# 2- Viral Replication and Pathogenesis

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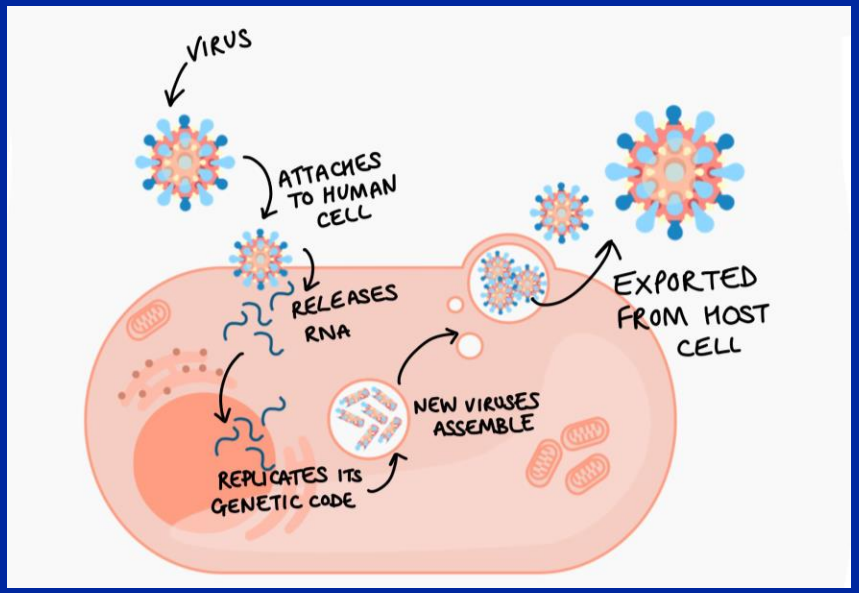
# Objectives

1. Understand the steps of viral replication
2. Differentiate DNA and RNA viral replication
3. Understand steps of viral pathogenesis
4. Factors affecting viral pathogenesis
5. Outcomes of viral infections
6. Host Responses to Viral Infections

# Viral Replication

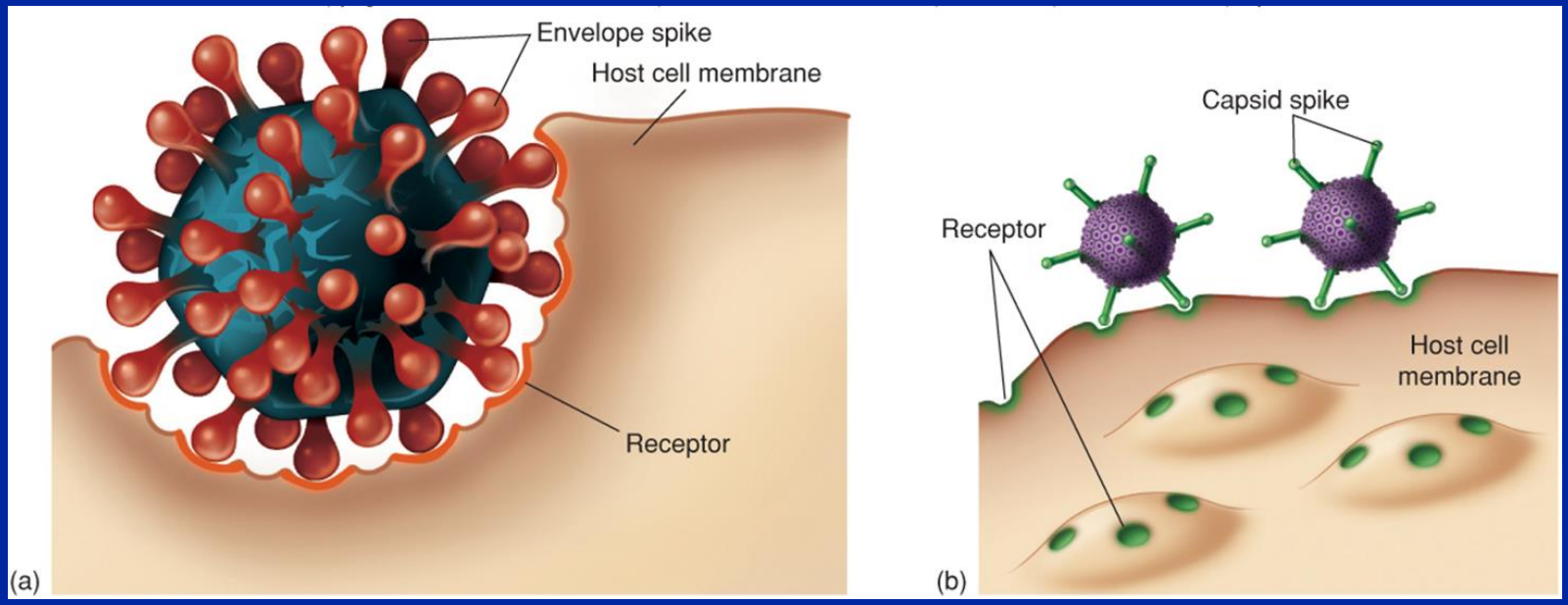
- The host cell is absolutely necessary for viral multiplication




1. adsorption (attachment)
2. entry
3. uncoating
4. transcription
5. synthesis of virus components
6. assembly
7. release

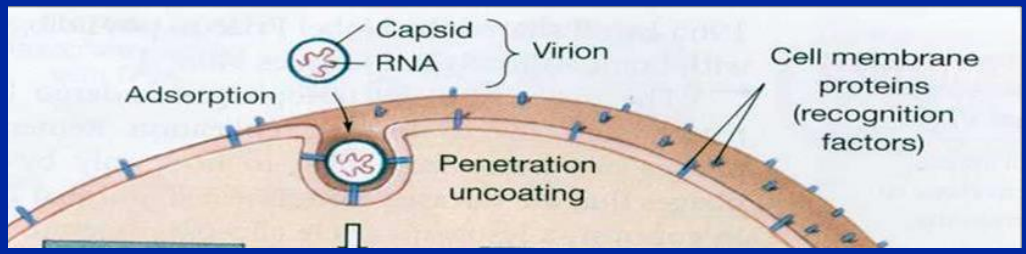
# 1. Adsorption (attachment):

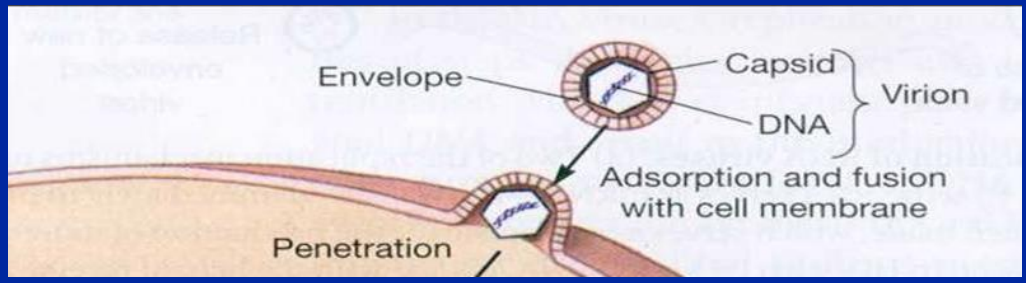
- random collision
- interaction between specific proteins on viral surface and specific receptors on target cell membrane (tropism)
- some viruses may use more than one host cell receptor
- able to infect a limited spectrum of cell types



# 2. Entry (penetration):

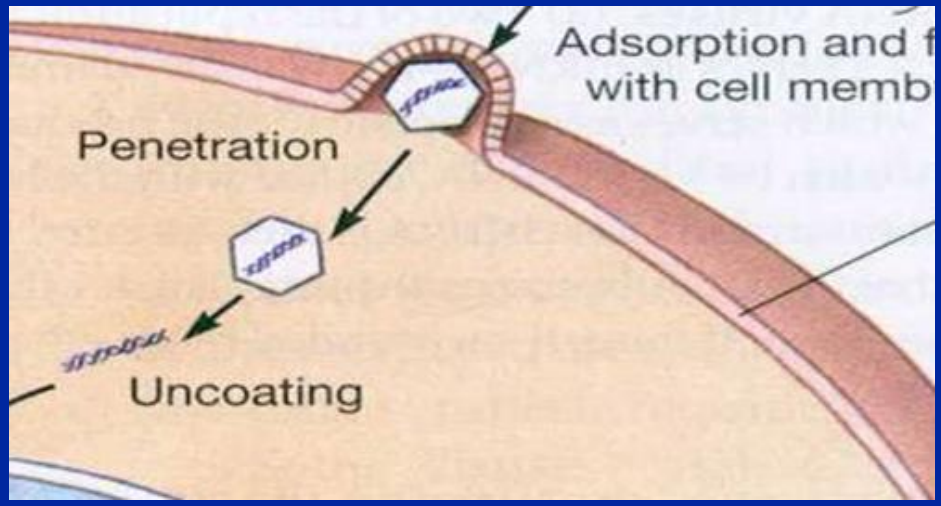
- Flexible cell membrane of the host is penetrated by the whole virus or its nucleic acid
- 2 mechanisms
- Endocytosis:  entire virus engulfed by the cell and enclosed in a vacuole or vesicle
- The viral envelope can also directly fuse with the host cell membrane



# 3. Uncoating

- release of viral genome
- cell enzymes (lysosomes) strip off the virus protein coat
- virion can no longer be detected; known as the “eclipse period”



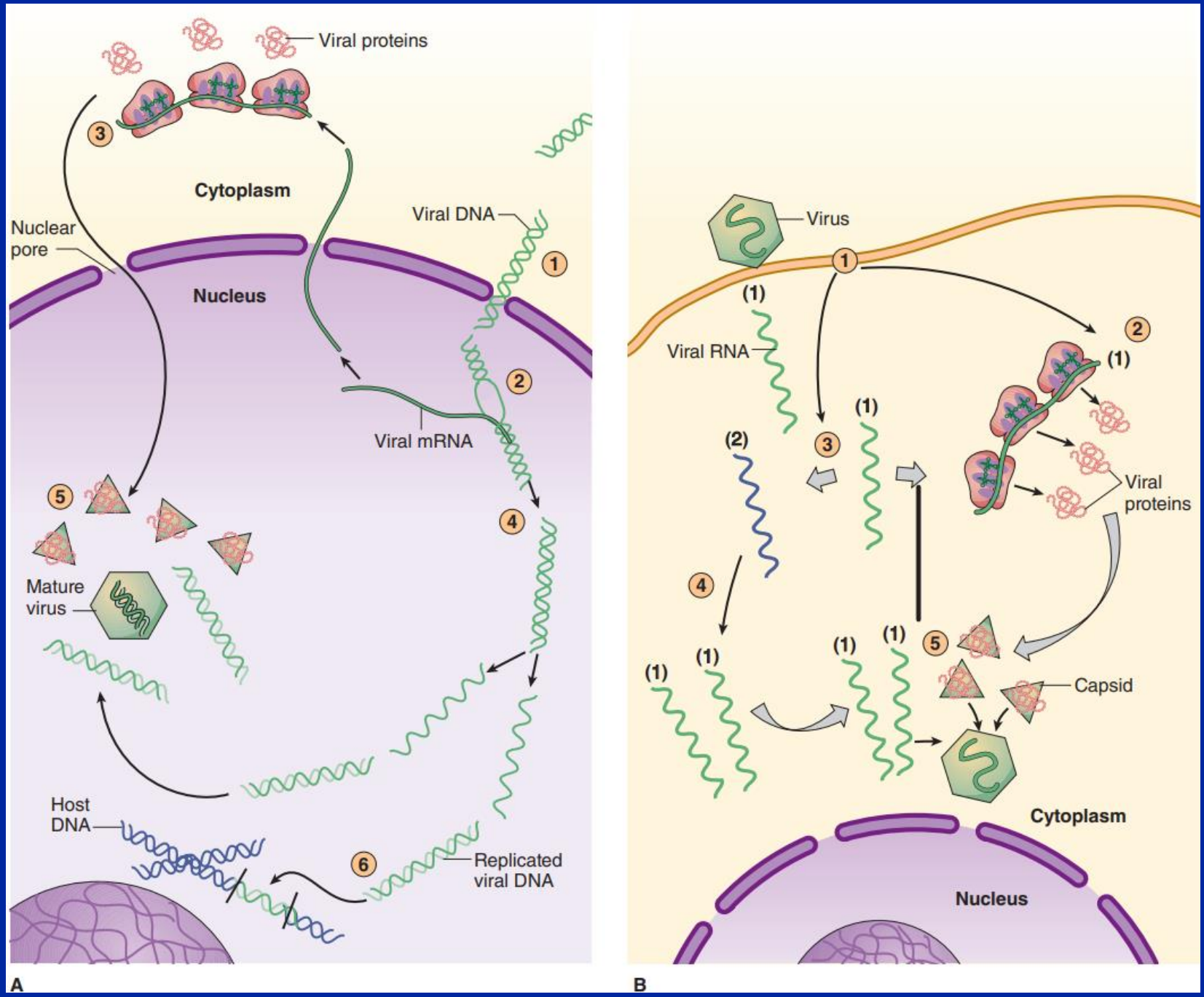
# 4. Transcription/Translation

**a) DNA viruses:**

- replicate their DNA in host cell nucleus mediated by viral enzymes
- synthesize capsid and other proteins in cytoplasm using host cell enzymes
- new viral proteins move to nucleus where they combine with new DNA to form new viruses

**b) RNA viruses:**

- "+" sense RNA acts as mRNA - viral proteins are made immediately in cytoplasm mediated by viral enzymes
- "-" sense RNA - $I^{st}$ makes a "+" sense RNA copy via viral enzyme

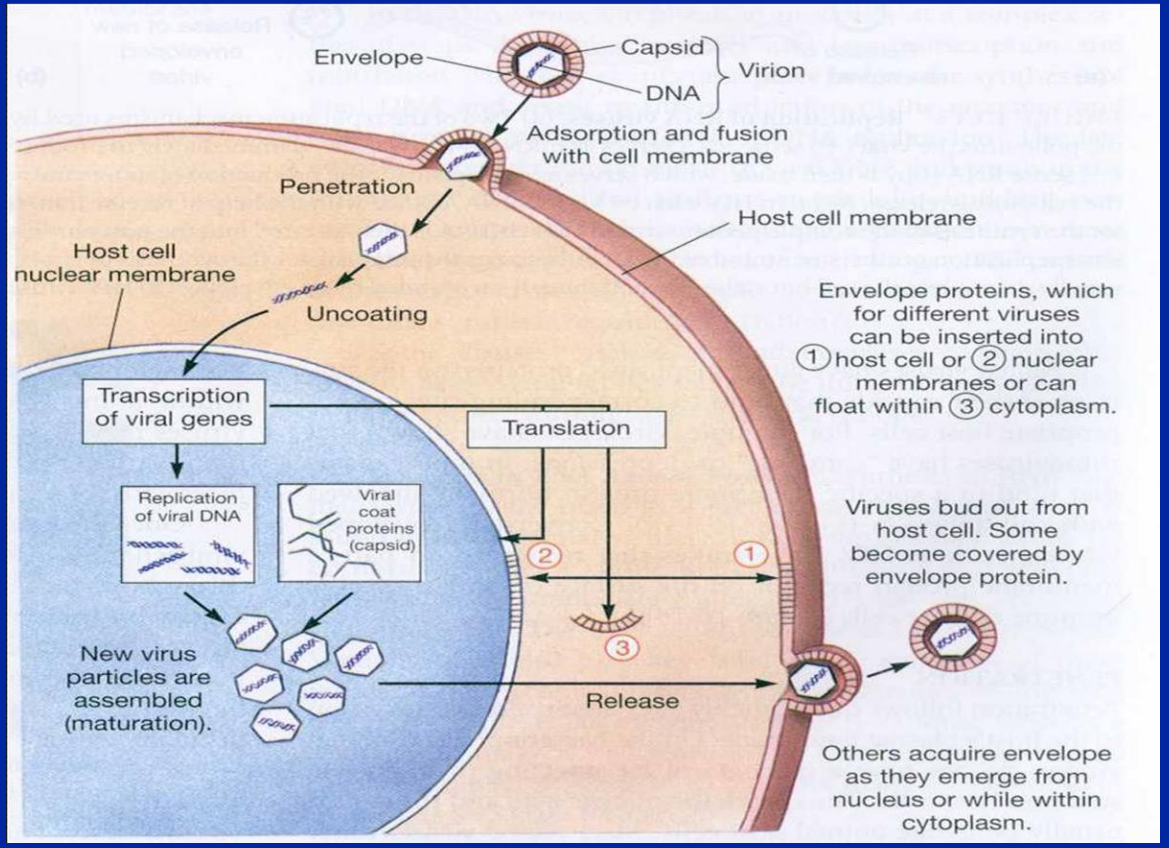

Viral proteins
3
Cytoplasm
Nuclear pore
Viral DNA
1
Nucleus
2
Viral mRNA
5
4
Mature virus
Host DNA
6
Replicated viral DNA
A
Virus
1
(1)
Viral RNA
2
(1)
(1)
(2)
3
Viral proteins
4
(1)
(1)
(1)
(1)
5
Capsid
Cytoplasm
Nucleus
B

# 5. Synthesis

- Protein synthesis - 2 types
  - structural
  - non-structural (enzymes for replication)
- Nucleic acid synthesis
  - new virus genome
  - most often by a virus - coded polymerase or replicase; with some DNA viruses a cell enzyme carries this out

# 6. Assembly

- Mature virus particles are constructed from the growing pool of parts
- may take place in cell nucleus, cytoplasm or (with most enveloped viruses) at the plasma membrane



# 7. Release

- Nonenveloped and complex viruses are released when the cell lyses or ruptures
- Enveloped viruses are liberated by budding or exocytosis
- Anywhere from 3,000 to 100,000 virions may be released, depending on the virus
- Entire length of cycle- anywhere from 8 to 36 hours

# Viral Pathogenesis

- The process by which a viral infection leads to disease
- The majority of viral infections are subclinical
- The consequences of viral infections depend on the interplay between a number of viral and host factors

# Factors in Viral Pathogenesis

- Entry into the Host
- Course of Infection (Primary Replication, Systemic Spread, Secondary Replication)
- Cell/Tissue Tropism
- Effects of viral infection on cells (Cellular Pathogenesis)
- Cell/Tissue Damage
- Host Immune Response
- Virus Clearance or Persistence
- Viral shedding

# Steps in Viral pathogenesis

1. Viral Entry & Primary Replication
2. Viral Spread & Cell tropism
3. Cellular injury & Clinical illness
4. Recovery from infection
5. Viral clearance or persistence
6. Viral shedding

# Viral Entry

- Skin - through cuts or abrasions, animal bites e.g. Rabies virus
- Respiratory tract e.g. Influenza, Parainfluenza virus
- Gastrointestinal tract e.g. Rotavirus, Poliovirus
- Conjunctiva and other mucous membranes
- Genitourinary tract e.g. HIV
- Directly into Bloodstream by
  - Needles : HBV, HIV
  - Blood transfusions : HIV, HCV, HBV
  - Insect vectors : Arboviruses

# Routes of Transmission

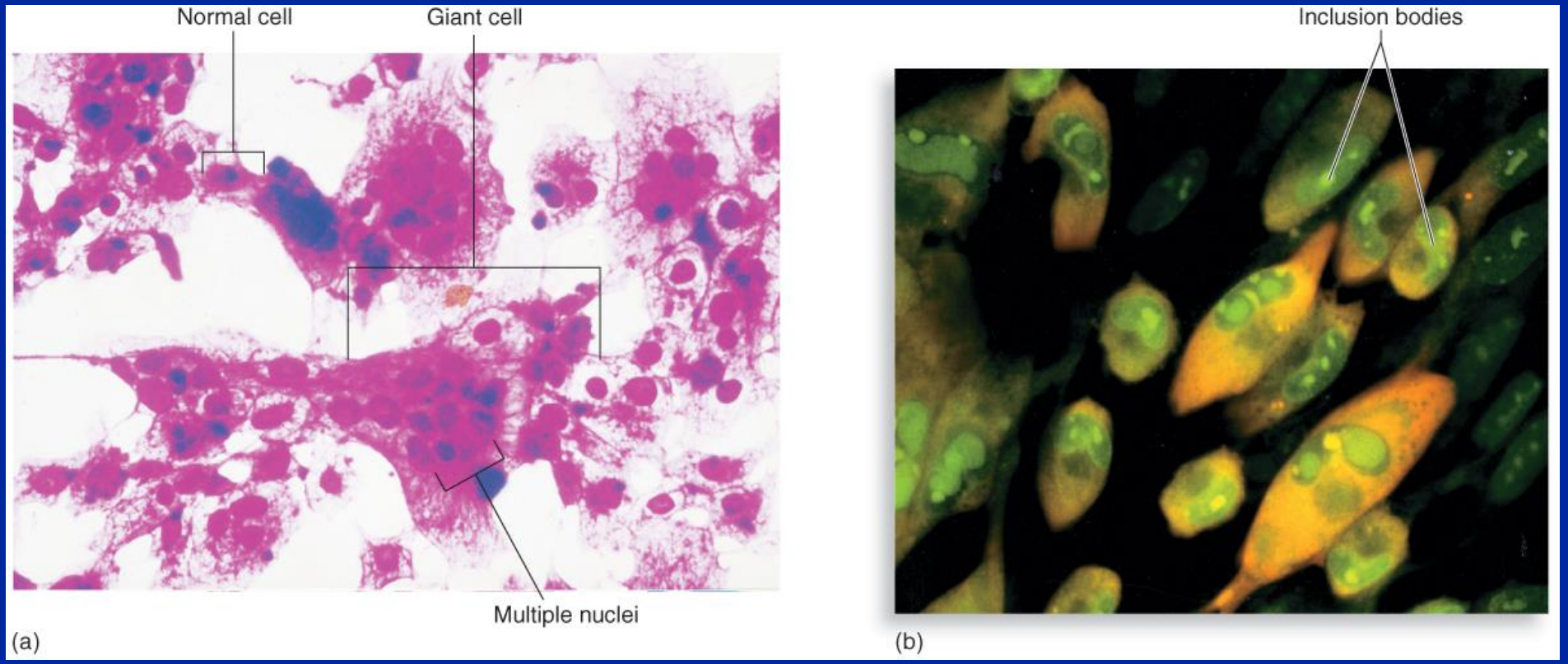
- Horizontal transmission:
  - Direct contract (secretions, blood etc.)
  - Respiratory (aerosol)
  - Contaminated inanimate objects
  - Insect vector (mosquitoes, ticks, etc.)
  - Zoonoses
- Vertical transmission:
  - Mother to fetus [Transplacental (Congenital), Perinatally]

# Course of Viral Infection

- **Primary Replication**
  - Viruses usually replicate at the site of initial entry into the host.
  - The infection remains localized at the site of entry
- **Systemic Spread**
  - Many viruses produce disease at sites distant from point of entry
  - After primary replication, they spread via blood, neurons or lymphatics to other organs.
  - Presence of virus in blood is called VIREMIA
  - Viral spread is determined by its organ & cell specificity – CELL TROPISM
- **Secondary Replication**
  - Secondary replication takes place at susceptible organs/tissues following systemic spread.

# Effects of Viral Infection on Cells

- Cells can respond to viral infections in following ways:
  - No apparent change
  - Cell death or lysis e.g. poliovirus
  - Cellular proliferation e.g. Molluscum
  - Malignant transformation e.g. Oncogenic viruses
  - Cytopathic effects as in tissue cultures
    - Cytopathic effects- virus-induced damage to the cell that alters its microscopic appearance
    - Inclusion bodies- compacted masses of viruses or damaged cell organelles


Normal cell
Giant cell
Multiple nuclei
(a)
Inclusion bodies
(b)

# Outcome of Viral Infection

- Clinical outcome – subclinical (Inapparent) or clinical (apparent) infections. Clinical infections can be:

1. Acute Infection
   - Complete recovery
   - Recovery with residual effects
   - Proceed to chronic infection (latency)
2. Chronic Infection
   - Silent subclinical infection for life
   - A long silent period before disease
   - Reactivation to cause acute disease
   - Chronic disease with relapses and excerbations
   - Cancers

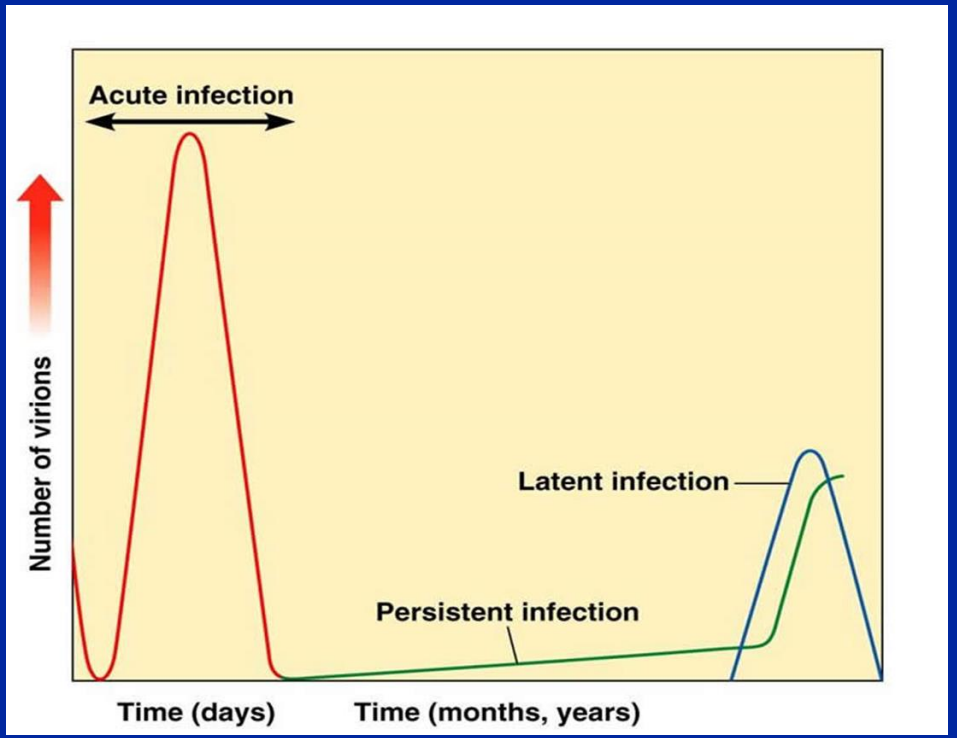
# Virus Shedding

- Last stage in pathogenesis
- Necessary step to maintain a viral infection in a population of hosts
- Usually occurs from the site of entry
- Occurs at different stages of disease depending on the agent
- Represents the time at which an infected individual is infectious to contacts
- In certain cases, shedding does not occur e.g. Rabies

# Viral Persistence

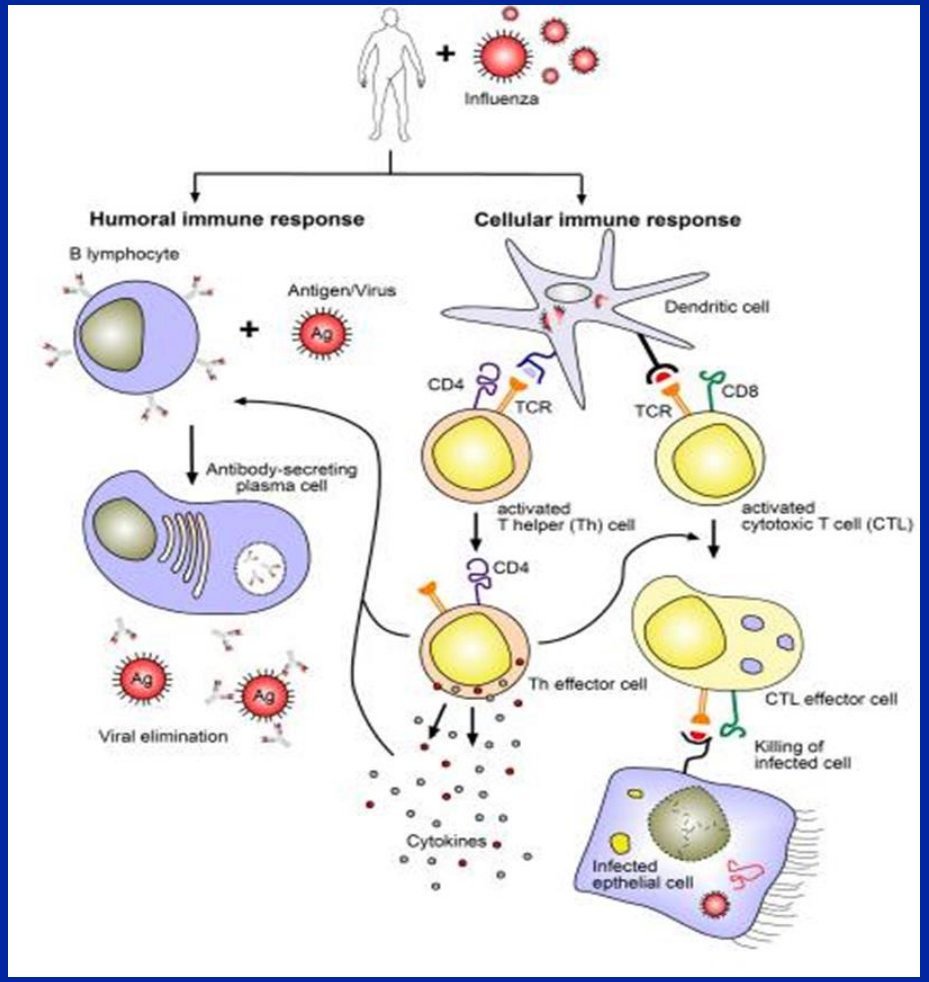
Majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of persistent infections:

1. Chronic infections – virus is continuously detected but at low levels
2. Latent infections - virus remains completely latent following primary infection. Intermittent flare ups of disease



# Host Responses to Viral Infections

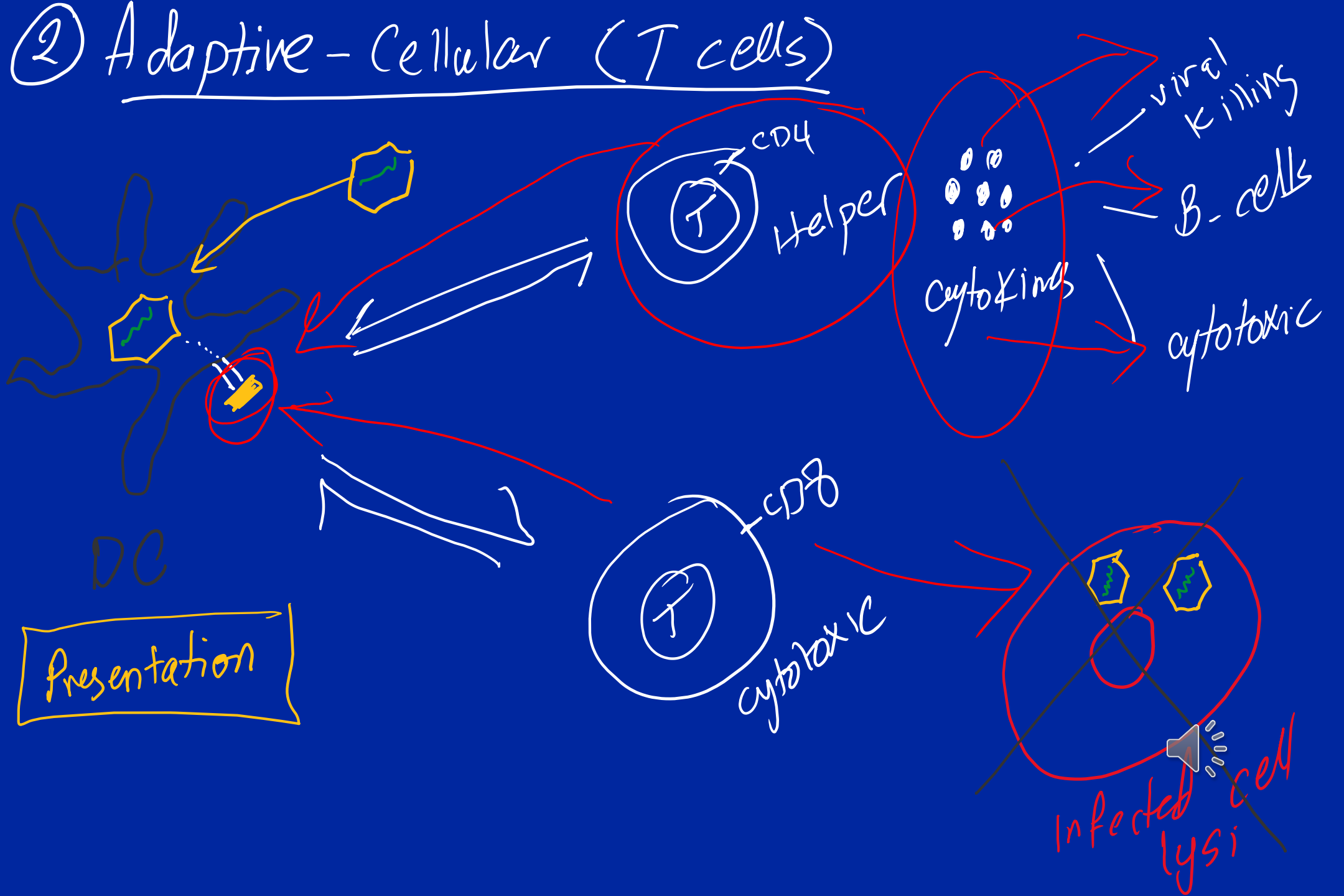
- Innate immunity – Interferons
- Humoral response – protects the host against reinfection by same virus
  - IgG & IgM : Blood & tissue
  - IgA : mucosal surfaces of respiratory & gastrointestinal tract
  - Neutralising Abs prevents initiation of infection
- Cellular response – recovery from viral infection, destroy viral infected cells
- Mostly gives lifelong protection



# ① Innate – Interferons (INF)

* cytokines (protein) ← INF-α, INF-β, INF-γ } type I ⇒ anti-viral effect (RNA)
* Secreations: body cells + Immune cells (Mac)
* Effect: rapid (hours) + None specific
* Mechanism

# ② Adaptive - Cellular (T cells)



## ③ Adaptive - Humoral (B-cells)

A* Attachment (IgA)
neutralization


B* Antibody mediated killing


C* T- Helper B cells activation

viral defense ≡ HIV