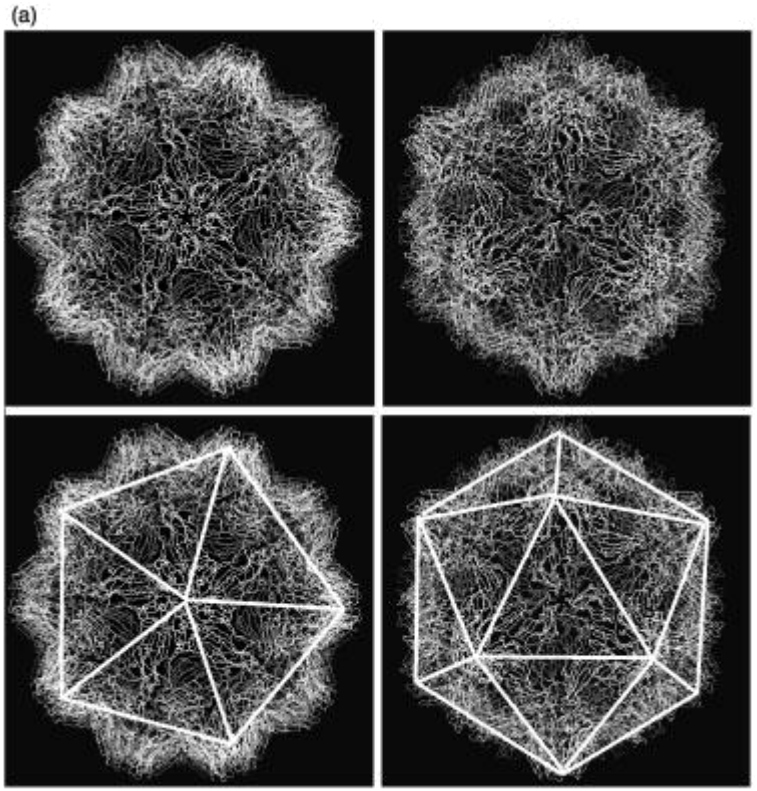
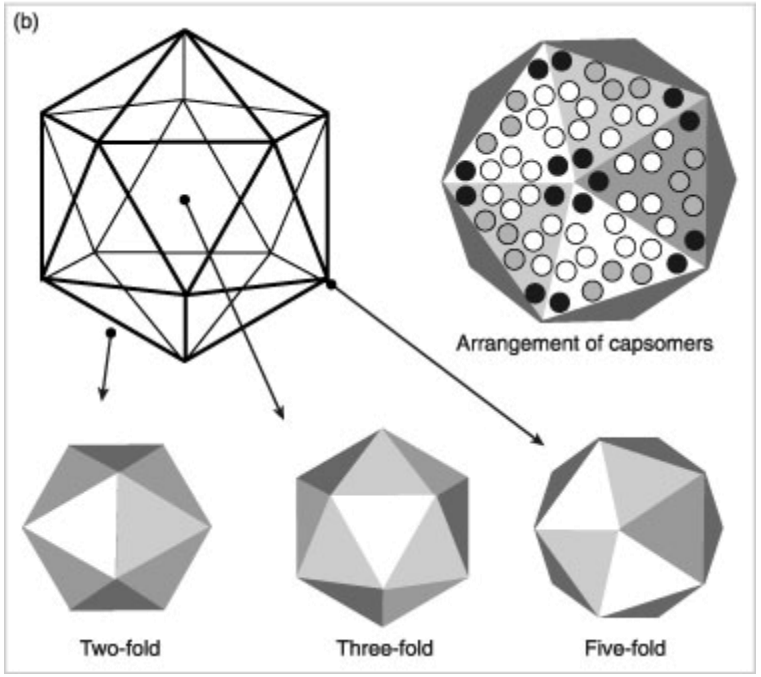




Icosahedral capsids

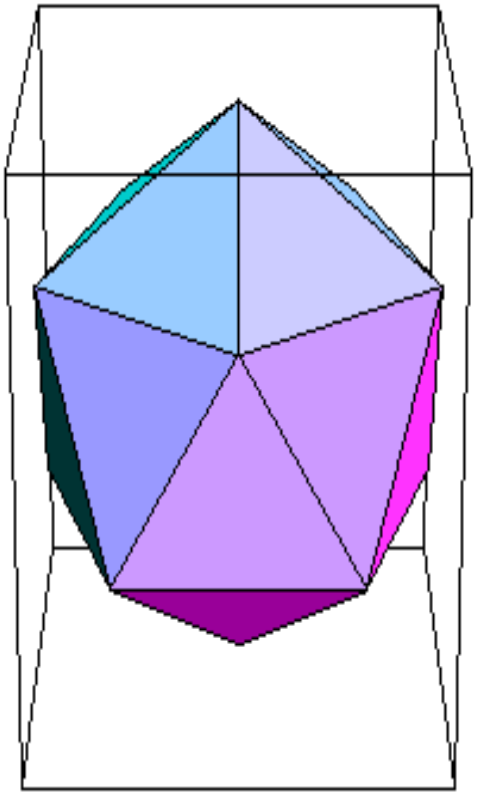


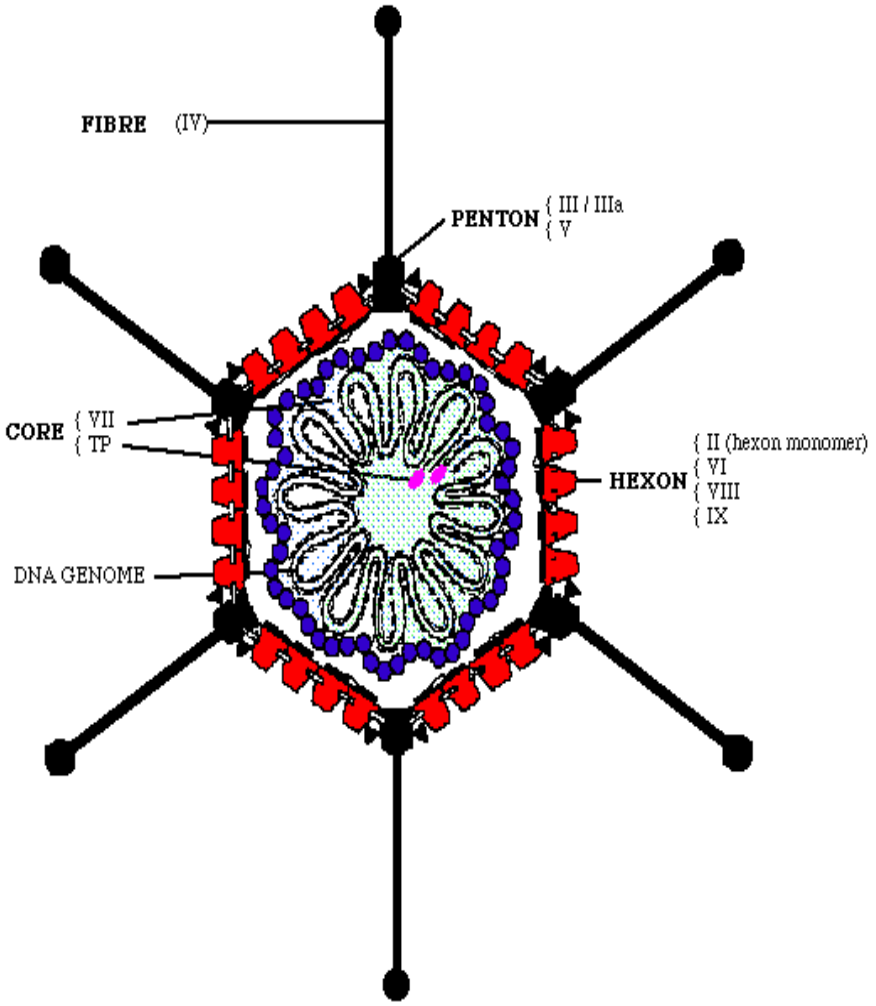
a) Crystallographic structure of a simple icosahedral virus.



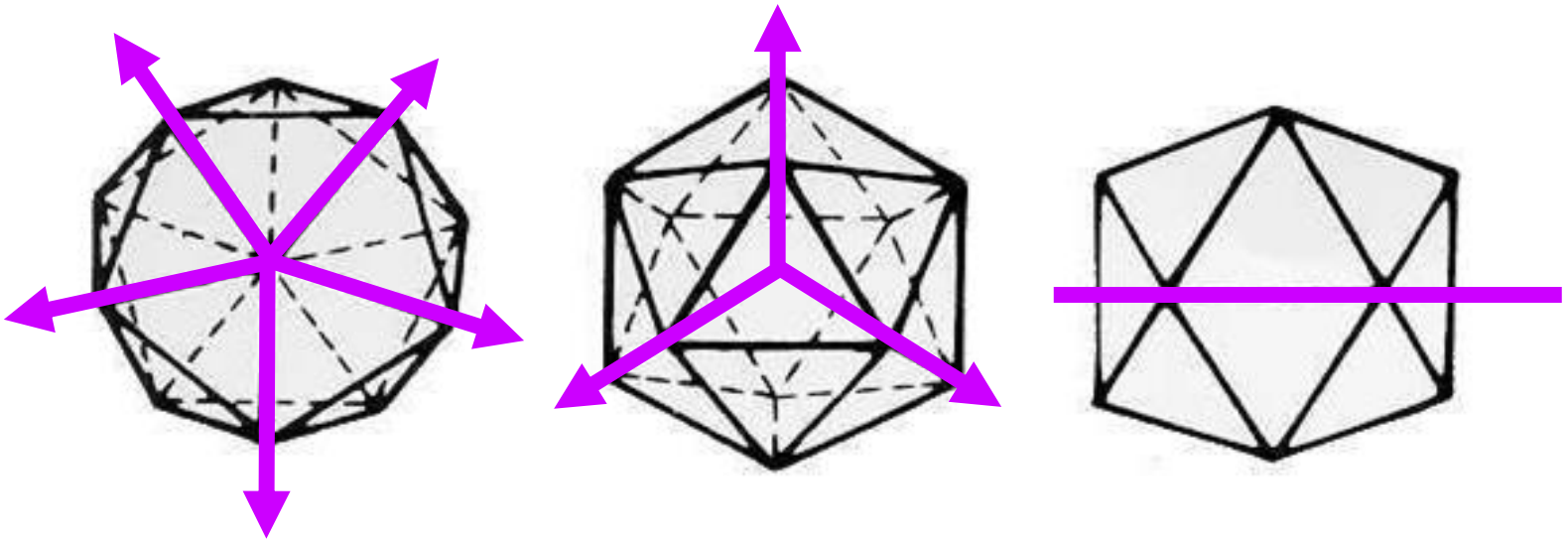
b) The axes of symmetry

Cubic or icosahedral symmetry



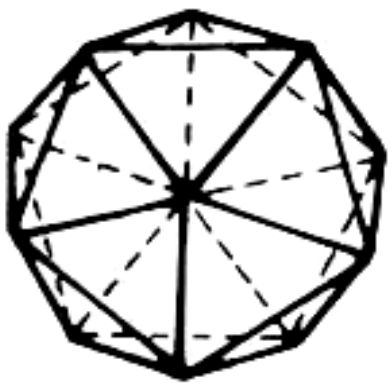


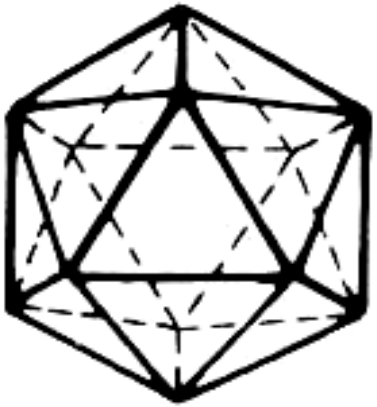
ICOSAHEDRAL SYMMETRY

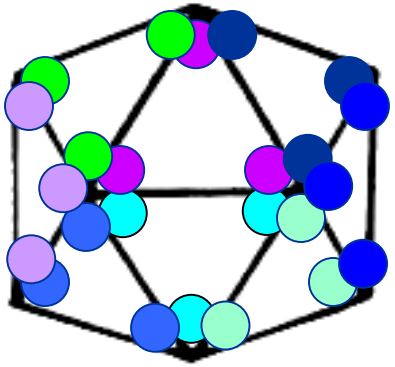


5-FOLD **3-FOLD** **2-FOLD**

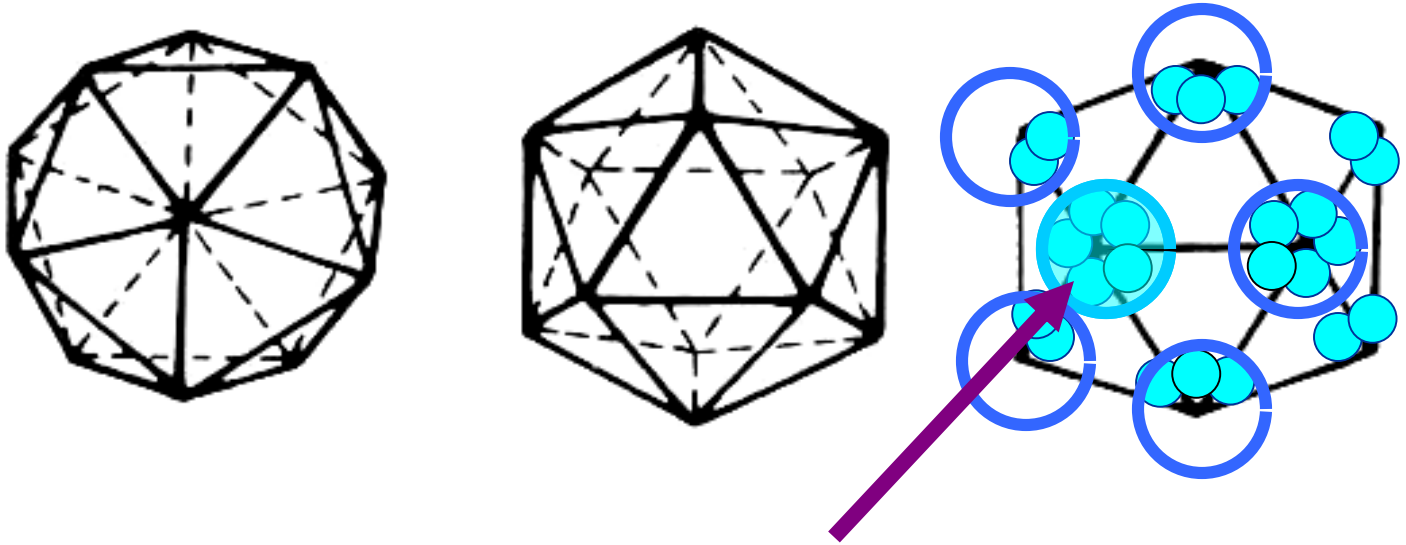
ICOSAHEDRAL SYMMETRY



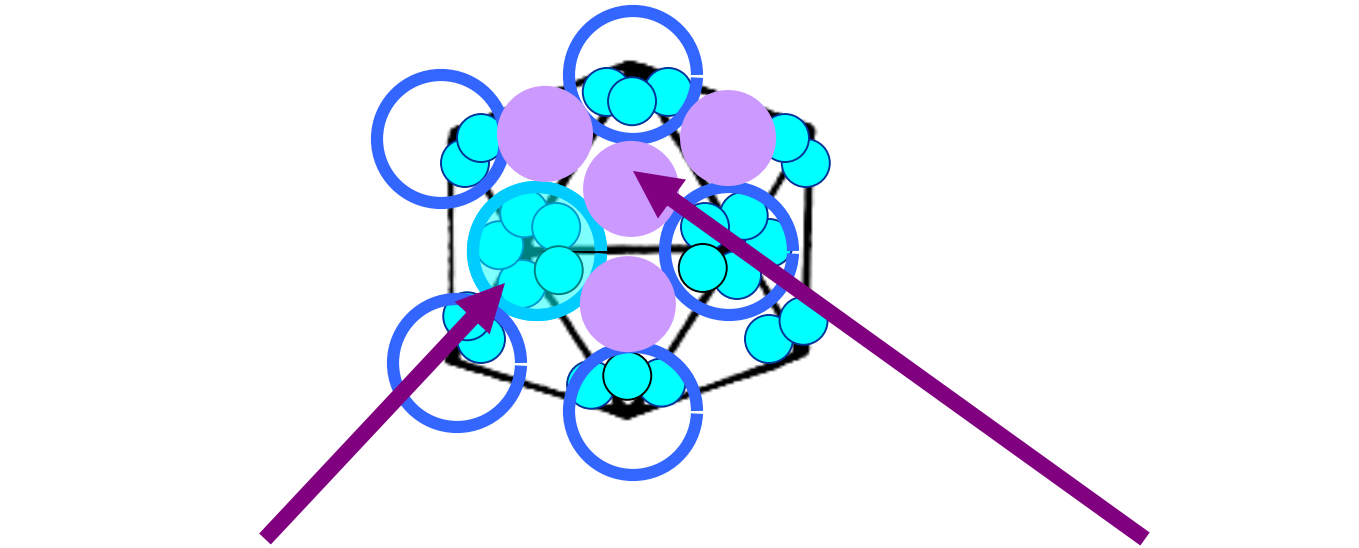




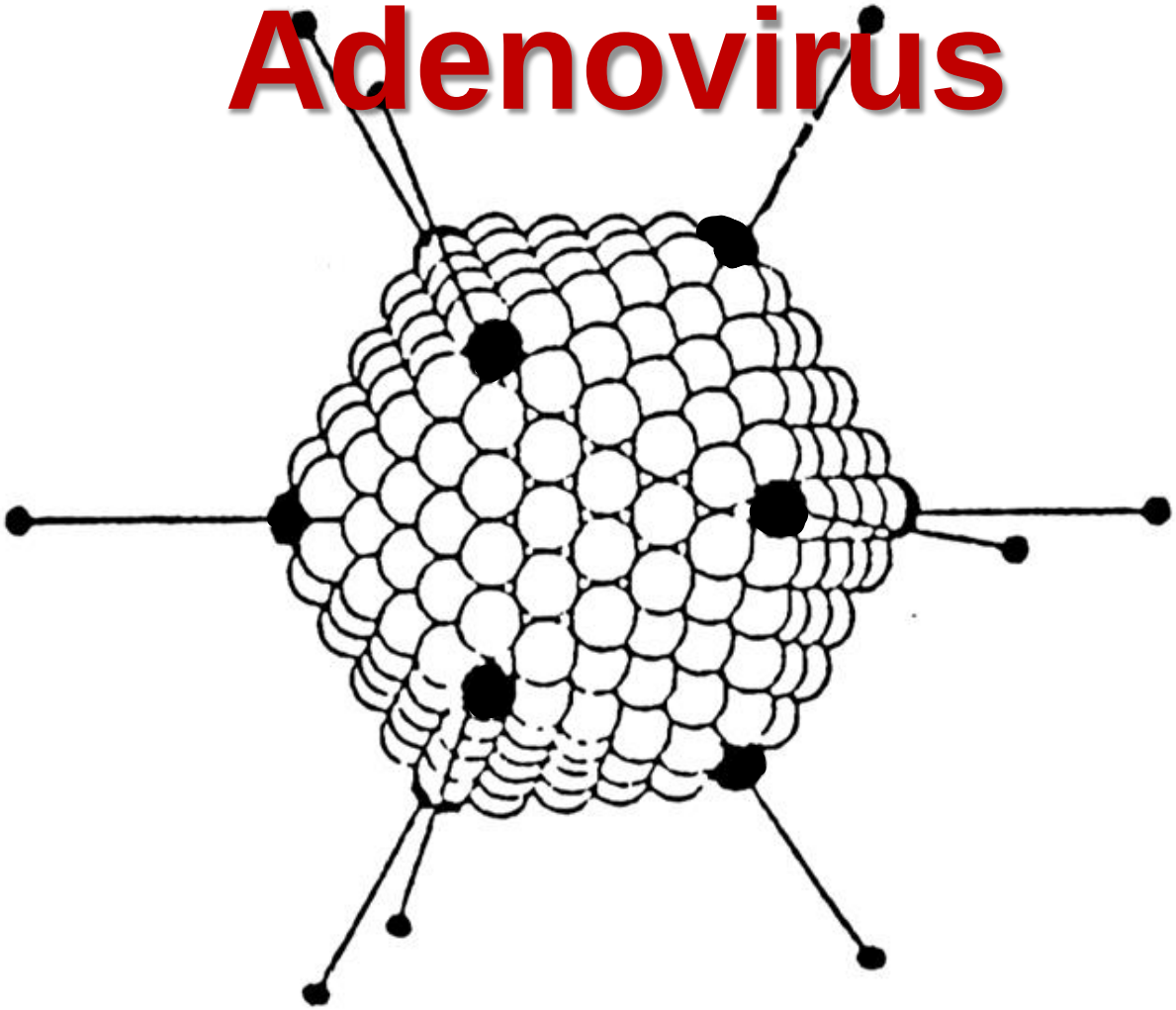
ICOSAHEDRAL SYMMETRY



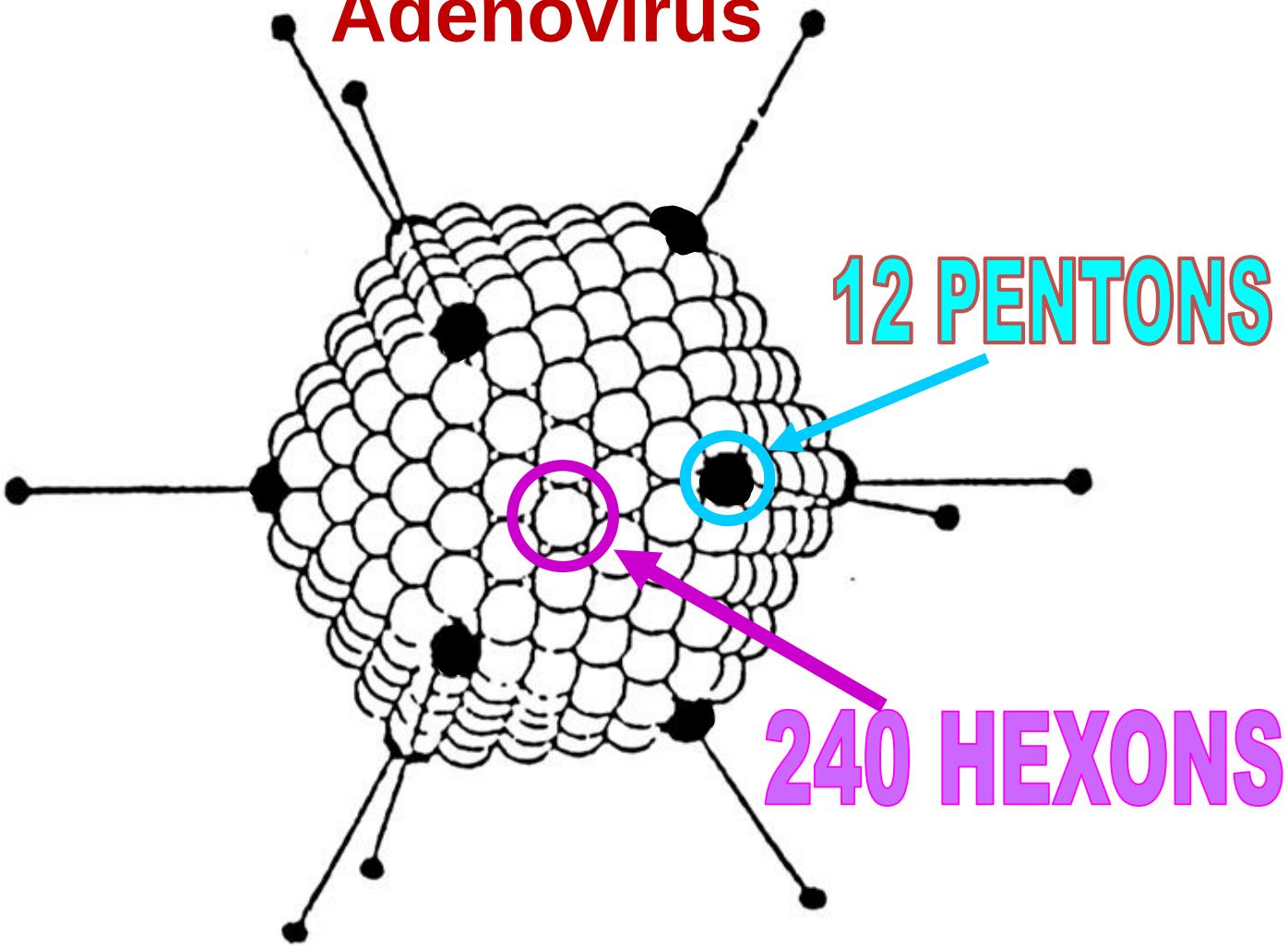
ICOSAHEDRAL SYMMETRY



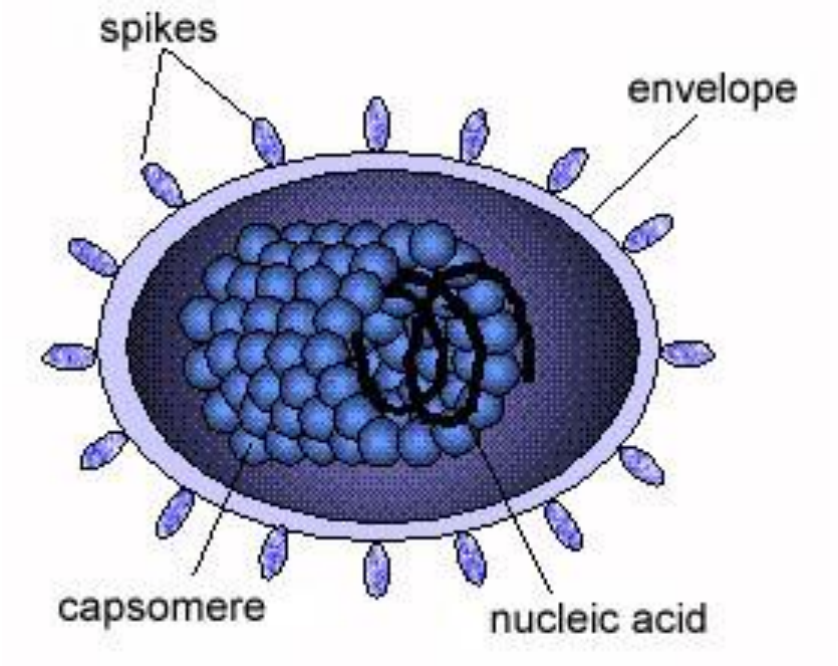
Adenovirus



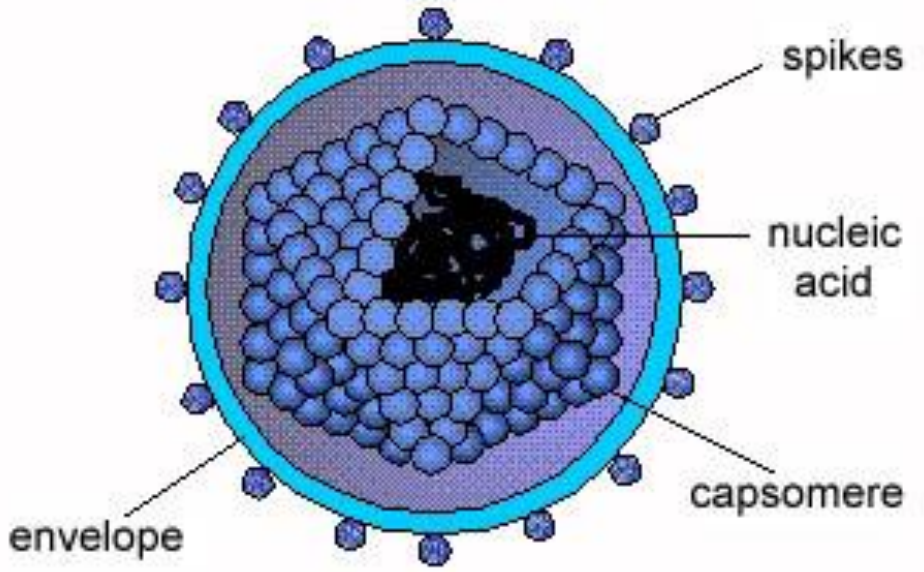
Adenovirus



Enveloped helical virus



Enveloped icosahedral virus



Helical

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

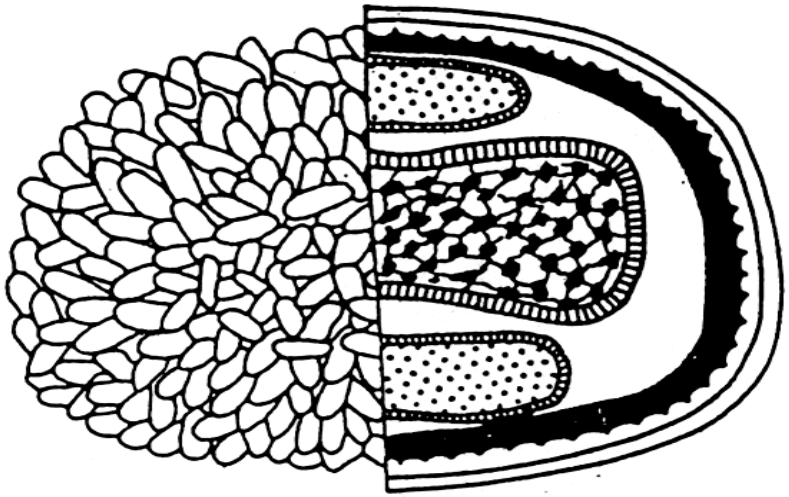
Icosahedral

- 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 viruses

- Have additional or special structures
- Examples:
- Poxviruses – lack normal capsid – instead, layers of lipoprotiens and fibrils on surface

surface view



cross section

A bacteriophage

- A bacteriophage is any one of a number of viruses that infect bacteria. They do this by injecting genetic material, which they carry enclosed in an outer protein capsid. The genetic material can be ssRNA, dsRNA, ssDNA, or dsDNA ('ss-' or 'ds-' prefix denotes single-strand or double-strand) along with either circular or linear arrangement.

Phage - viruses have a polyhedral head, helical tail and fibers for attachment.

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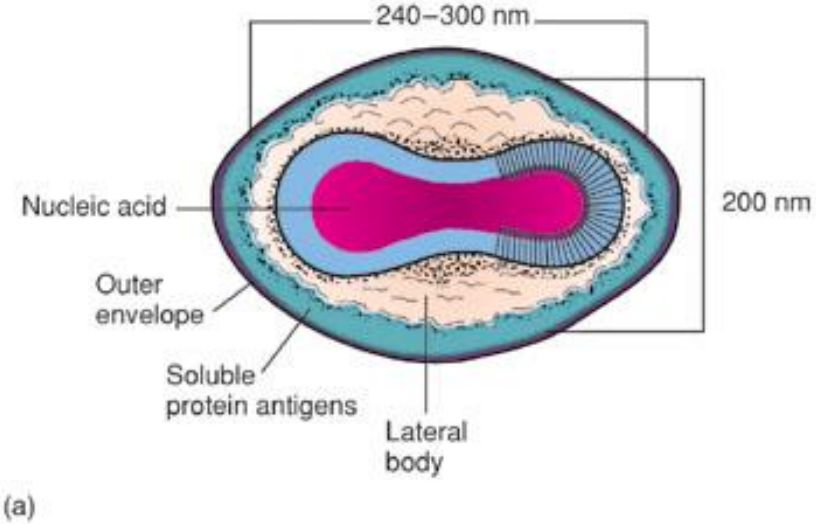

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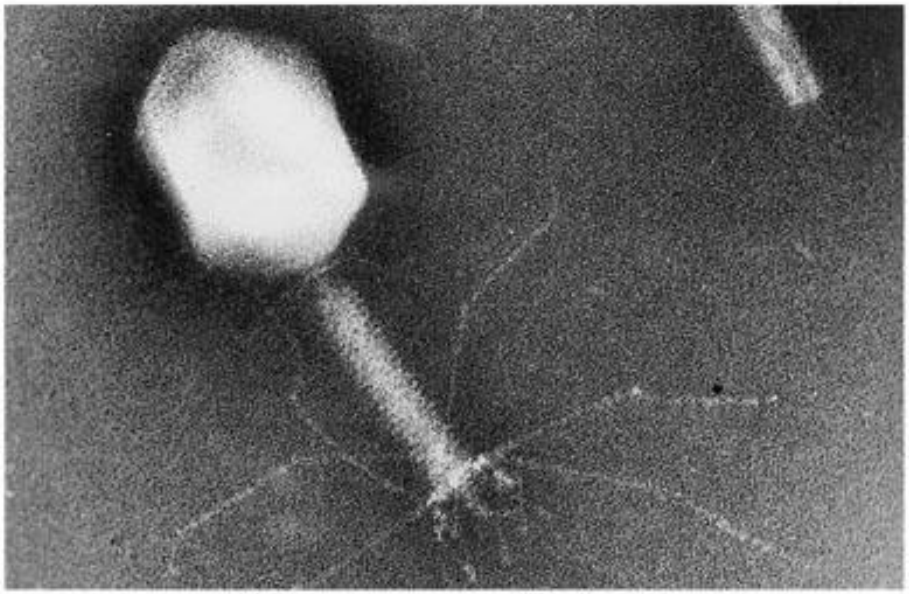

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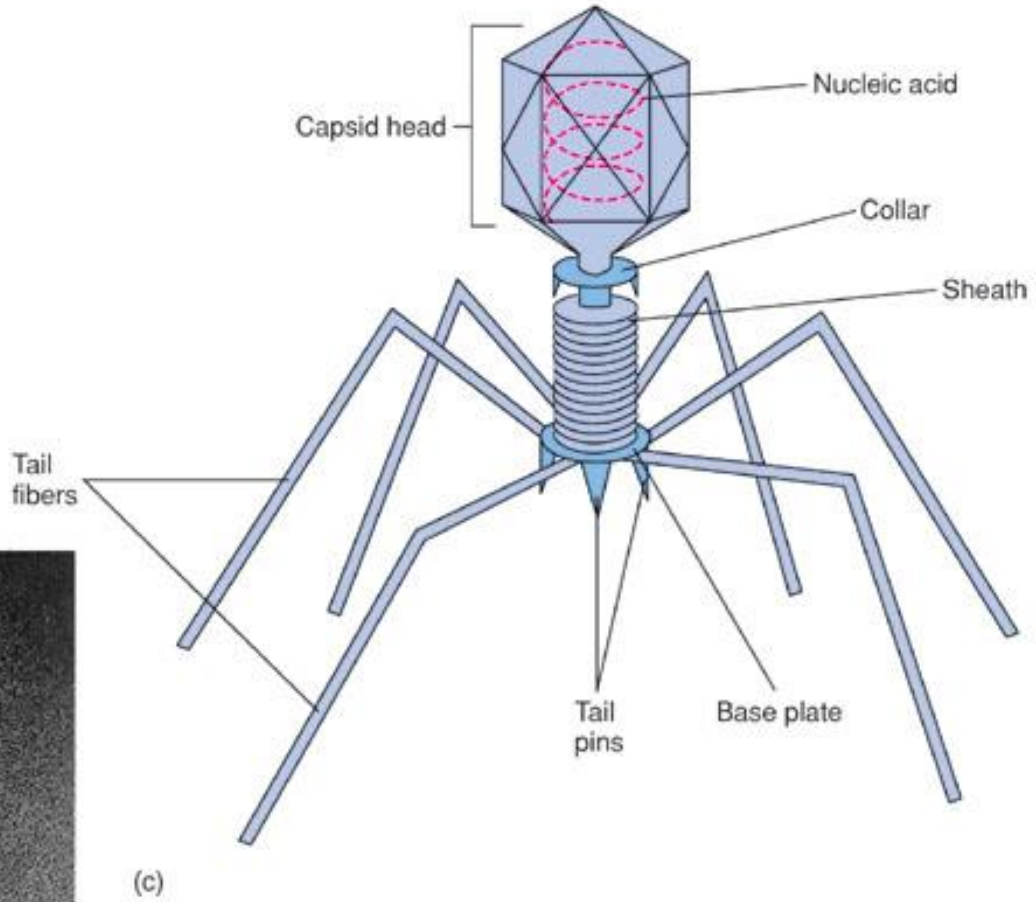


(c)

Classification of viruses

- Nucleic acid
- Capsid
- Presence of envelope
- Replication strategy

CLASSIFICATION
NUCLEIC ACID

- RNA or DNA
- segmented or non-segmented
- linear or circular
- single-stranded or double-stranded
- if single-stranded RNA
  - is genome mRNA (+) sense or complementary to mRNA (-) sense

ENVELOPE

- OBTAINED BY BUDDING THROUGH A CELLULAR MEMBRANE (except poxviruses)
- POSSIBILITY OF EXITING CELL WITHOUT KILLING IT
- CONTAINS AT LEAST ONE VIRALLY CODED PROTEIN
  - ATTACHMENT PROTEIN
- **LOSS OF ENVELOPE RESULTS IN LOSS OF INFECTIVITY**

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

The Baltimore classification system

Based on genetic contents and replication strategies of viruses. According to the Baltimore classification, viruses are divided into the following seven classes:

1. dsDNA viruses
2. ssDNA viruses
3. dsRNA viruses
4. (+) sense ssRNA viruses (codes directly for protein)
5. (-) sense ssRNA viruses
6. RNA reverse transcribing viruses
7. DNA reverse transcribing viruses

where "ds" represents "double strand" and "ss" denotes "single strand".

Virus Classification
- the Baltimore classification

- All viruses must produce mRNA, or (+) sense RNA
- A complementary strand of nucleic acid is (–) sense

- The Baltimore classification has + RNA as its central point

- Its principles are fundamental to an understanding of virus classification and genome replication, but it is rarely used as a classification system in its own right

Viral genome strategies

- dsDNA (herpes, papova, adeno, pox)
- •ssDNA (parvo)
- •dsRNA (reo, rota)
- •ssRNA (+) (picorna, toga, flavi, corona)
- •ssRNA (-) (rhabdo, paramyxo, orthomyxo,
- bunya, filo)
- •ssRNA (+/-) (arena, bunya)
- •ssRNA (+RTase) (retro, lenti)

Sub-viral agents

- **Satellites**
  - Contain nucleic acid
  - Depend on co-infection with a helper virus
  - May be encapsidated (satellite virus)
  - Mostly in plants, can be human e.g. hepatitis delta virus
  - If nucleic acid only = virusoid
- **Viroids**
  - Unencapsidated, small circular ssRNA molecules that replicate autonomously
  - Only in plants, e.g. potato spindle tuber viroid
  - Depend on host cell polII for replication, no protein or mRNA
- **Prions**
  - No nucleic acid
  - Infectious protein e.g. BSE

Viroids & Prions

- **Viroids**
  - ss RNA genome and the smallest known pathogens.
  - Affects plants

- **Prions**
  - Infectious particles that are entirely protein.
  - No nucleic acid
  - Highly heat resistant
  - Animal disease that affects nervous tissue
  - Affects nervous tissue and results in
    - Bovine spongiform encepahltits (BSE) “mad cow disease”,
    - scrapie in sheep
    - kuru & Creutzfeld-Jakob Disease (CJD) in humans

Viroids

- Viroids are small (200-400nt), circular RNA molecules with a rod-like secondary structure which possess no capsid or envelope which are associated with certain plant diseases. Their replication strategy like that of viruses - they are obligate intracellular parasites.
- Viroids do not encode any proteins and unlike satellites they are not dependent on the presence of another virus

Viroid replication

- Viroids utilize cellular RNA polymerases for their replication
- Replication is performed by “rolling circle mechanism”
- The resulting long RNA molecule is cut in pieces and ligated either autocatalytically or by cellular factors (depending on a viroid)
- So in a sense, at least some viroids are ribozymes...

Examples of plants, infected with various viroids

Hepatitis δ virus – a chimeric molecule, half viroid, half satellite

- Viroid like properties
- Rod-like RNA molecule
- Rolling circle replication
- Self-cleaving activty

- Satellite like properties
- Encodes a protein, which is necessary both for encapsidation and replication
- Dependent on presence another virus – HBV
- Genome larger than for viroids (1640 nt)

Prions

- Prions are rather ill-defined infectious agents believed to consist of a single type of protein molecule with no nucleic acid component. Confusion arises from the fact that the prion protein & the gene which encodes it are also found in normal 'uninfected' cells. These agents are associated with diseases such as Creutzfeldt-Jakob disease in humans, scrapie in sheep & bovine spongiform encephalopathy (BSE) in cattle.

Prions

Prions are proteinaceous transmissible pathogens responsible for a series of fatal neurodegenerative diseases (in humans, Creutzfeld-Jakob disease and kuru, in animals, bovine spongioform encephalopathy)

A prion (**pro**teinaceous **in**fectious particle, analogy for virion) is a type of infectious agent that does not carry the genetic information in nucleid acid!

Prions are proteins with the pathological conformation that are believed to infect and propagate the conformational changes of the native proteins into the the abnormally srtructured form

Disease name	Natural host	Prion name	PrP isoform
Scrapie	Sheep, goat	Scrapie prion	$OvPrP^{Sc}$
Transmissible mink encephalopathy (TME)	Mink	TME prion	$MkPrP^{Sc}$
Chronic wasting disease (CWD)	Elk, mule deer	CWD prion	$MDePrP^{Sc}$
Bovine spongioform encephalopathy (BSE)	Cattle	BSE prion	$BovPrP^{Sc}$
Feline spongioform encephalopathy (FSE)	Cat	FSE prion	$FePrP^{Sc}$
Exotic unguale encephalopathy (EUE)	Greater kudu, nyala	EUE prion	$NyaPrP^{Sc}$
Kuru	Human	Kuru prion	$HuPrP^{Sc}$
Creutzfeldt-Jakob disease (CJD)	Human	CJD prion	$HuPrP^{Sc}$
Gerstmann-Straussler-Scheinker syndrome (GSS)	Human	GSS prion	$HuPrP^{Sc}$
Fatal familial insomnia (FFI)	Human	FFI prion	$HuPrP^{Sc}$

Prion diseases: rare neurodegenerative disorders (one person per million)

1. Sporadic (85 %)

In the sixth or seventh decade, rapidly progressive (death in less than a year)

Creutzfeldt-Jakob disease (CJD)

2. Familial (inherited-15%)

Mutations in the PrP gene that favour the transition from the cellular form to the pathological form of PrP

Gerstmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI)

3. Transmissible (rare; a source of great concern)

Propagation of kuru disease in New Guinea natives (ritualistic cannibalism)

Recently, it has been discovered that BSE had been transmitted to humans in Europe after consumption of infected beef, producing a variant of the CJD called vCJD

Transmissible spongioform encephalopathy (TSE)=prion disease

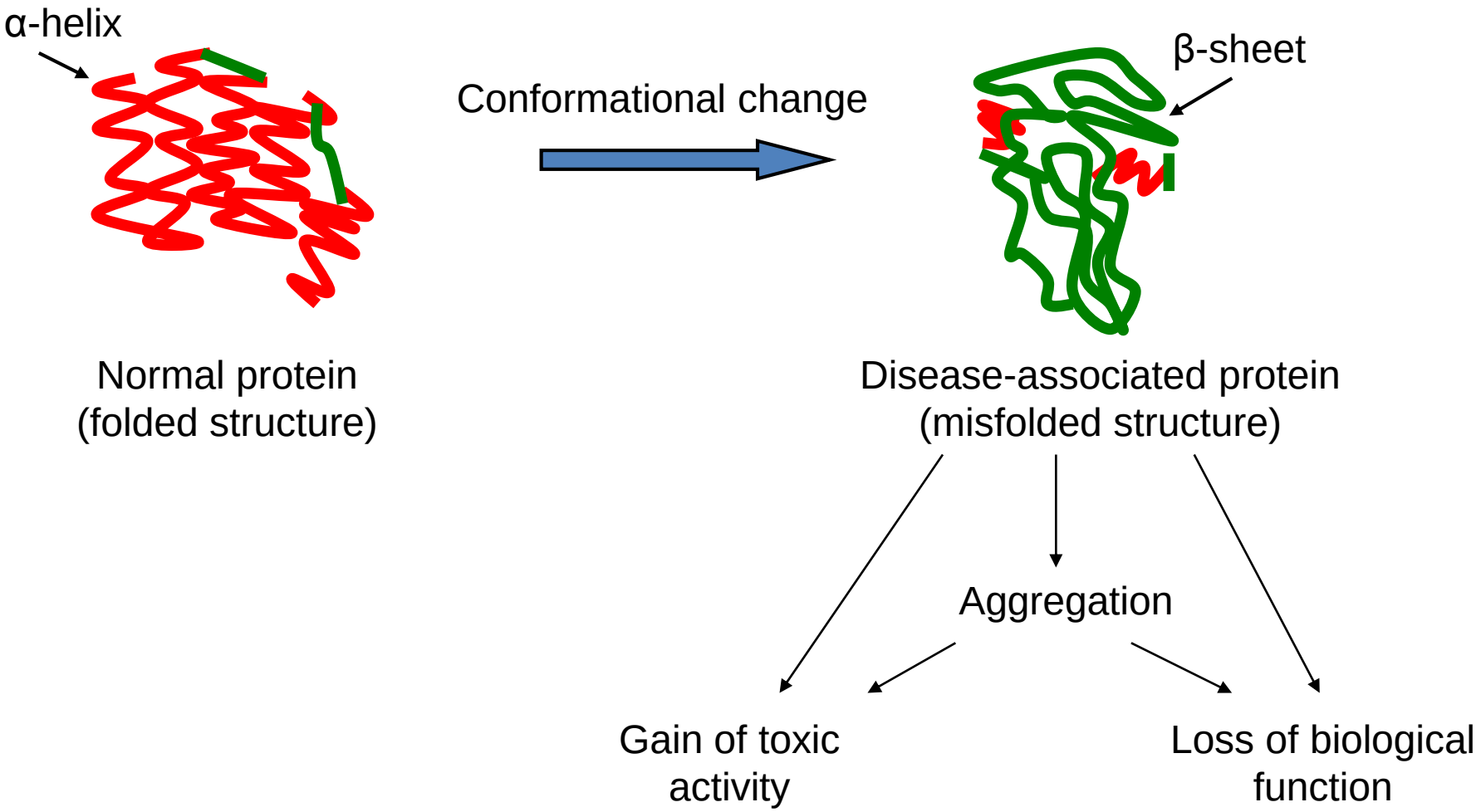
A group of progressive conditions that affect the brain and nervous system of humans and animals and are transmitted by prions

The pathology: vacuolar degeneration, neuronal loss, astrocytosis and amyloid plaque formation

The clinical signs: loss of motor functions (lack of coordination, ataxia, involuntary jerking movements), personality changes, depression, insomnia, confusion, memory problems, dementia, progressive tonic paralysis, death

Definitive diagnostic test: biopsy of brain tissue (histopathological examination and immunostaining for $PrP^{Sc)}$

There is no cure


α-helix
Conformational change
β-sheet
Normal protein
(folded structure)
Disease-associated protein
(misfolded structure)
Aggregation
Gain of toxic
activity
Loss of biological
function

PrP^C	PrP^{Sc}
The normal protein	The abnormal, disease-producing protein
is called PrP^C (for cellular)	is called PrP^{Sc} (for scrapie)
is a transmembrane glycoprotein (neurons, lymphocytes); its function is unknown; it binds Cu^{2+} (regulation its homeostasis)	has the same amino acid sequence (primary structure)
has dominant secundary structure α-helix	has dominant secundary structure β-sheets
is easily soluble	is insoluble
is monomeric and easily digested by proteases	is multimeric and resistant to digestion by proteases
is encoded by a gene designated PRNP located on the chromosome 20	When PrP^{Sc} comes in contact with PrP^C, it converts the PrP^C into more of itself These molecules bind to each other forming aggregates

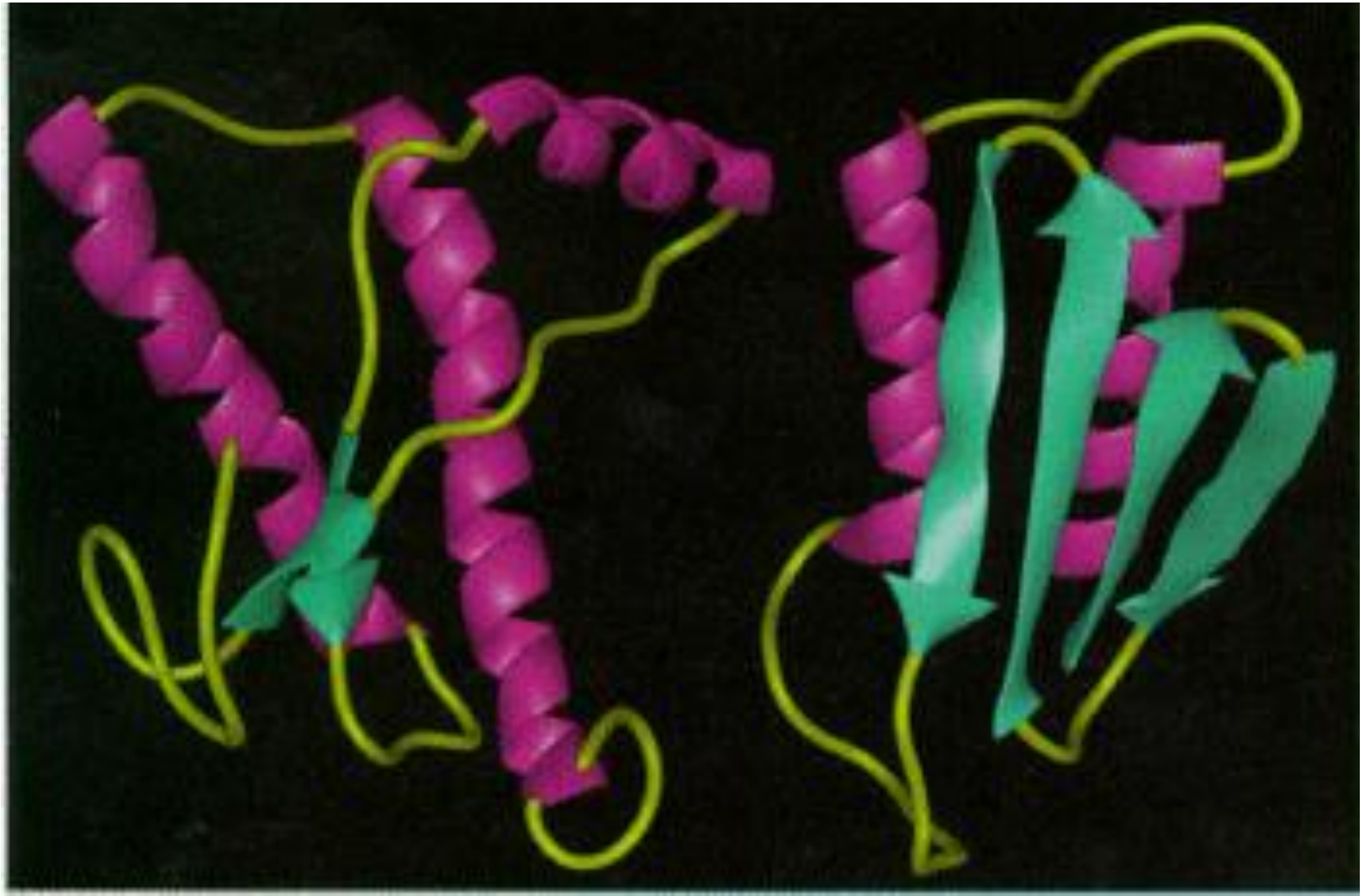
Molecular models of the structure of:

PrP^{C}

Predominantly α-helix (3)

PrP^{Sc}

β-sheets (40%), α-helix (30%)

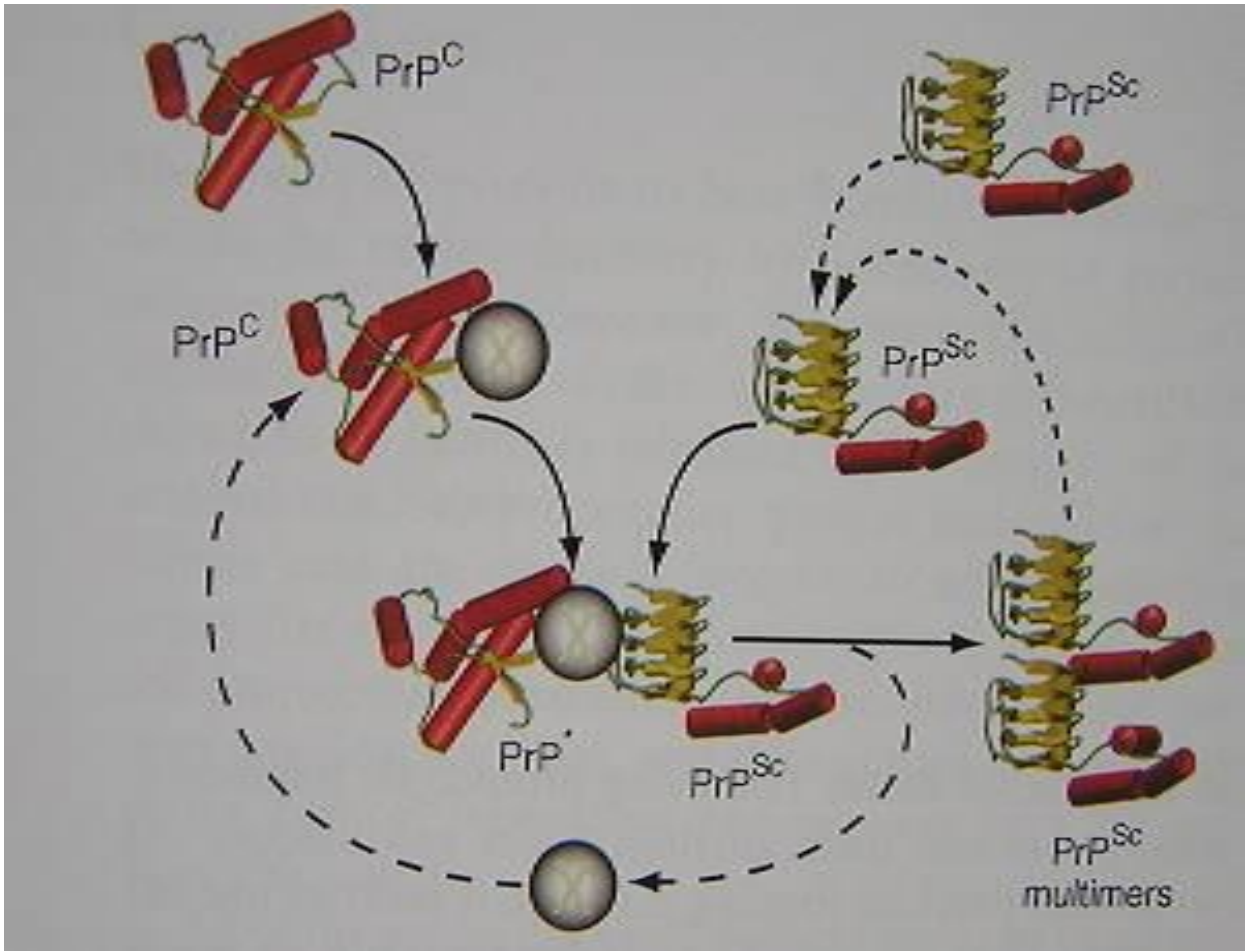


Replication cycle

The presence of an initial PrP^{Sc}: exogenous (infectious forms) or endogenous (inherited or sporadic forms)

This first prion will initiate PrP^{Sc} accumulation by sequentially converting PrP^{C} molecules into PrP^{Sc} in replication cycle

PrP^{Sc} molecules aggregate



Summary

The prions are proteins that carry information for self-reproduction (contradict the central dogma of modern biology)

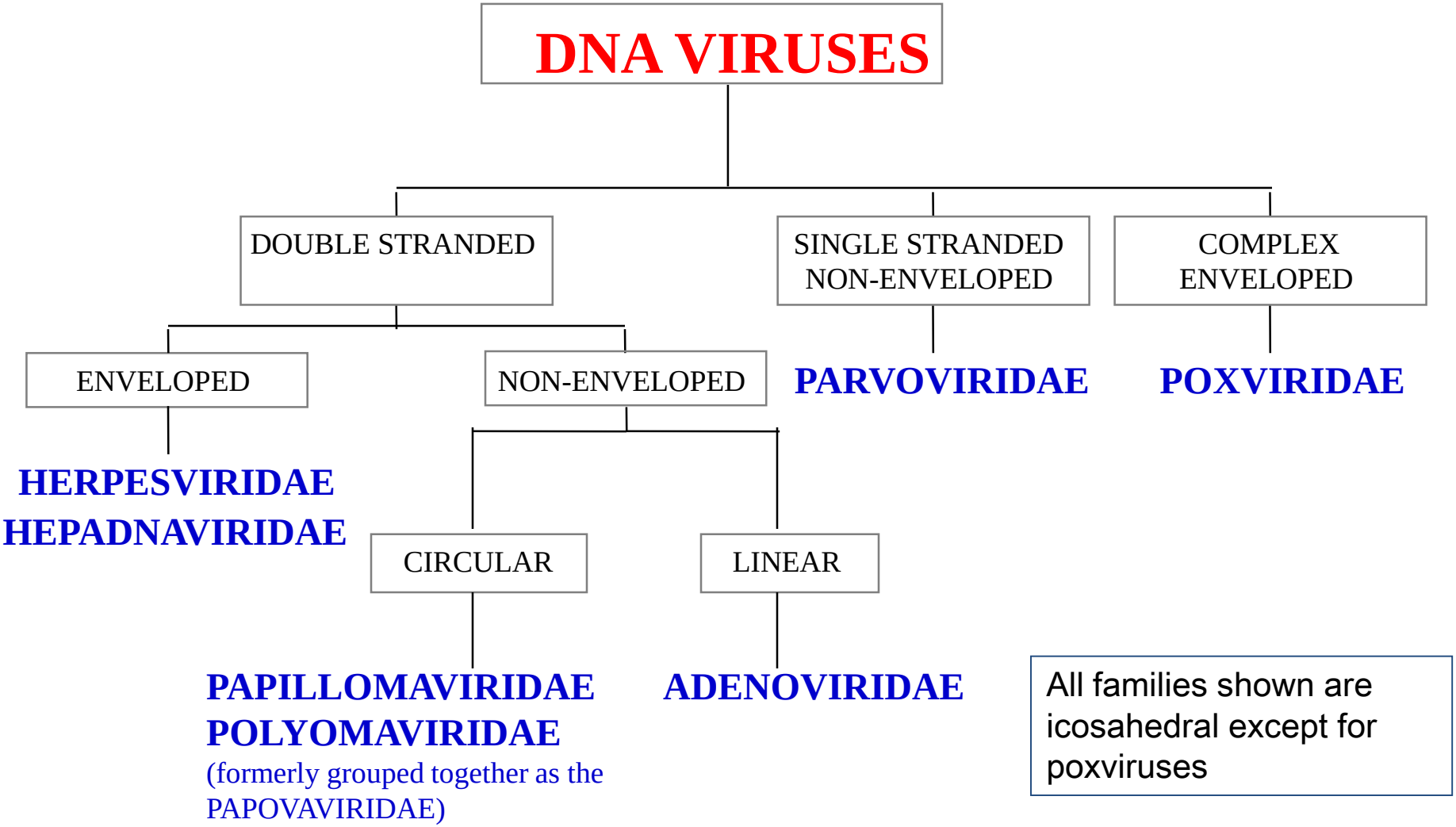
The prions are expressed in cells of healthy humans and animals; their abnormal conformations (PrP^{Sc}) are insoluble, resistent to digestion and aggregate

The PrP^{Sc} attacks the native prion PrP^{C}, changes its conformation into an abnormal form and causes an exponential production of insoluble proteins; they aggregate and form the fibrillar structure

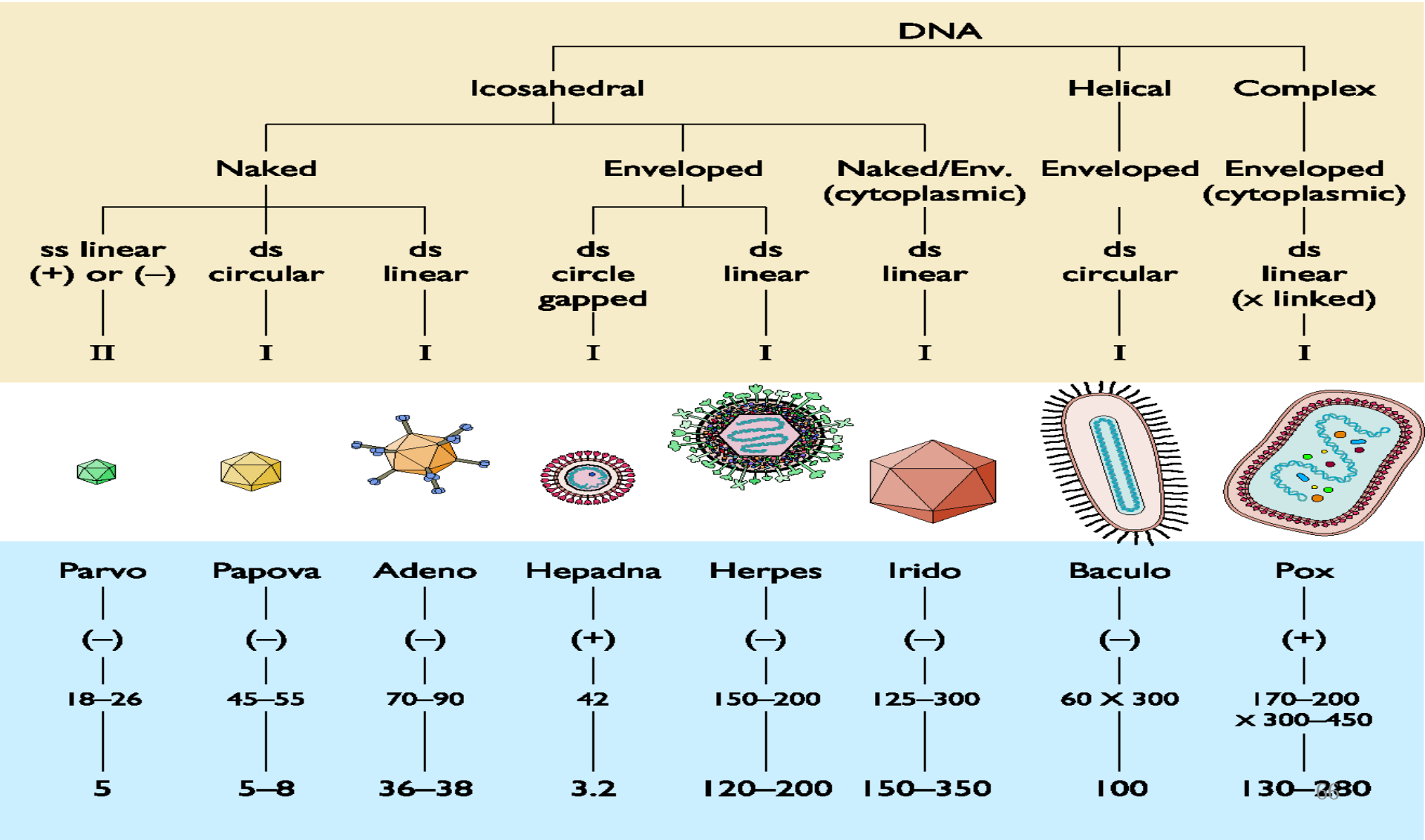
Prion disease are rare fatal degenerative disorders; a portion of them can be transmitted; this mechanism is not clear (e.g. transmision of BSE to human)

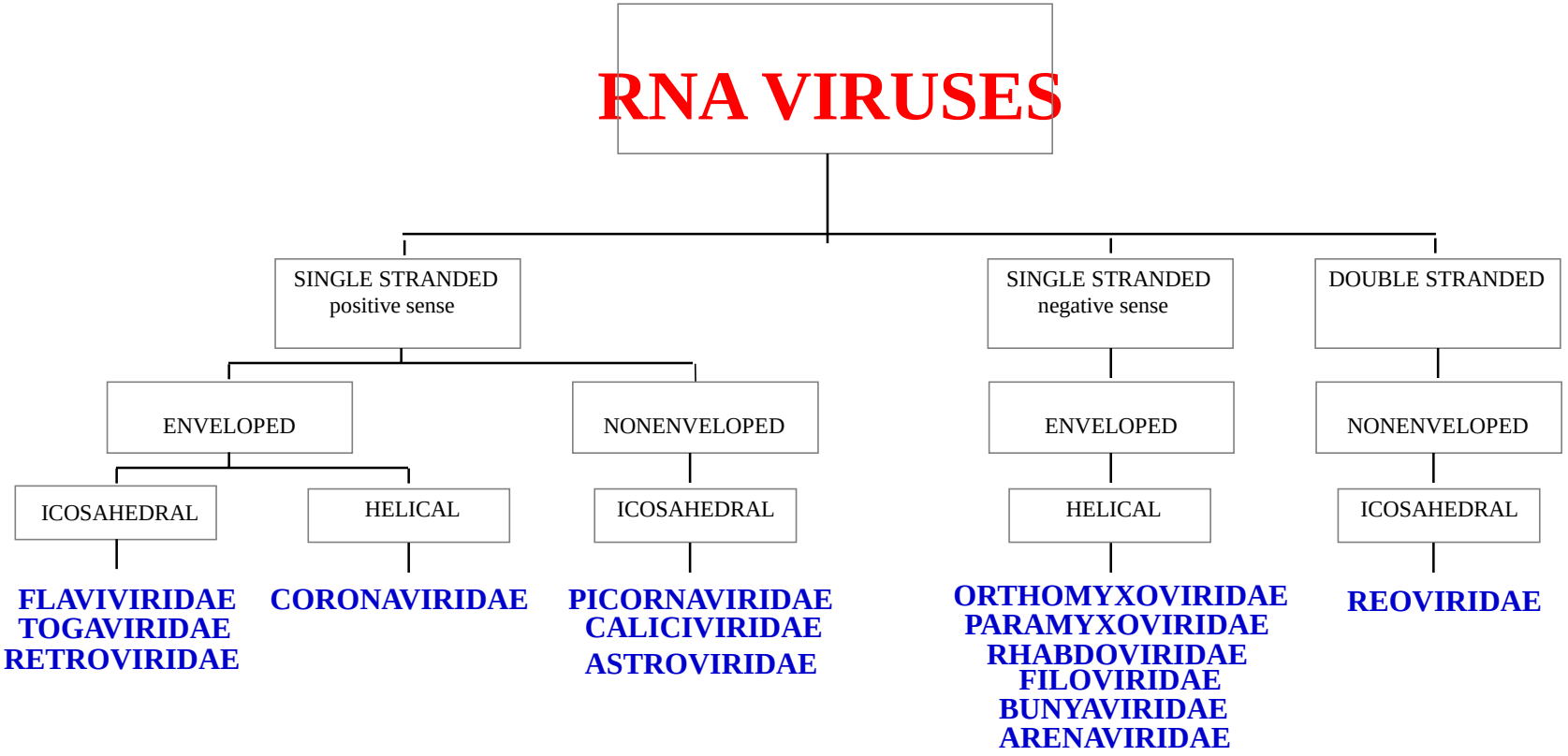
One part of the prion protein can cause apoptosis, or programmed cell death

Prions induce no immune reactions within the human

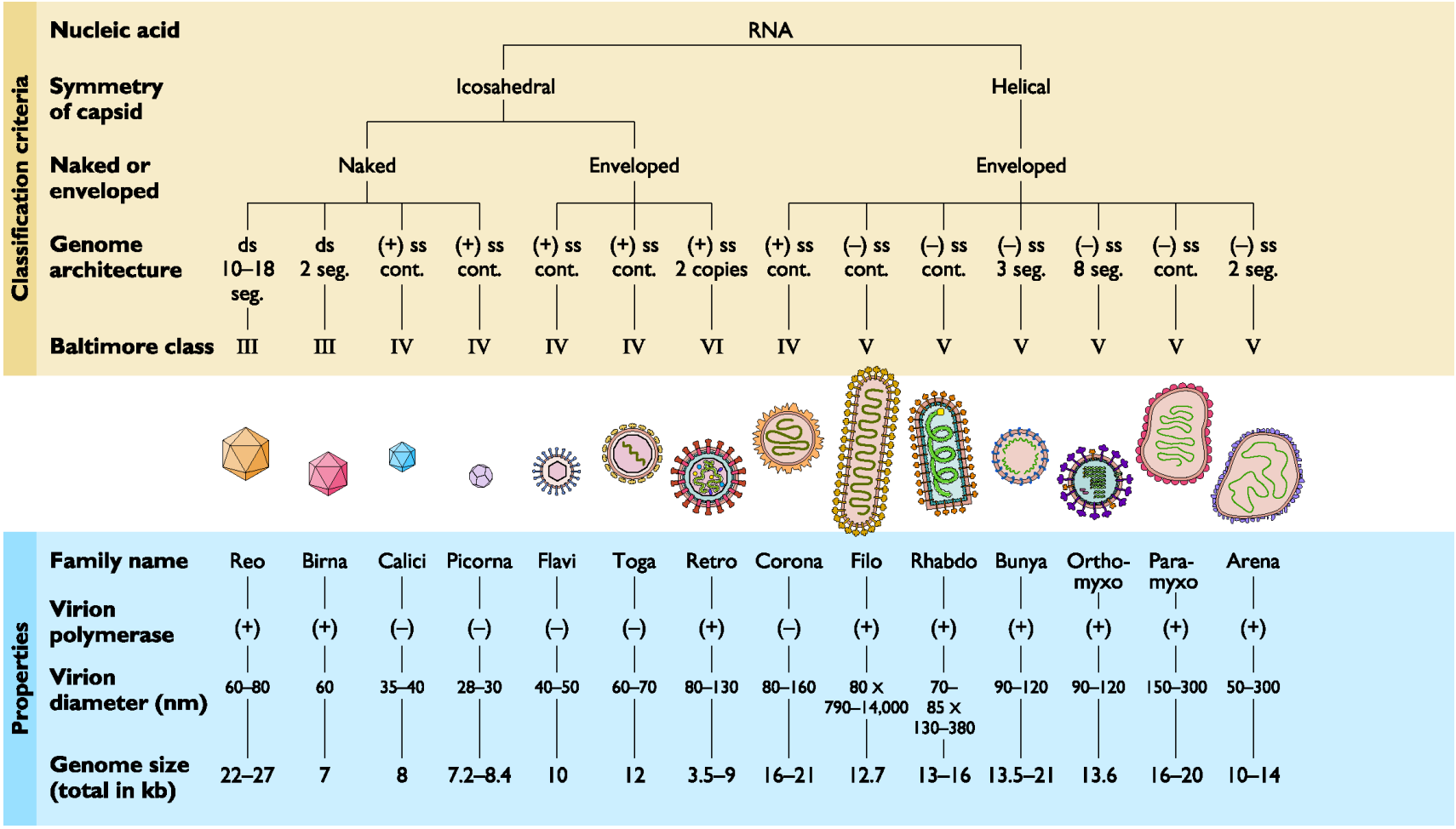

DNA VIRUSES
DOUBLE STRANDED
SINGLE STRANDED NON-ENVELOPED
COMPLEX ENVELOPED
ENVELOPED
NON-ENVELOPED
PARVOVIRIDAE
POXVIRIDAE
HERPESVIRIDAE
HEPADNAVIRIDAE
CIRCULAR
LINEAR
PAPILLOMAVIRIDAE
POLYOMAVIRIDAE
(formerly grouped together as the PAPOVAVIRIDAE)
ADENOVIRIDAE
All families shown are icosahedral except for poxviruses

DNA viruses

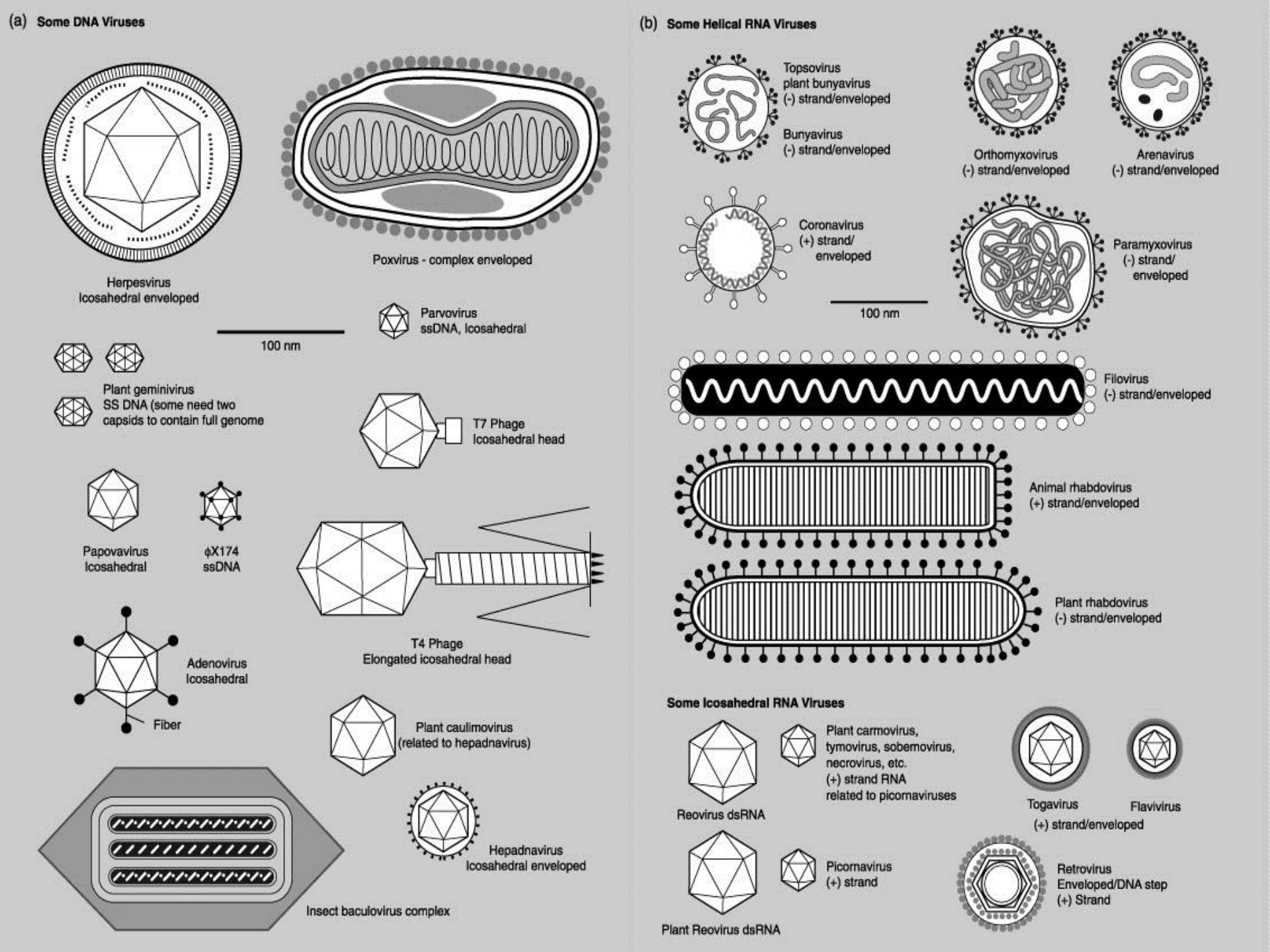

DNA
Icosahedral
Helical
Complex
Naked
Enveloped
Naked/Env. (cytoplasmic)
Enveloped
Enveloped (cytoplasmic)
ss linear (+) or (–)
ds circular
ds linear
ds circle gapped
ds linear
ds linear
ds circular
ds linear (x linked)
II
I
I
I
I
I
I
I
Parvo
Papova
Adeno
Hepadna
Herpes
Irido
Baculo
Pox
(–)
(–)
(–)
(+)
(–)
(–)
(–)
(+)
18–26
45–55
70–90
42
150–200
125–300
60 X 300
170–200 X 300–450
5
5–8
36–38
3.2
120–200
150–350
100
130–280

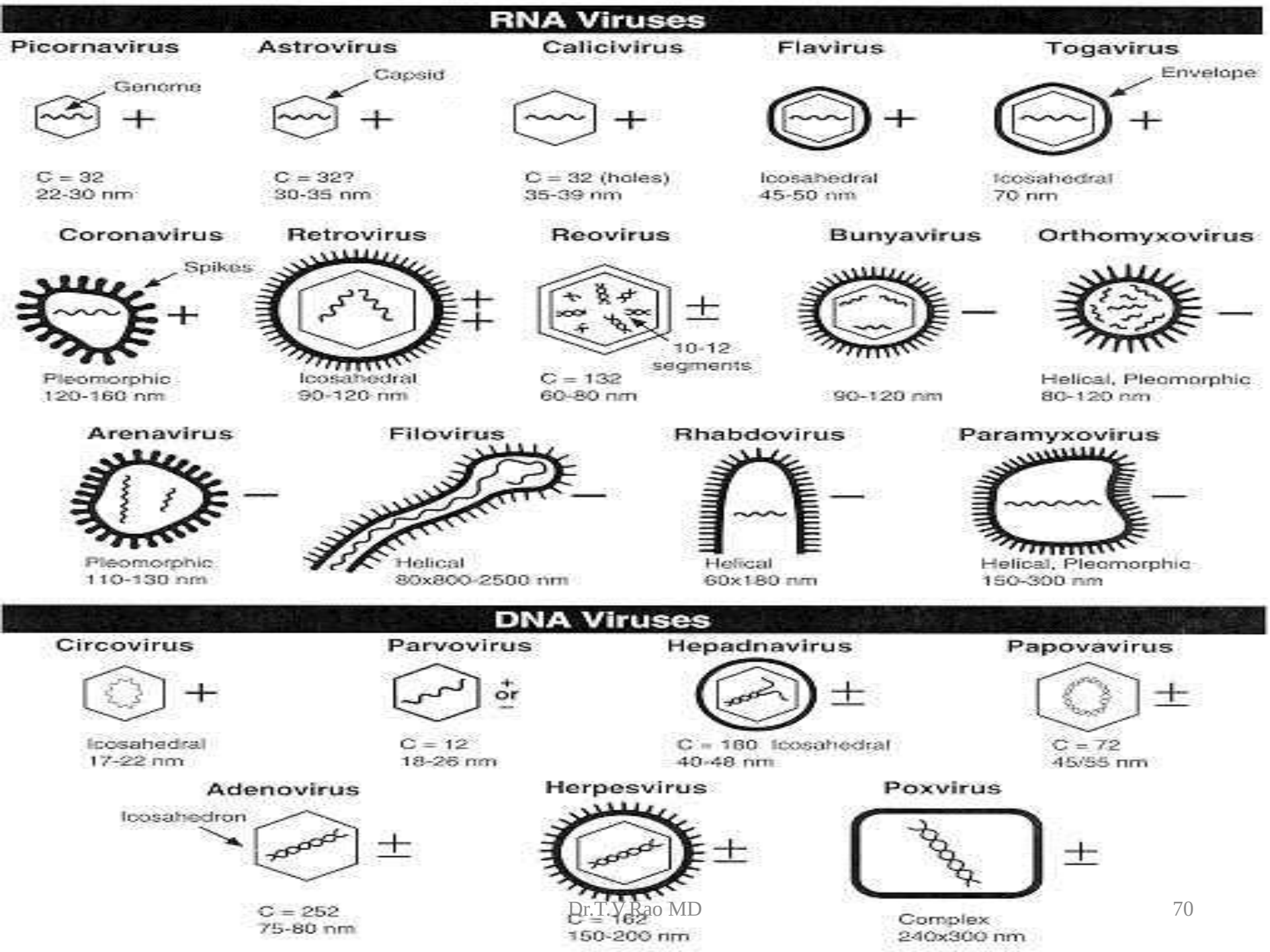

RNA VIRUSES
SINGLE STRANDED positive sense
SINGLE STRANDED negative sense
DOUBLE STRANDED
ENVELOPED
NONENVELOPED
ENVELOPED
NONENVELOPED
ICOSAHEDRAL
HELICAL
ICOSAHEDRAL
HELICAL
ICOSAHEDRAL
FLAVIVIRIDAE
TOGAVIRIDAE
RETROVIRIDAE
CORONAVIRIDAE
PICORNAVIRIDAE
CALICIVIRIDAE
ASTROVIRIDAE
ORTHOMYXOVIRIDAE
PARAMYXOVIRIDAE
RHABDOVIRIDAE
FILOVIRIDAE
BUNYAVIRIDAE
ARENAVIRIDAE
REOVIRIDAE

RNA viruses



From Principles of Virology Flint et al ASM Press


(a) Some DNA Viruses
Herpesvirus
Icosahedral enveloped
Poxvirus - complex enveloped
Parvovirus
ssDNA, Icosahedral
100 nm
Plant geminivirus
SS DNA (some need two
capsids to contain full genome
T7 Phage
Icosahedral head
Papovavirus
Icosahedral
ϕX174
ssDNA
T4 Phage
Elongated icosahedral head
Adenovirus
Icosahedral
Fiber
Plant caulimovirus
(related to hepadnavirus)
Hepadnavirus
Icosahedral enveloped
Insect baculovirus complex
(b) Some Helical RNA Viruses
Topsovirus
plant bunyavirus
(-) strand/enveloped
Bunyavirus
(-) strand/enveloped
Orthomyxovirus
(-) strand/enveloped
Arenavirus
(-) strand/enveloped
Coronavirus
(+) strand/
enveloped
100 nm
Paramyxovirus
(-) strand/
enveloped
Filovirus
(-) strand/enveloped
Animal rhabdovirus
(+) strand/enveloped
Plant rhabdovirus
(-) strand/enveloped
Some Icosahedral RNA Viruses
Reovirus dsRNA
Plant carmovirus,
tymovirus, sobemovirus,
necrovirus, etc.
(+) strand RNA
related to picornaviruses
Togavirus
Flavivirus
(+) strand/enveloped
Picornavirus
(+) strand
Retrovirus
Enveloped/DNA step
(+) Strand
Plant Reovirus dsRNA


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
Circovirus
Icosahedral
17-22 nm
Parvovirus
or
C = 12
18-26 nm
Hepadnavirus
C = 180 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

BASIC STEPS IN VIRAL LIFE CYCLE

- ADSORPTION
- PENETRATION
- UNCOATING AND ECLIPSE
- SYNTHESIS OF VIRAL NUCLEIC ACID AND PROTEIN
- ASSEMBLY
- RELEASE