Virus Classification, Replication, Transmission, & Pathogenesis

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Characteristics of Viruses

1. Tiny infectious particle

   – Nucleic acid (RNA/DNA) + protective protein coat (capsid)

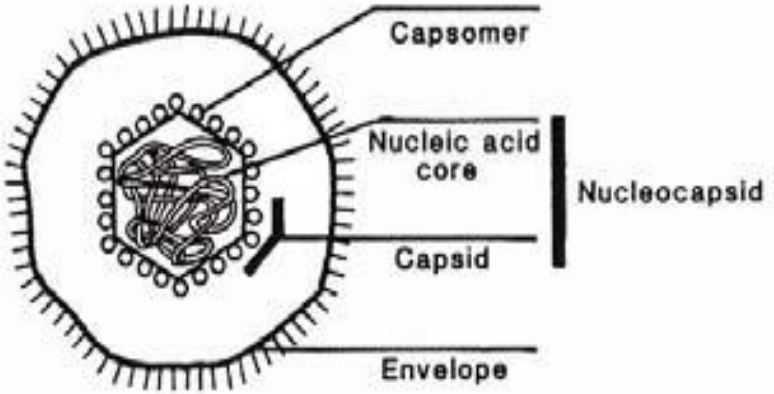
1. Viruses not cells – smaller than cells.
2. Structurally simple
3. Intracellular parasites (only replicate inside a living cell)
4. Viruses found in bacteria, plants, insects, fish etc.

6. Virions - non-living particles

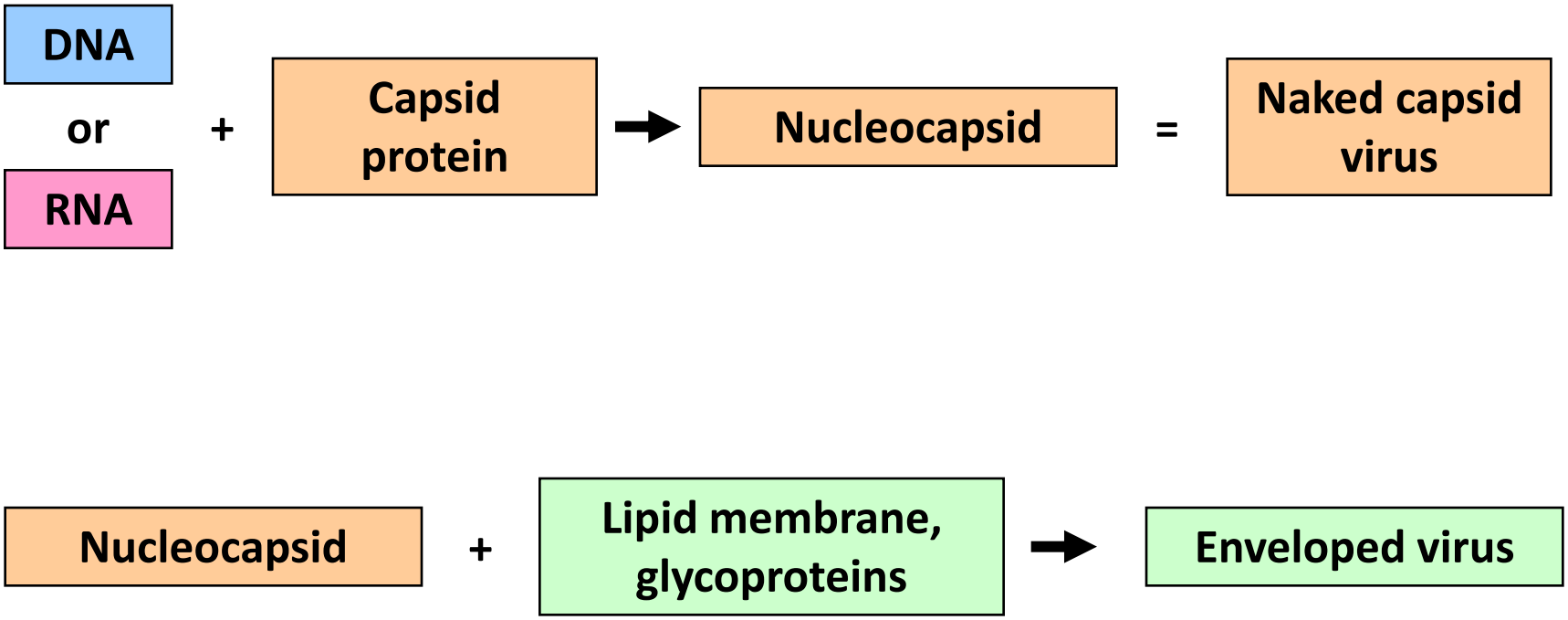
   - Infect an appropriate host cell in order to replicate.

Structure of Viruses

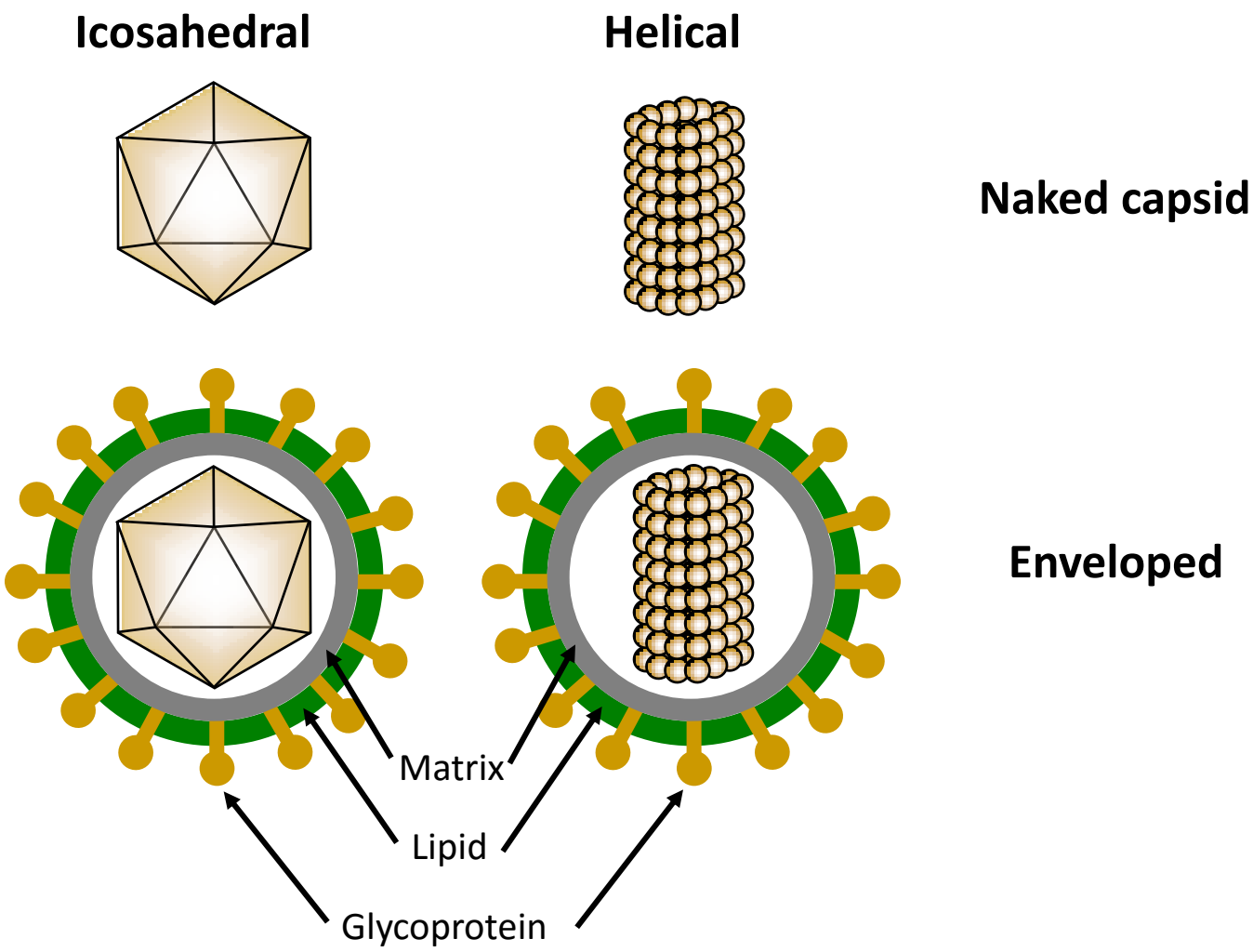
1. **Core** - genetic material
   - RNA or DNA, Not both
2. Protein coat or **capsid**
   – Protects viral genome
   - Core + capsid = **nucleocapsid**
3. Nucleocapsid
   – either **icosahedral** or **helical** symmetry
4. Many animal virus particles are surrounded by a lipoprotein **envelope**



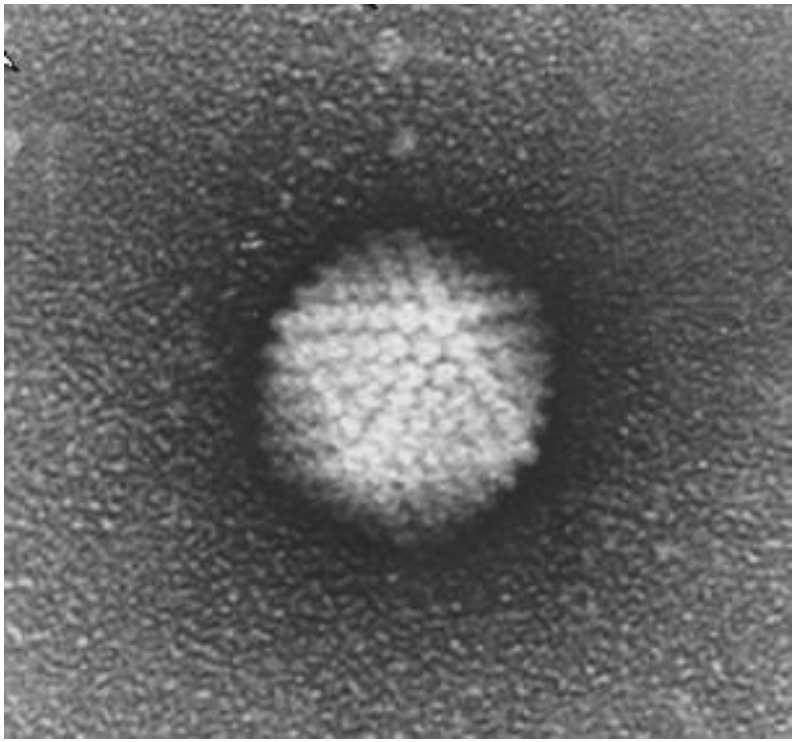
Basic virus structure



Capsid symmetry

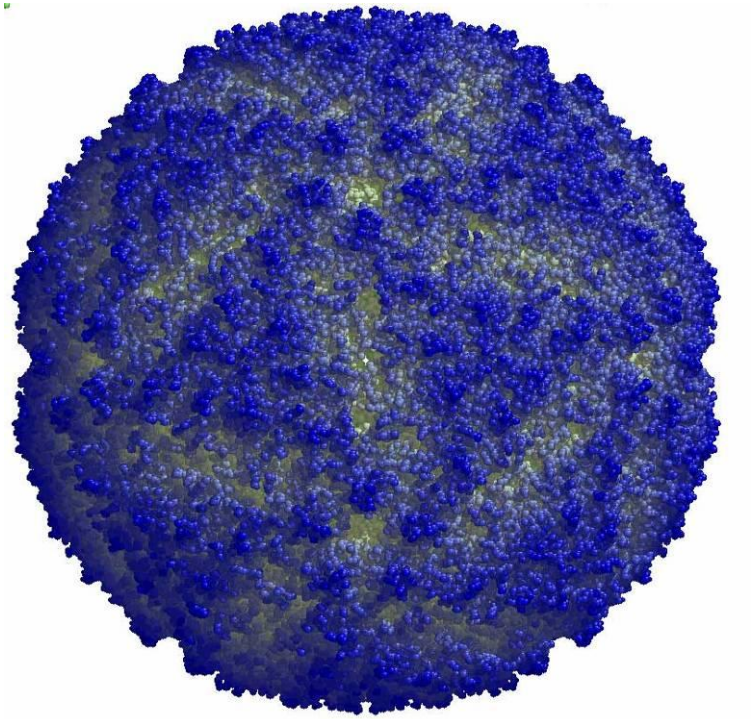


Icosahedral naked capsid viruses



http://www.ncbi.nlm.nih.gov/ICTVdb/Images/Ackerman/Animalvi/Adenovir/799-16.htm

Adenovirus
Electron micrograph



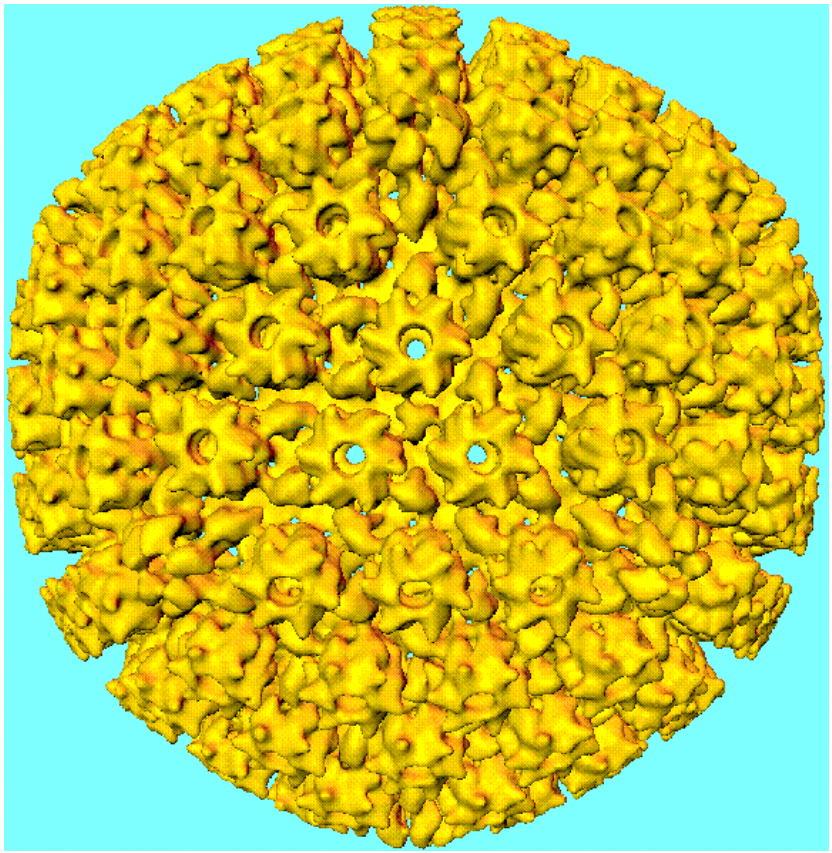
http://virology.wisc.edu/virusworld/ICTV8/fmd-foot-and-mouth-ictv8.jpg

Foot and mouth disease virus
Crystallographic model

Icosahedral enveloped viruses

http://web.uct.ac.za/depts/mmi/stannard/emimages.html

Herpes simplex virus
Electron micrograph



http://virology.wisc.edu/virusworld/images/herpescapsid.GIF

Herpes simplex virus
Nucleocapsid cryoEM model

Properties of naked capsid viruses

- Capsid is resistant to
  - Drying
  - Heat
  - Detergents
  - Acids
  - Proteases
- Consequences
  - Can survive in the gastrointestinal tract
  - Retain infectivity on drying
  - Survive well on environmental surfaces
  - Spread easily via fomites
  - Must kill host cells for release of mature virus particles

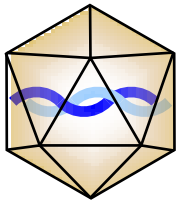
Adapted from Murray, P.R. Rosenthal K.S., Pfaller, M.A. (2005) Medical Microbiology, 5th edition, Elsevier Mosby, Philadelphia, PA , Box 6-4

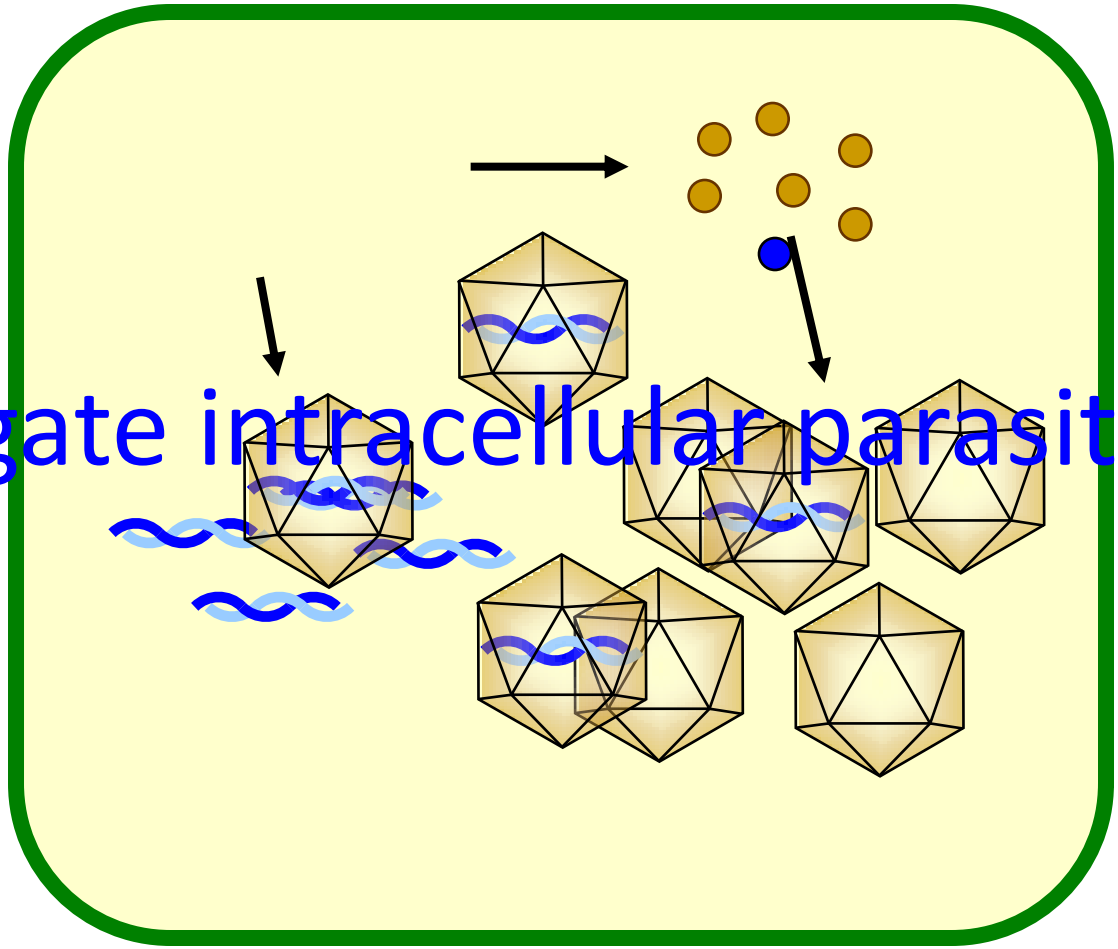
Properties of enveloped viruses

- Envelope is sensitive to
  - Drying
  - Heat
  - Detergents
  - Acid
- Consequences
  - Must stay wet during transmission
  - Transmission in large droplets and secretions
  - Cannot survive in the gastrointestinal tract
  - Do not need to kill cells in order to spread

Adapted from Murray, P.R. Rosenthal K.S., Pfaller, M.A. (2005) Medical Microbiology, 5th edition, Elsevier Mosby, Philadelphia, PA Box 6-5

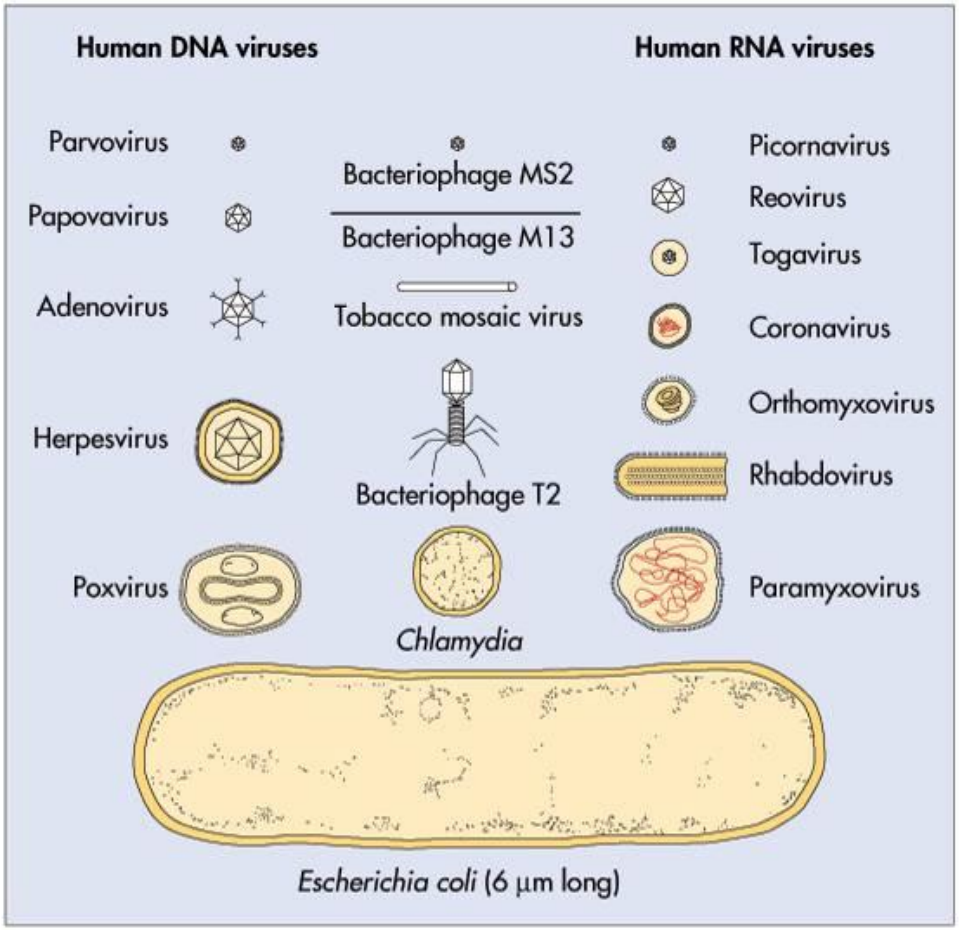
Viruses defined



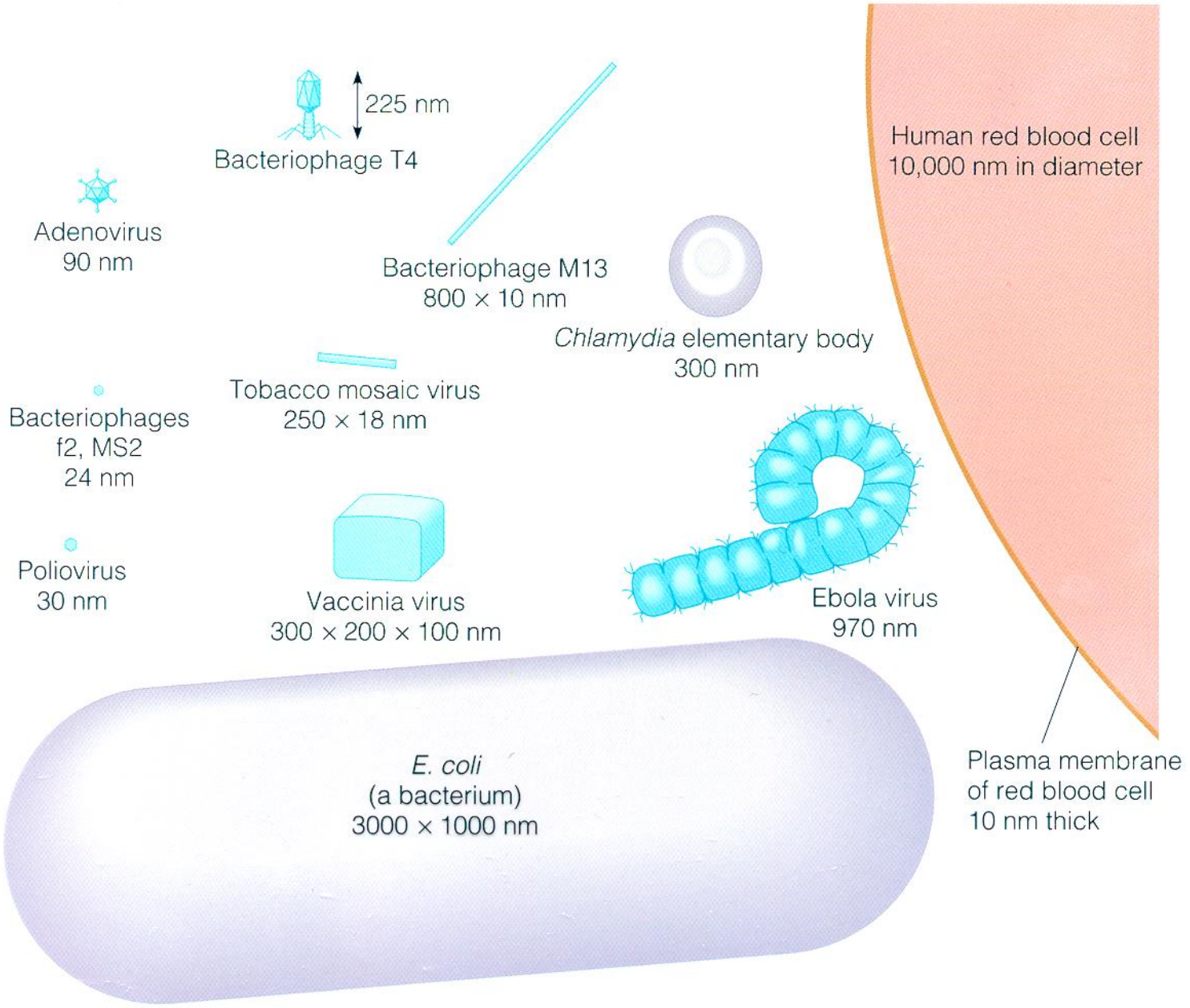


Obligate intracellular parasites

Structures compared



From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 6-4.


225 nm
Bacteriophage T4
Adenovirus
90 nm
Bacteriophage M13
800 × 10 nm
Human red blood cell
10,000 nm in diameter
Chlamydia elementary body
300 nm
Tobacco mosaic virus
250 × 18 nm
Bacteriophages
f2, MS2
24 nm
Poliovirus
30 nm
Vaccinia virus
300 × 200 × 100 nm
Ebola virus
970 nm
E. coli
(a bacterium)
3000 × 1000 nm
Plasma membrane
of red blood cell
10 nm thick

Classification of viruses that cause human diseases

Two types:

1. Traditional
2. Baltimore (new)

Classification of Human Viruses

1. Traditional – based on:

– Disease produced (e.g. herpes, yellow fever, etc)

- Part of the body affected (e.g. hepatitis virus; viral enteritis)
- Location where disease first seen (e.g. Ross River virus, Ebola virus)
- Type of nucleic acid (e.g. DNA viruses, RNA viruses)
- not very useful.

Traditional Classification of Viruses

- **Family** – “viridae”

  e.g. Herpesviridae
- **Subfamily/Genus** – “virinae”

  e.g. Alpha Herpesvirinae
- **Species** – “virus”

  e.g. Herpes Simplex Virus (HSV)

DNA virus family – Virion Properties

Family	Diameter	Symmetry	Nature
Parvoviridae	20 nm	Icosahedral	ss DNA, linear
Papovaviridae	45-55 nm	Icosahedral	dsDNA, circular
Adenoviridae	70 nm	Icosahedral	dsDNA, linear
Herpesviridae	150 nm	Icosahedral	dsDNA, linear
Poxviridae	250 nm	Complex	dsDNA, linear
Hepadnaviridae	42 nm	Icosahedral	dsDNA, circular

RNA virus family – Virion Properties

Family	Diameter	Symmetry	Nature
Picornaviridae	25-30 nm	Icosahedral	ssRNA (+)
Caliciviridae	35-40 nm	Icosahedral	ssRNA (+)
Astroviridae	28-30 nm	Icosahedral	ssRNA (+)
Togaviridae	60-70 nm	Icosahedral	ssRNA (+)
Flaviviridae	40-50 nm	Icosahedral	ssRNA (+)
Coronaviridae	75-160 nm	Helical	ssRNA (-)
Paramyxoviridae	150-300 nm	Helical	ssRNA (-)
Rhabdoviridae	180x75 nm	Helical	ssRNA (-)
Filoviridae	850x80 nm	Helical	ssRNA (-)
Orthomyxoviridae	80-120 nm	Helical	ssRNA (-), 7-8 seg
Arenaviridae	110-130 nm	Helical	ssRNA (-), 2 seg
Bunyaviridae	90-120 nm	Helical	ssRNA (-), 3 seg
Reoviridae	60-80 nm	Icosahedral	dsRNA 10-12 seg
Retroviridae	80-100 nm	Icosahedral	ssRNA (+)

Human Herpesviruses

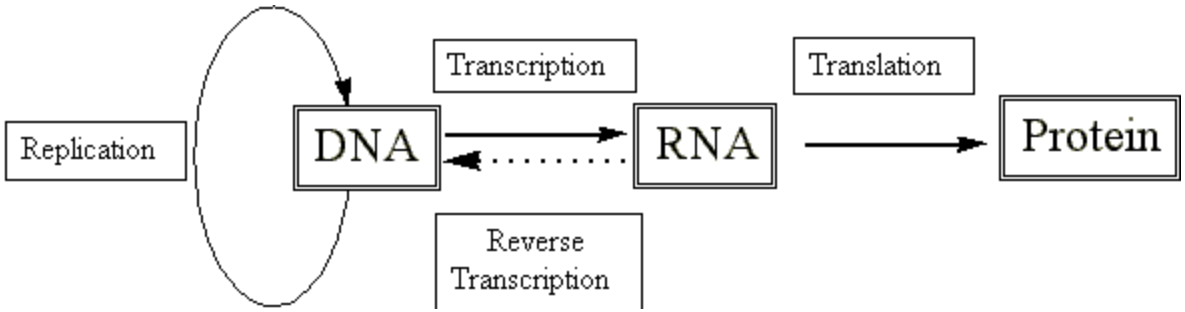
Virus	Subfamily	Disease	Site of Latency
Herpes Simplex Virus I	α	Orofacial lesions	Sensory Nerve Ganglia
Herpes Simplex Virus II	α	Genital lesions	Sensory Nerve Ganglia
Varicella Zoster Virus	α	Chicken Pox Recurs as Shingles	Sensory Nerve Ganglia
Cytomegalovirus	β	Microcephaly/Mono	Lymphocytes
Human Herpesvirus 6	β	Roseola Infantum	CD4 T cells
Human Herpesvirus 7	β	Roseola Infantum	CD4T cells
Epstein-Barr Virus	γ	Infectious Mono	B lymphocytes, salivary
Human Herpesvirus 8	γ	Kaposi's Sarcoma	Kaposi's Sarcoma Tissue

Classification of viruses that cause human diseases

2. Baltimore Classification – based on:

- Type of nucleic acid
- Method of replication

Central Dogma (Information flow)



Host cell can:

1. Copy RNA from DNA (transcription) – RNA polymerase II
2. Copy DNA from DNA (replication) – DNA polymerase
3. **Cannot** copy DNA from RNA

Baltimore classification

- **Central theme**

  – all viruses must generate (+) sense mRNA

  mRNA -> proteins -> replication

- **Precise mechanism of replication may differ**
- **7 groups of virus genomes**

  - Replication strategy dependent on genome type

- **By convention**:

  - Top strand of coding DNA written in 5’-3’ direction (+ve sense)

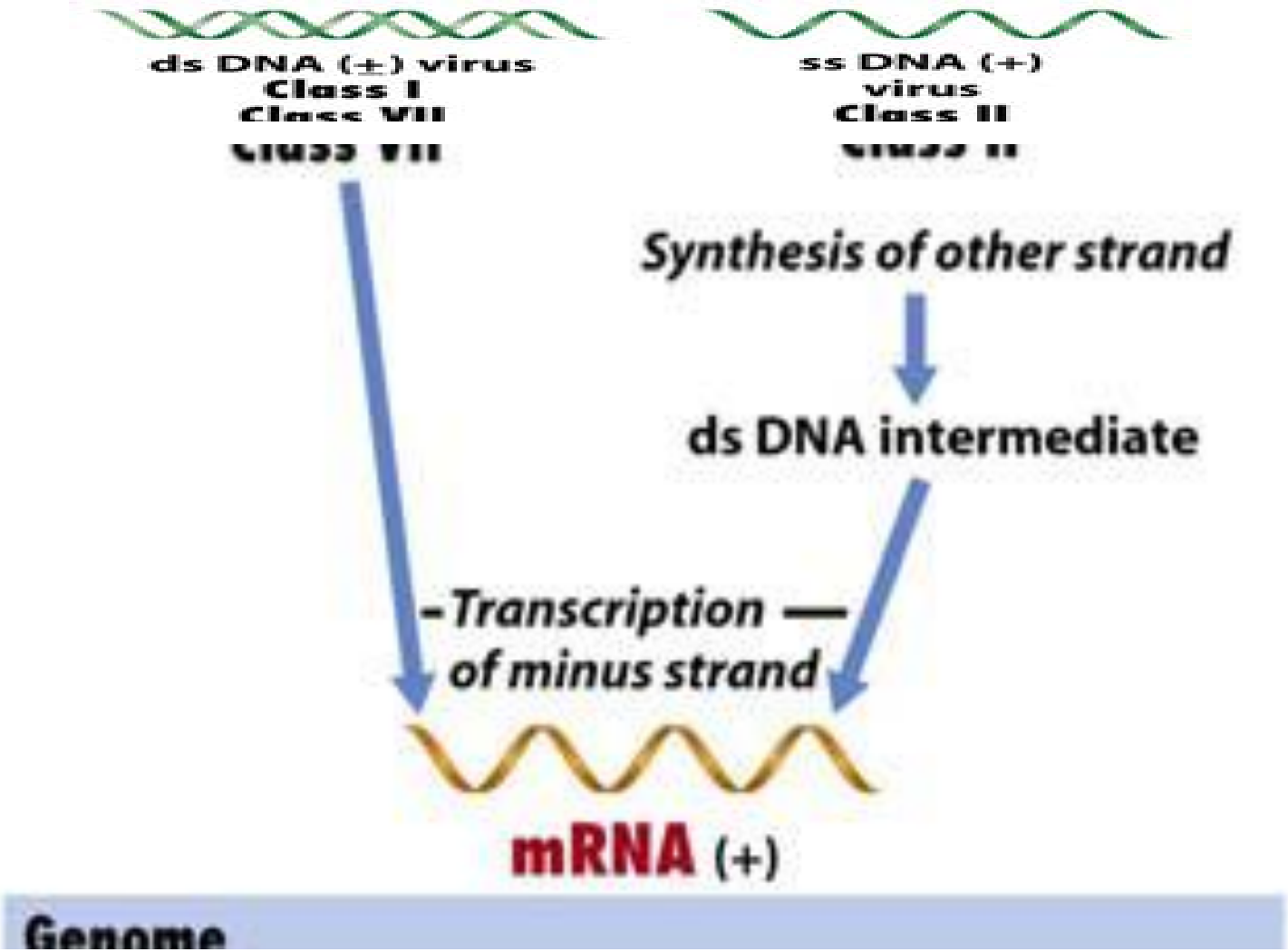
  - mRNA is also +ve sense

Baltimore classification of viruses

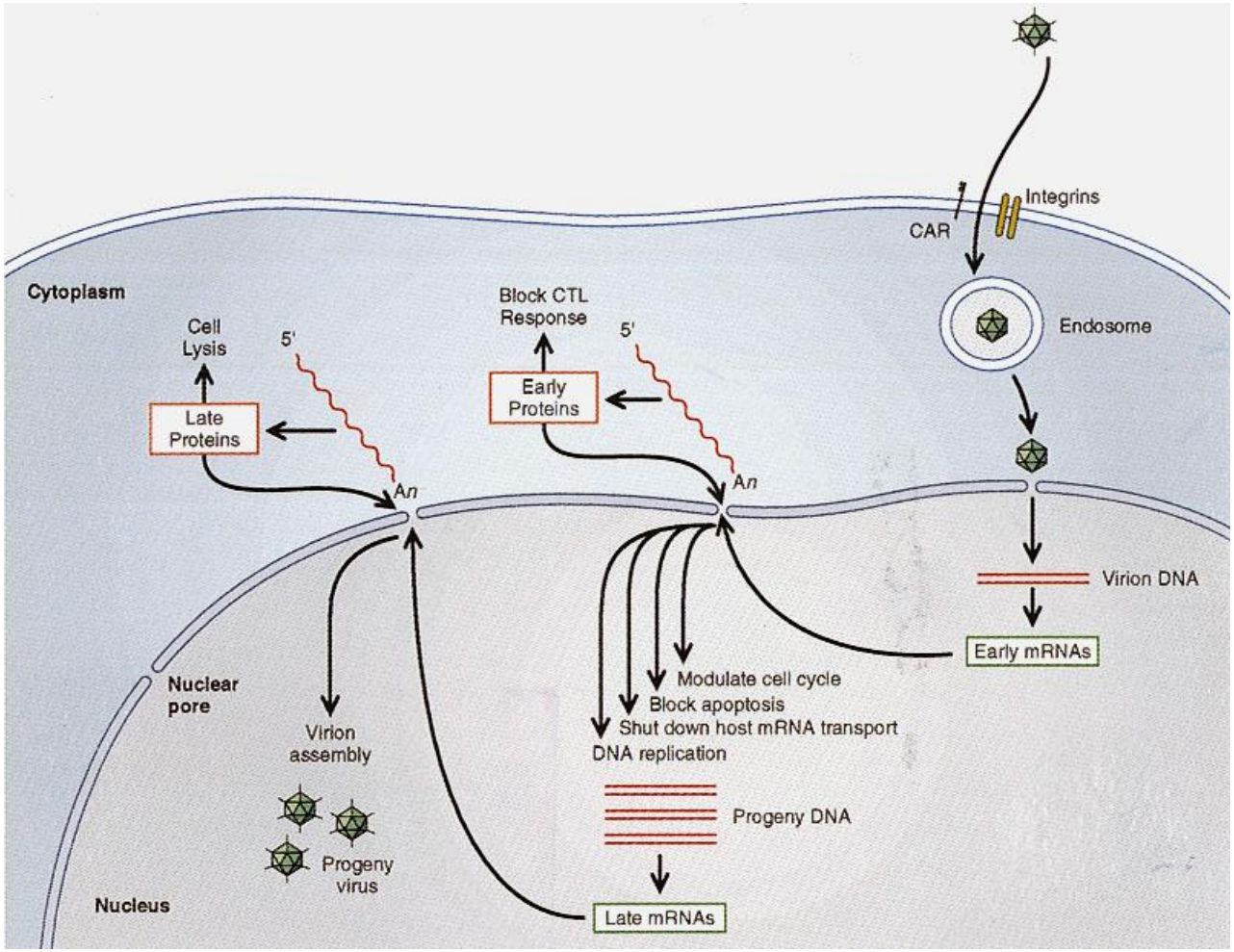
Seven classes:

1. dsDNA viruses
2. ssDNA viruses
3. dsRNA viruses
4. (+) sense ssRNA viruses
5. (-) sense ssRNA viruses
6. (+) sense ssRNA with DNA intermediate
7. dsDNA with RNA intermediate

Formation of mRNA by DNA viruses



Adenovirus replication cycle



(From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Fig. 67-5.)

The growth cycle of Hepatitis B virus

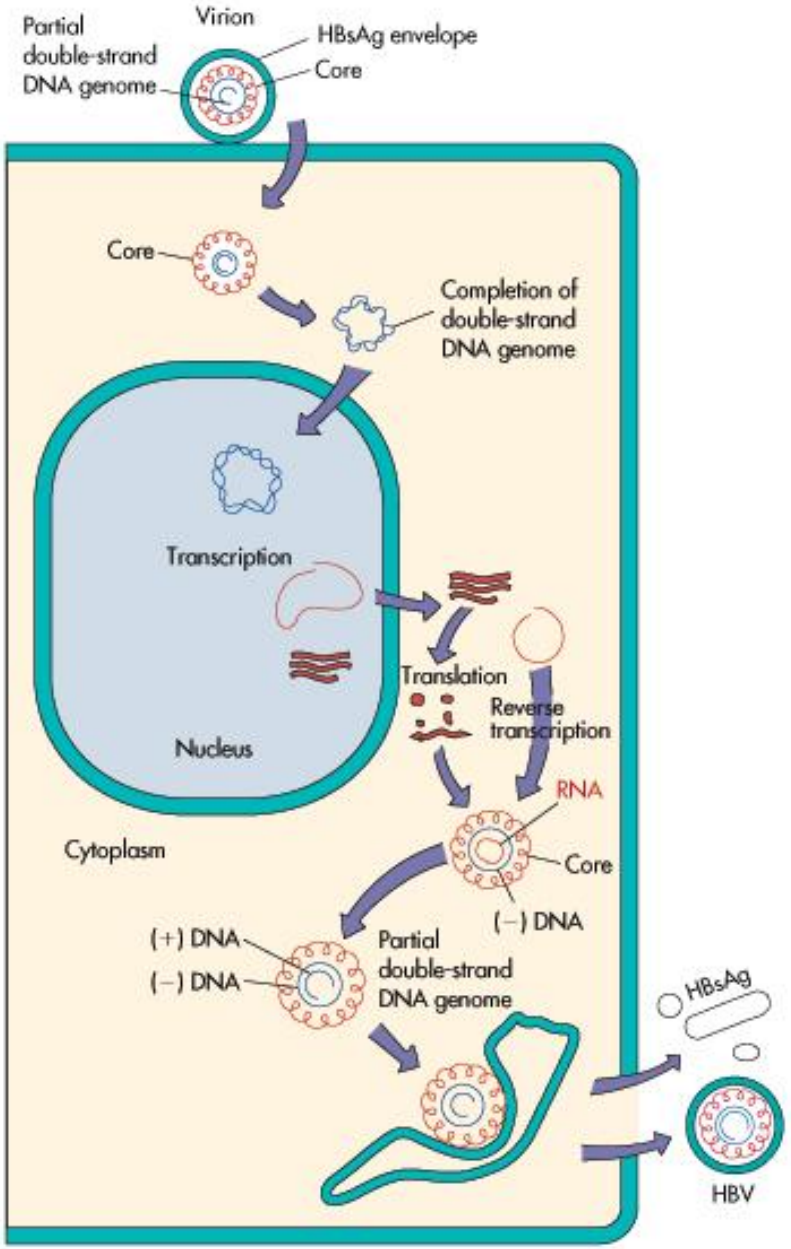
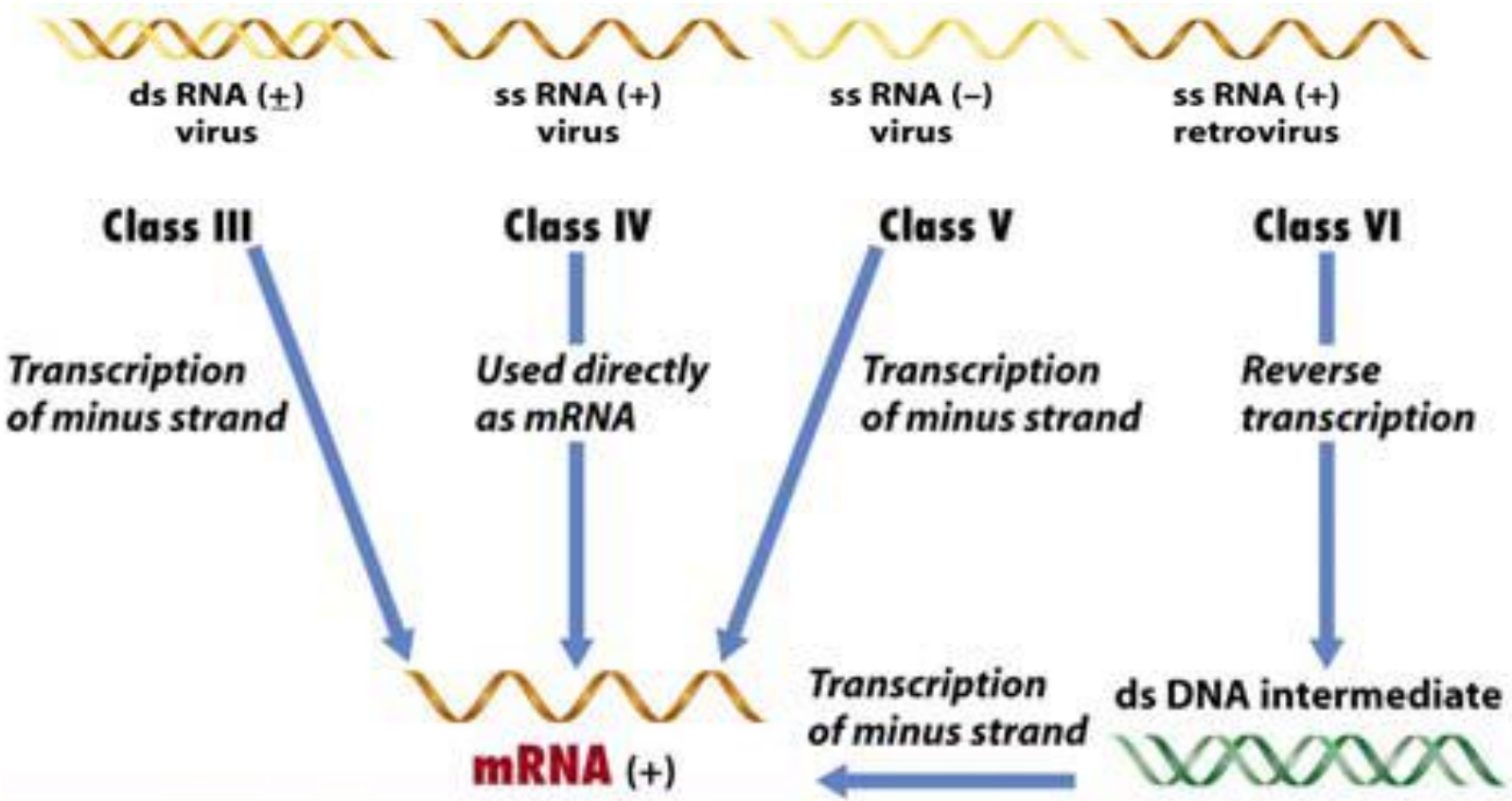


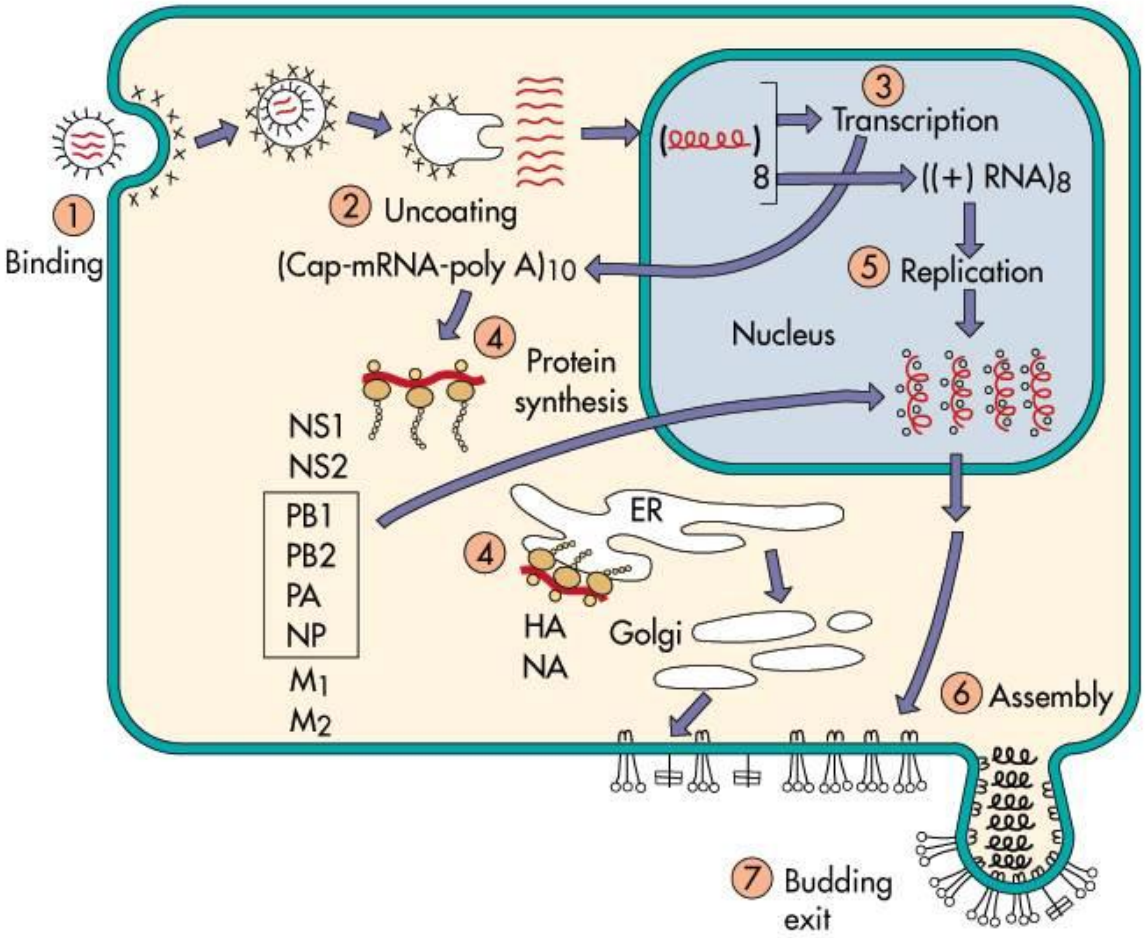
Figure 66-5

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 66, published by Mosby Philadelphia,,

Formation of mRNA by RNA viruses

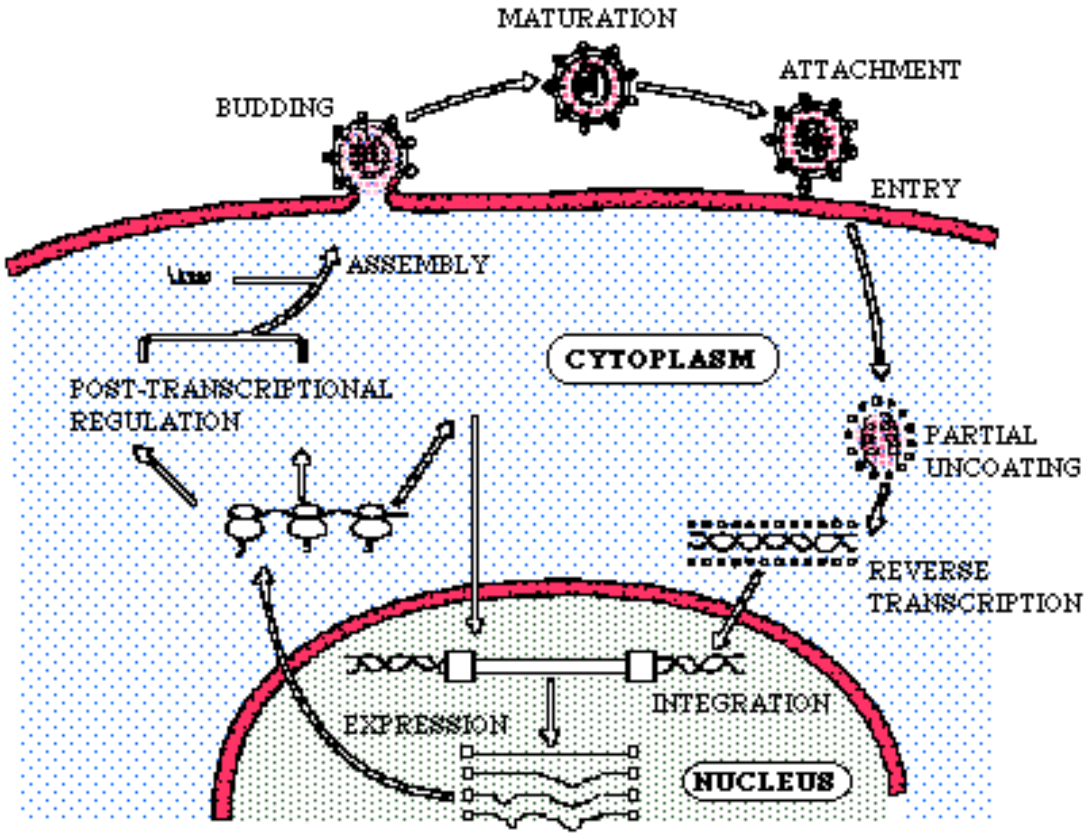


Influenza replication



From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Figure 60-2.

Retroviruses - Replication



Host range and tissue specificity (tropism)

1. A particular virus can usually only infect a particular species or host (**host range) or even only a particular cell or tissue in that host (tissue tropism or specificity).**
2. Specificity is controlled by the correspondence between viral attachment molecules (ligands) and host cell receptors

Examples of host and tissue specificity - Viruses that infect:

(a) Only humans – measles, mumps, chickenpox

(b) More than one species – polio (humans & non-human primates);

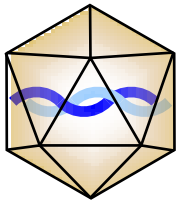
(c) Cross species barriers – zoonotic viruses – e.g. rabies – wild animals & humans)

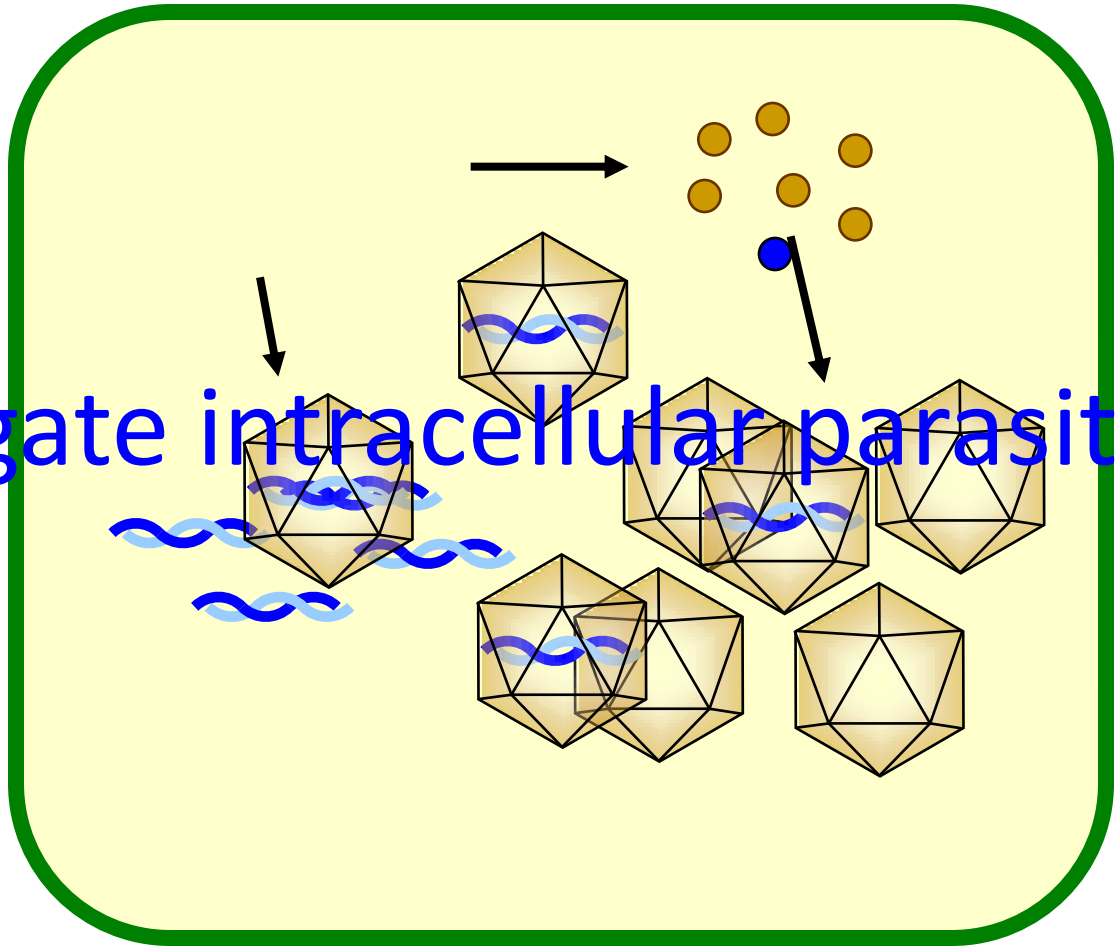
(d) Demonstrate strong tissue tropism – e.g. polio virus – muscle cells and neuronal cells;

Replication of animal viruses

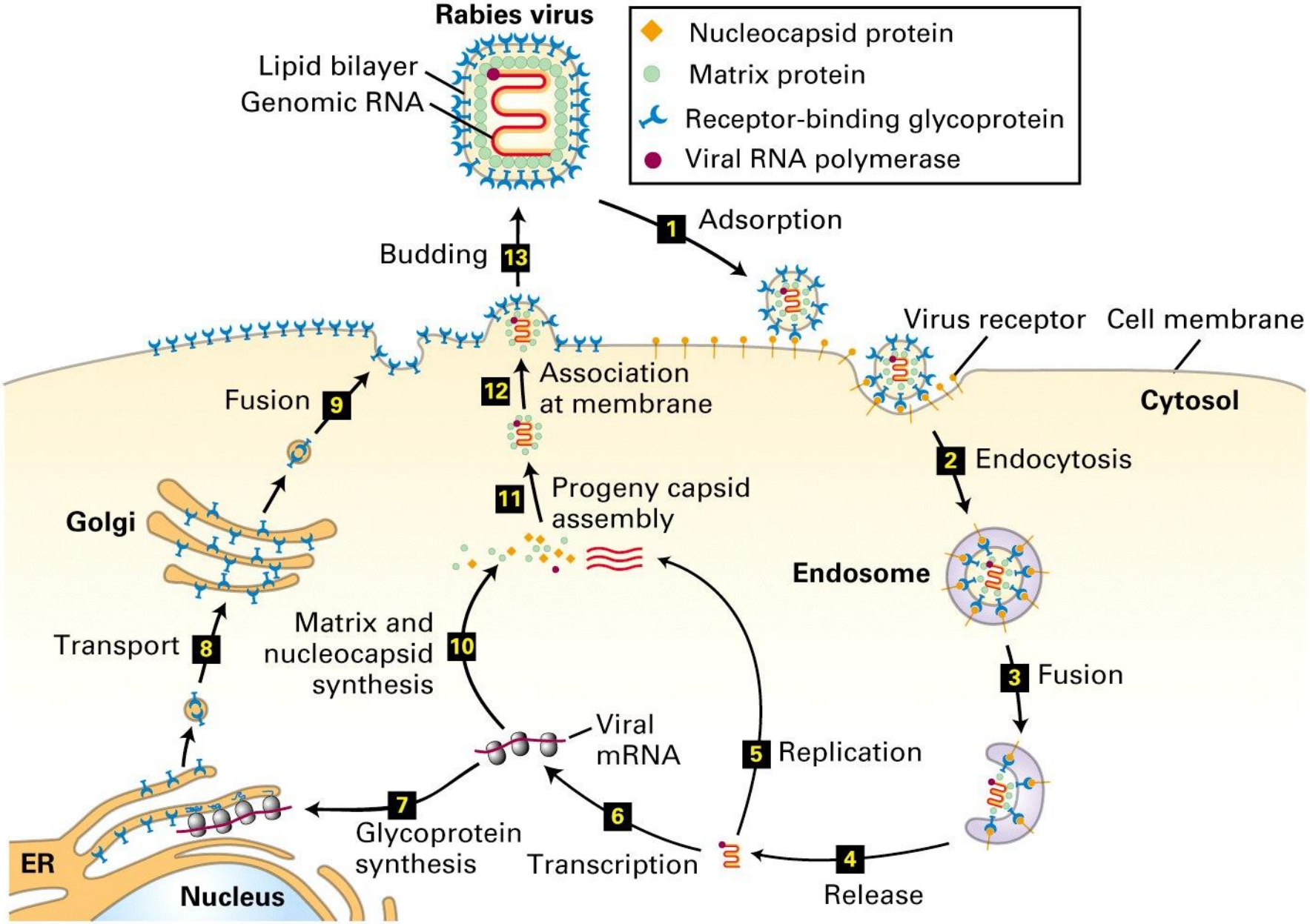
1. **Penetration**
   - endocytosis or
   - fusion
2. **Uncoating**
   - viral or host enzymes
3. **Replication/Biosynthesis**
   - Production of nucleic acid and proteins
4. **Maturation**
   - Nucleic acid and capsid proteins assembly
5. **Release**
   - By budding (enveloped viruses)
   - Rupture/lysis (naked viruses)

Viruses defined

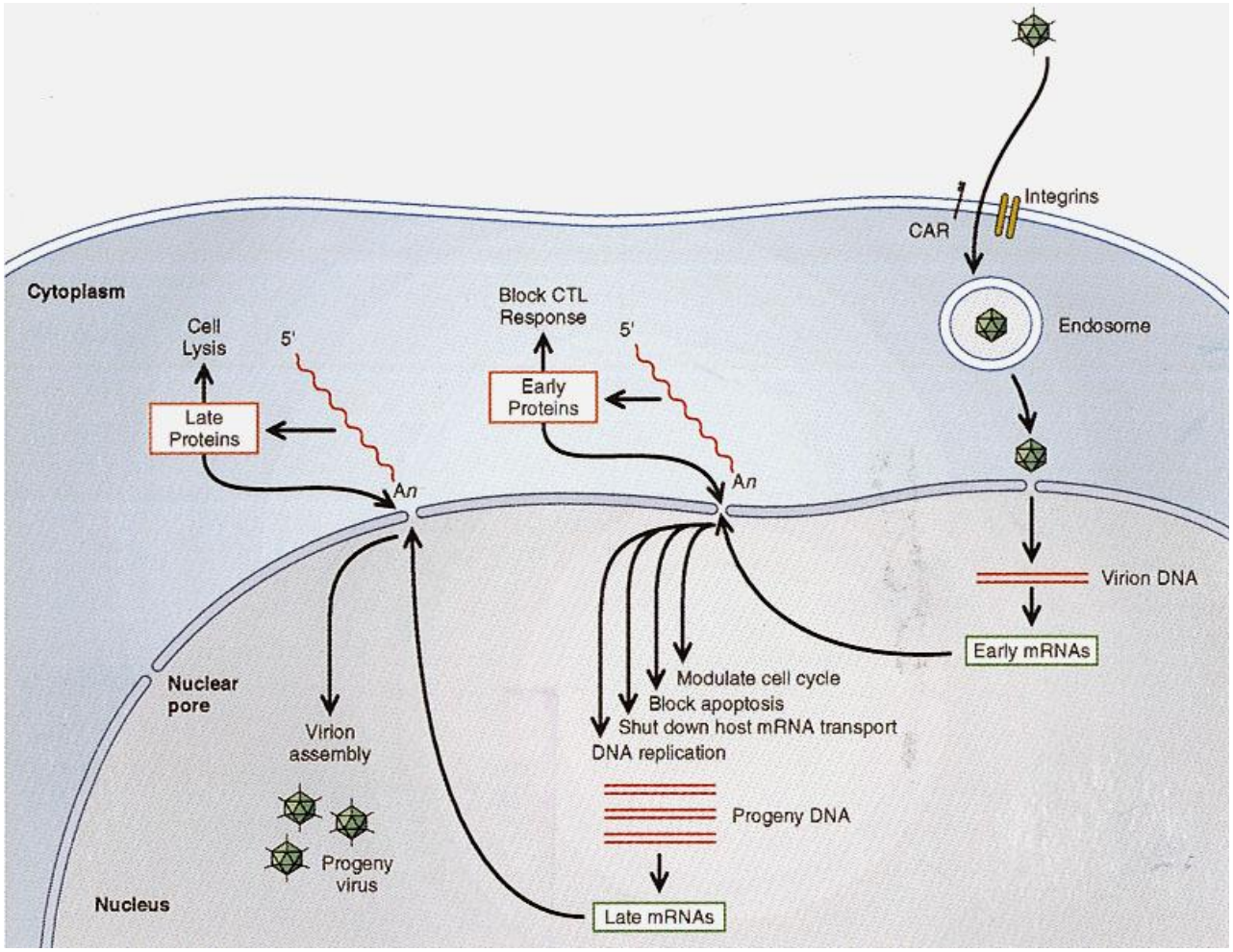




Obligate intracellular parasites

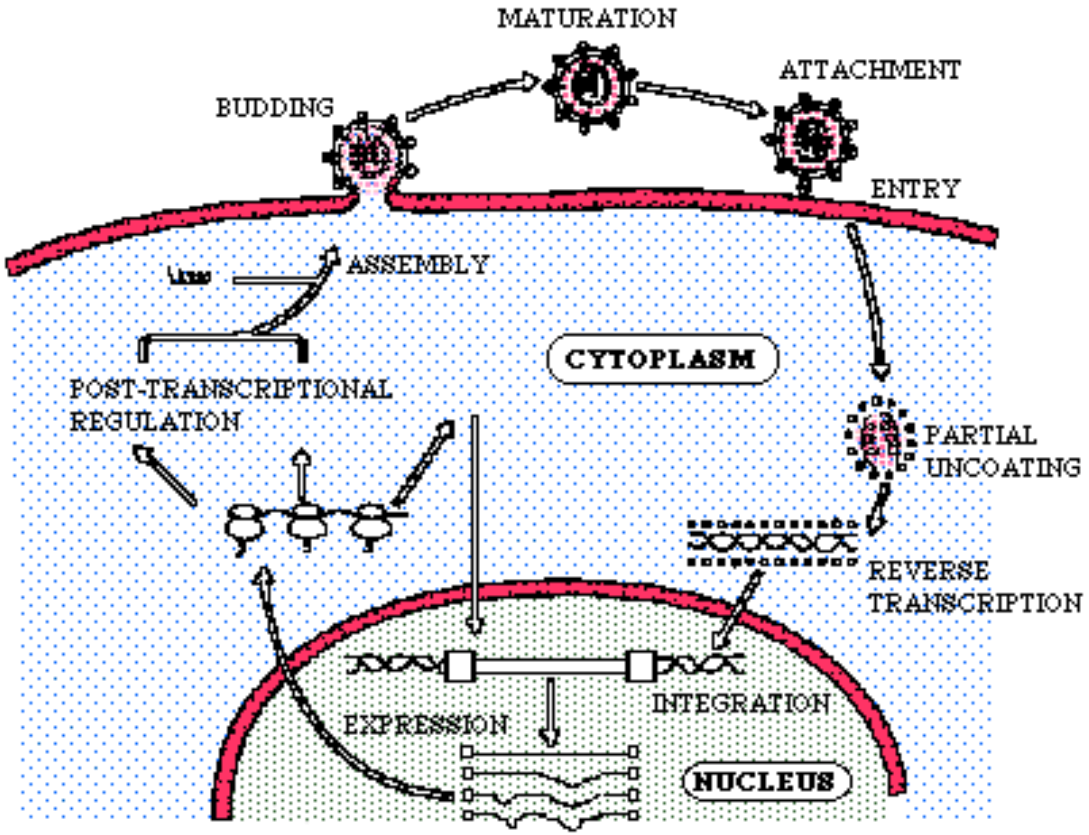

Rabies virus
Lipid bilayer
Genomic RNA
Nucleocapsid protein
Matrix protein
Receptor-binding glycoprotein
Viral RNA polymerase
1 Adsorption
Virus receptor
Cell membrane
Cytosol
2 Endocytosis
Endosome
3 Fusion
4 Release
5 Replication
6 Transcription
7 Glycoprotein synthesis
ER
Nucleus
Viral mRNA
10 Matrix and nucleocapsid synthesis
11 Progeny capsid assembly
12 Association at membrane
13 Budding
Golgi
8 Transport
9 Fusion

Adenovirus replication cycle



(From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Fig. 67-5.)

Retroviruses - Replication



Transmission of viral diseases

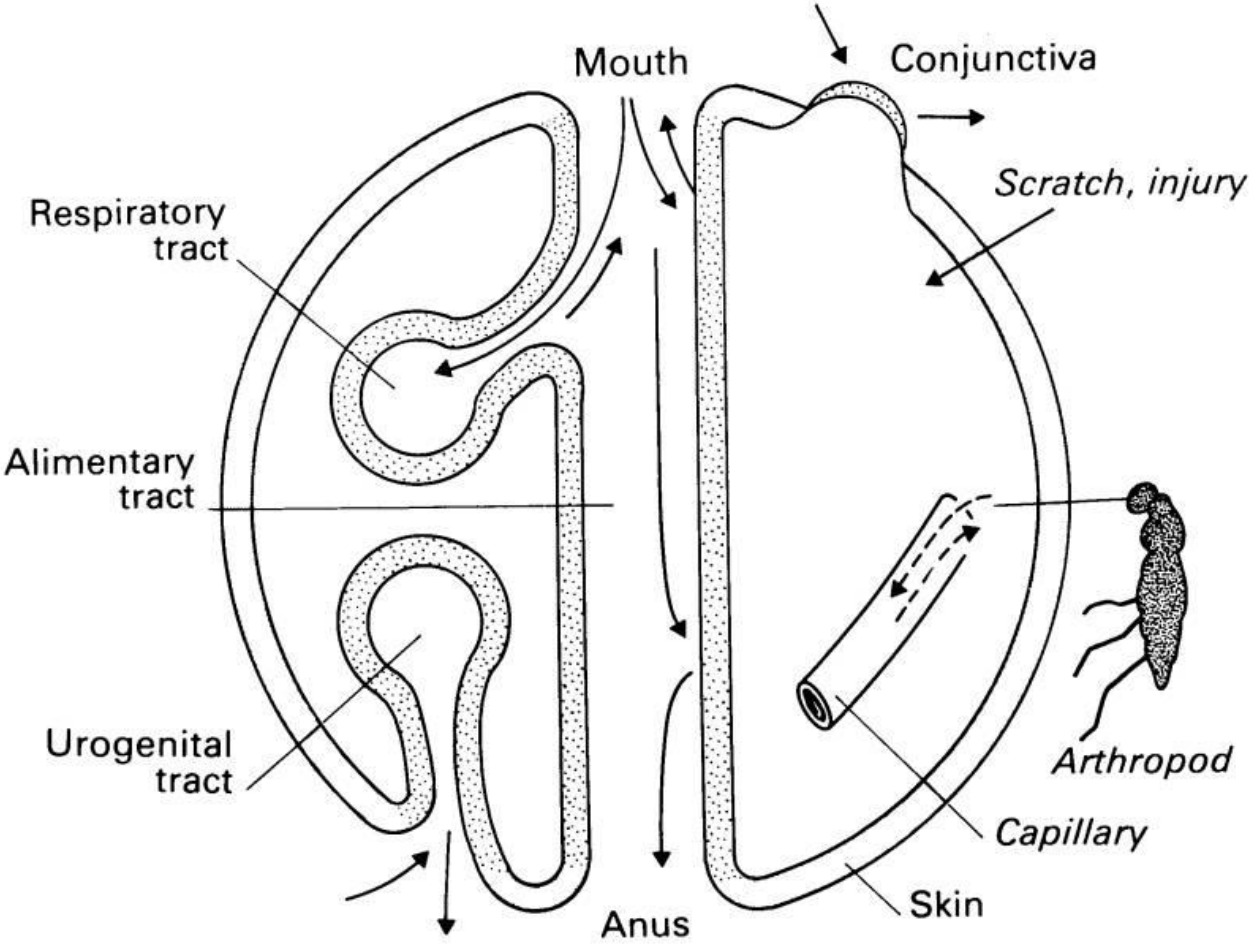
1. Airborne transmission – viruses shed from:
   - Upper respiratory tract (common cold, influenza);
   - Skin lesions (e.g. chicken pox, herpes viruses).

2. Fecal-oral transmission – viruses shed in the feces
   –contaminated water/food – e.g. Hepatitis A virus

3. Body fluids transmission – e.g. blood (HIV-1)

4. Vector transmission – viruses carried by insects and arthropods – arboviruses (*arthropod borne viruses).*
5. Foetal and neonatal transmission
   – MTCT e.g. HIV

Routes of entry and shedding



Portals of entry of viruses into the host, and sites of shedding from the host. (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-2)

Respiratory tract

- Most important entry site
- Specific cell receptors (epithelial cells)
- Replication at reduced temp 33-deg C

  - Localized infections (most)

  - Systemic infections (some)

Alimentary tract

- Most acquired by ingestion
- Stability at low pH (entero-, rota-, caliciviruses)
- Naked viruses (mostly)
- Major courses of viral diarrhea (rota, calici viruses)
  - Localized infections (rota, calici)
  - Systemic/generalized infections (polio, HAV, HEV)
- Rectum
  - HIV and other STIs

Skin

- Largest organ in body
  - Keratinized cells/dead cells (outer layer)
    -> tough & impermeable barrier
  - Abrasions/artificial puncture
    -> some viruses replicate (local lesions e.g. papilloma, pox)
  - Via bite of arthropod vectors (mosquito, tick, sandfly)
    (**Arboviruses)**
  - Via iatrogenic (i.e. human intervention)
    -> HBV, HCV, HIV via contaminated needles/blood transfusion

Other routes

1. **Genital tract**

   -> HHV-2 (= HSV2), Papillomaviruses produce localized lesions

   -> HIV, HTLV, HBV, HCV (no local lesions, but sexually transmitted)

2. **Conjuctiva/Eye**

   -> Rare route

   -> Some adenoviruses, few enteroviruses

Types of viral infections

1. **Acute lytic infections – virus causes disease with well-defined symptoms (**e.g. measles, mumps, common cold).
   - Release of new virus particles -> cell lysis and death.
   - Result: - long-lasting immunity (most)
   - Recovery and protected for life
   - If mutation occurs: - immunity not protective
2. **Subclinical infections –** person infected , no specific signs or symptoms
   – Just general malaise, slight fever , lymphadenopathy etc
   - Recovery: – often unaware of having had a disease
   - Serologic tests: detection of antibodies to virus

   Examples:

   – Rubella (German measles)

   – Polio, hepatitis B and C are other examples of diseases

Types of viral infections

3. Persistent viral infections – virus is not eliminated by the immune system.

a. Latent infections – after a primary infection, virus remains dormant in some host cells and can be reactivated some time later because of stress or immunosuppression.

Examples – cold sores; varicella (chicken pox)-> zoster (shingles)

b. Slow infections – many years after the initial disease a new form of the disease slowly emerge – different symptoms.

Example – measles in childhood can be followed by subacute sclerosing panencephalitis (SSPE) in adolescence or young adulthood.

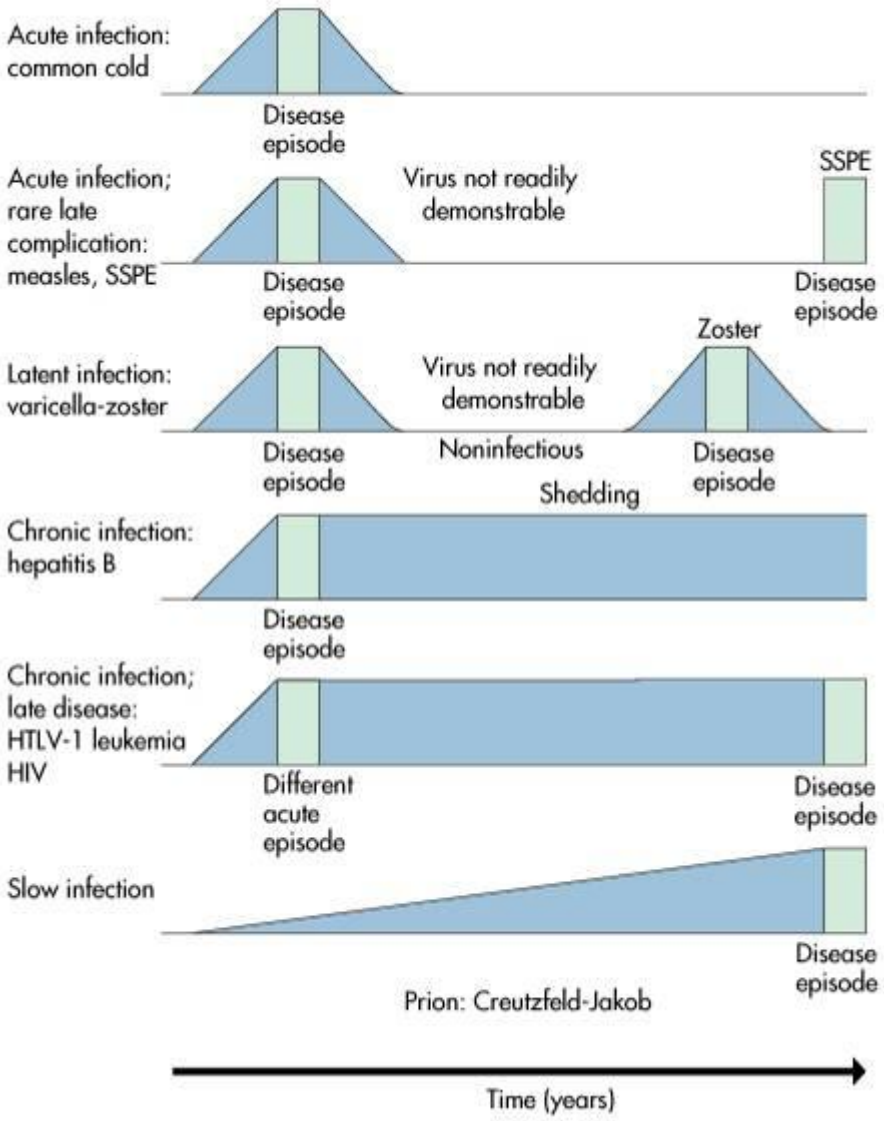
4 Chronic viral infections - person persistently infected with the virus – continues to shed the virus.

Examples include Hepatitis B and HIV.

5. Oncogenic viruses – viruses that can cause tumours.

Examples: Human papillomavirus (cervical cancer), EBV – Burkitts Lymphoma)

Modes of infection



From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 49-3

Viral Pathogenesis

- Process by which viral infection leads to disease
- Disease patterns
  - Localized
  - Systemic

Virus spread in the body

1. Localized infection

- Infection & initial replication in epithelial cells (site of entry)
- Spread of infection via sequential infection of neighbouring cells
- Little or no invasion beyond epithelium (Papilloma, Paramyxo, Influenza)

2. **Systemic/Generalized infections**

- Infection & replication at site of infection (epithelial cell)
- Spread via lymphatics -> regional lymph nodes
- Primary viremia -> target organ
- Secondary viremia
- 2ndary viremia could result in virus spread to other parts of the body

ACUTE INFECTIONS

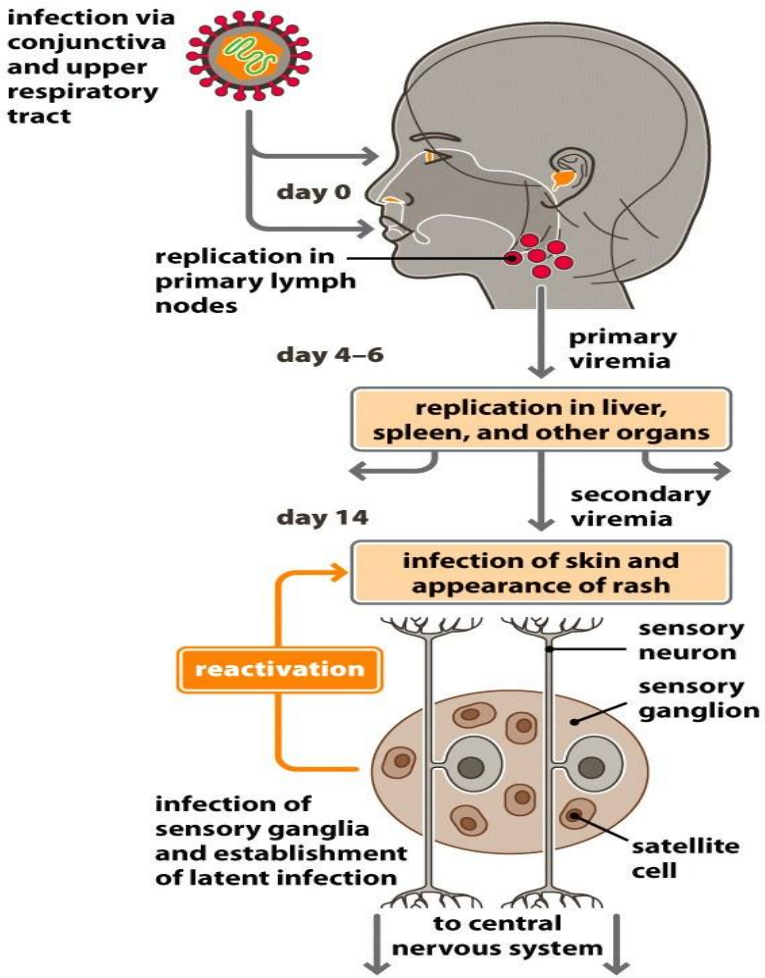
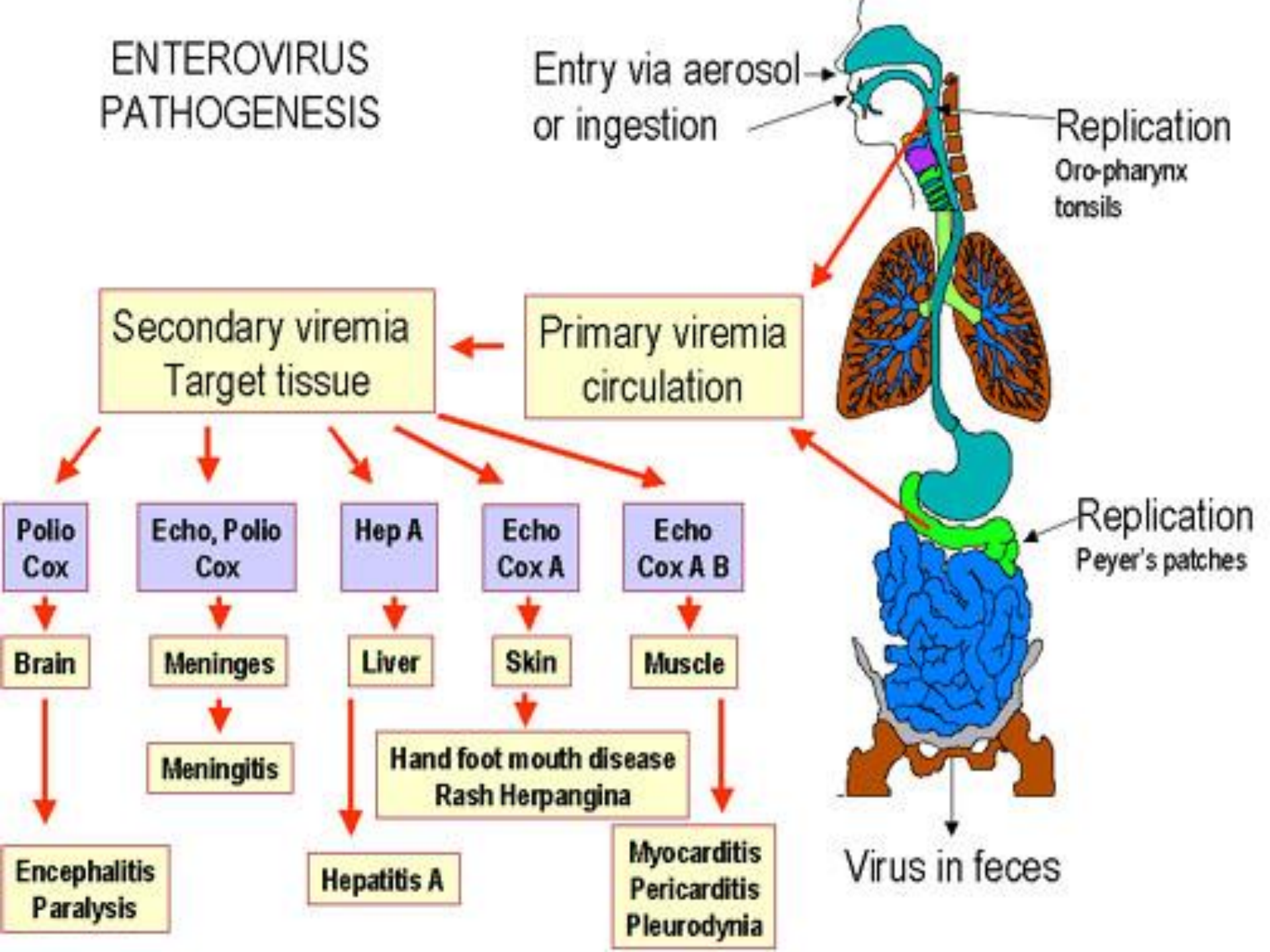


Figure 13.2 Microbiology: A Clinical Approach (© Garland Science)

ENTEROVIRUS PATHOGENESIS



Pathogenesis: cycle of infection

- Infection
- Primary site replication
- Spread (not all viruses)
- Secondary site replication (not all viruses)
- Shedding, transmission

Mechanisms of cell death

1. **Shutdown of cellular protein synthesis**
   - Viral proteins can interfere with cellular proteins
   - Competition for ribosomes
   - selective degradation of cellular mRNAs
2. **Shutdown of cellular nucleic acid synthesis**
   - Reduced mRNA transcription/cellular DNA synthesis
   - Cellular DNA degradation (e.g. Poxviruses)
3. **CPE of viral proteins**
   - Accumulation of viral components
   - Toxic viral proteins
   - Insertion of envelope proteins into cell membranes (integrity of cell membrane affected)

Mechanisms of Disease Production - 1

Viral damage to tissues & organs

- Lytic viruses
  -> Virus repli in liver (e.g. RVFV) -> liver damage
  -> Poliovirus replication in neurons -> paralysis
- Damage of epithelium
  (a) Respiratory tract
    -> 2ndary bacterial infections
  (b) Intestinal tract
    -> defective villus cells
    -> accumulation of fluid in lumen of gut (impaired absorption)
    -> diarrhea
    -> 2ndary bacterial infections (e.g. E.Coli) leading to further diarrhea

Mechanisms of Disease Production - 2

Immunopathology

1. Type I hypersensitivity (anaphylactic)
   -> Antigen-IgE (mast cells & basophils) interactions
   -> release of histamines etc
2. Type II hypersensitivity (ADCC)
   -> Antibody-Antigen (surface of infected cell) interaction
   -> Activation of complement cascade -> cell lysis
3. Type III hypersensitivity (immune complex mediated)
   -> Antigen-antibody reactions
   -> Cause inflammation and cell damage (infiltration of polymorphonuclear leukocytes – inflammatory rxns)
4. Type IV – Cell mediated hypersensitivity
   -> delayed hypersensitivity
   -> Mediated by T cells (not antibody) – involve inflammation, lymphocytic infiltration –> cytokines

Determinants of Viral Pathogenesis

Cellular & viral factors

1. Viral virulence
   -> Ability to promote replication & cell change
   -> Measure of pathogenicity
2. Host genetic factors
   -> Presence/absence of receptors (e.g CCR5 delta32 in HIV)

Age (young vs. old)

Immunological status

1. Normal vs. Immunocompromised
2. Primary vs. secondary infection
3. Pre-existing immunity (due to vaccination/prior infection)

Dual infections

For each virus, know:

- Classification –
  1. Family
  2. Genus/subfamily
  3. Nucleic acid type (RNA/DNA?), types/species (if any)
- Pathogenesis
  - transmission/entry/shedding
  - Replication (cytoplasmic vs nucleic?)
  - Spread (local vs systemic?)
  - immune response/counter response
  - damage/disease mechanism
- Diagnosis
- Treatment/prevention
  - Drugs (if available – e.g. HIV, HHVs, Influenza etc)
  - Vaccines (if available – measles, rubella, YF, etc)