Pathogenesis of viral infection

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Definitions

- **Viral Pathogenesis**
  - Viral pathogenesis is the step-by-step process through which viruses enter the body, interact with host cells, multiply, and ultimately cause disease. It explains how viral infections develop and progress to illness.

- **Key Concepts**
  - Viral pathogenesis is determined by the complex interaction between:
    - Viral factors (such as virulence, tropism, and replication rate)
    - Host factors (including immune response, genetic susceptibility, and age)
    - Environmental conditions that influence both virus and host

Definitions (Cont.)

- **Viral Virulence**
  - The ability of a virus to cause disease in an infected host
  - The degree of virulence determines the severity and progression of the infection.
    - A **virulent strain** causes significant disease
    - An **avirulent** or attenuated strain causes no or reduced disease
  - Virulence depends on
    - Dose
    - Virus strain (genetics)
    - Inoculation route - portal of entry
    - Host factors

Importance of Studying Viral Pathogenesis

- Understanding viral pathogenesis is crucial because it:
  - Reveals the molecular mechanisms behind viral diseases
  - Guides the development of effective antiviral treatments
  - Helps design preventive strategies and vaccines
  - Enables better prediction and control of viral outbreaks
  - Provides insights into emerging viral diseases

Factors affecting viral pathogenic mechanisms

Tissue Accessibility - The ability of a virus to reach and enter target tissues

Key Factors Influencing Accessibility:

- **Physical Barriers** (Mucus membranes, Tissue barriers, Epithelial surfaces)
- **Anatomical Considerations** (The path length the virus must travel within the host, Transport mechanisms through tissues and organs)
- **Natural Defense Systems** (Innate immune responses, Local tissue-specific defenses, Physiological barriers)

Viral Virulence Factors

Primary Functions:

- Barrier Penetration (Overcome physical barriers, Neutralize defensive substances)
- Host Defense Evasion (Counter immune responses, Avoid detection mechanisms)

Virulence factors enable the virus to

- Initiate infection
- Dissemination
- Replication Efficiency - Achieve sufficient viral load

Factors Involved in Viral Pathogenesis

- Transmission of the viruses
- Routes of entry.
- Viral adhesions
- Mode of viral spreading
- Viral pathogenesis at the cellular level
- Viral pathogenesis at the host level
- Mechanisms of Viral Persistence
- Cell/Tissue Tropism
- Damage caused by the virus

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Source of Transmission

- Person to person transmission
- Animal to person (zoonotic transmission)

Types of Transmission

Horizontal

- Skin contact
- Blood routes
- Respiratory routes
- Fecal-oral routes
- Genital contact

Vertical

- From the mother to her baby.
- During delivery through an infected birth canal

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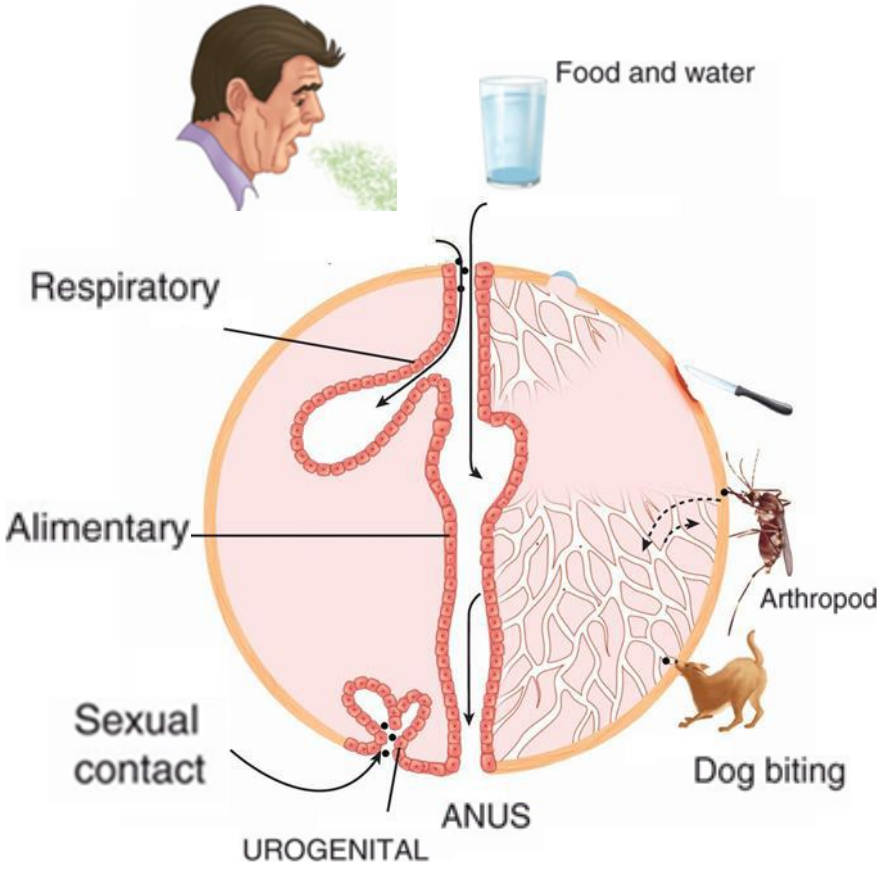
Body System/Route	Associated Viruses
Respiratory Tract	Adenoviruses, influenza
Ingestion	Rotaviruses, and Enteroviruses (acid and bile resistant)
Skin	Rabies, Papillomaviruses
Genitourinary Tract	Papillomaviruses, Herpes simplex virus 2, and HIV-1 and 2
Eyes	Some adenoviruses, influenza viruses



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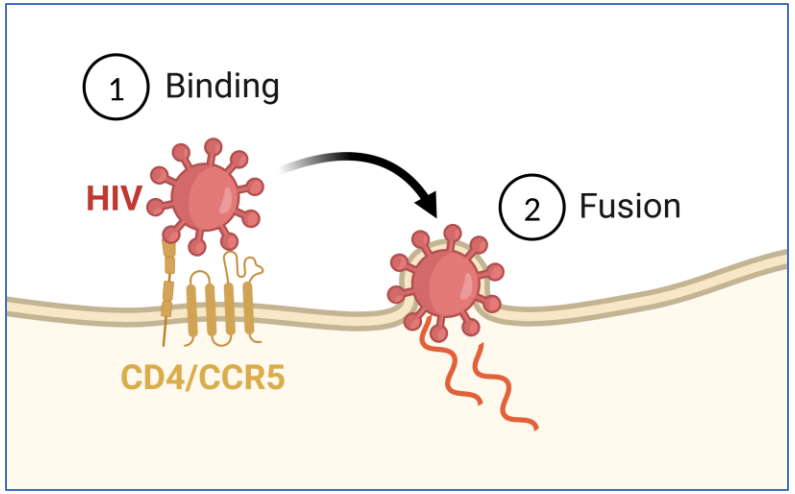
- All viral pathogens must bind to host cells, enter them, and replicate within them.
- Viral coat proteins serve as the ligands for cellular entry
- More than one ligand receptor interaction may be needed, for example
  - HIV glycoprotein (gp) 120 to enter host cells by binding to both CD4 and one of two receptors for chemokines (designated CCR5 and CXCR4).



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A. Extracellularly:

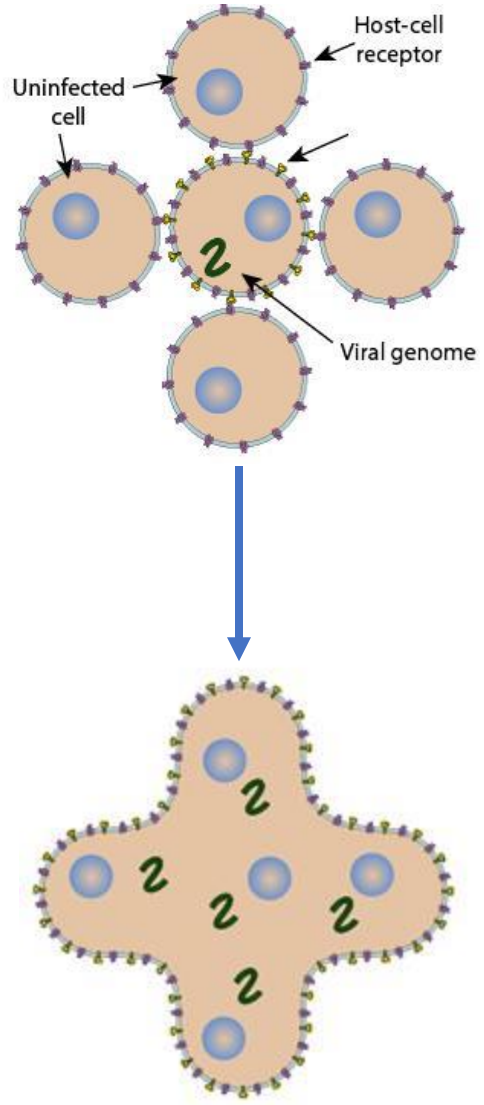
- Occurs by release of virus into the extracellular fluid and subsequent infection of the adjacent cell.

B. Intracellularly (syncytium)

- Occurs by fusion of infected cells with adjacent, uninfected cells or by way of cytoplasmic bridges between cells.
- Intracellular spread provides virus with a partially protected environment because the antibody defence does not penetrate cell membranes

C. Spread to cells beyond adjacent cells

- Occur through the lymphatics.
- Through infected migratory cells such as lymphocytes and macrophages may spread the virus within local tissue.



Syncytium

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1. **Abortive infection**
   - Virus not produced
2. **Productive infection**
   - Virus produced
3. **Non-productive infection**
   - Virus not produced but viral NA Present

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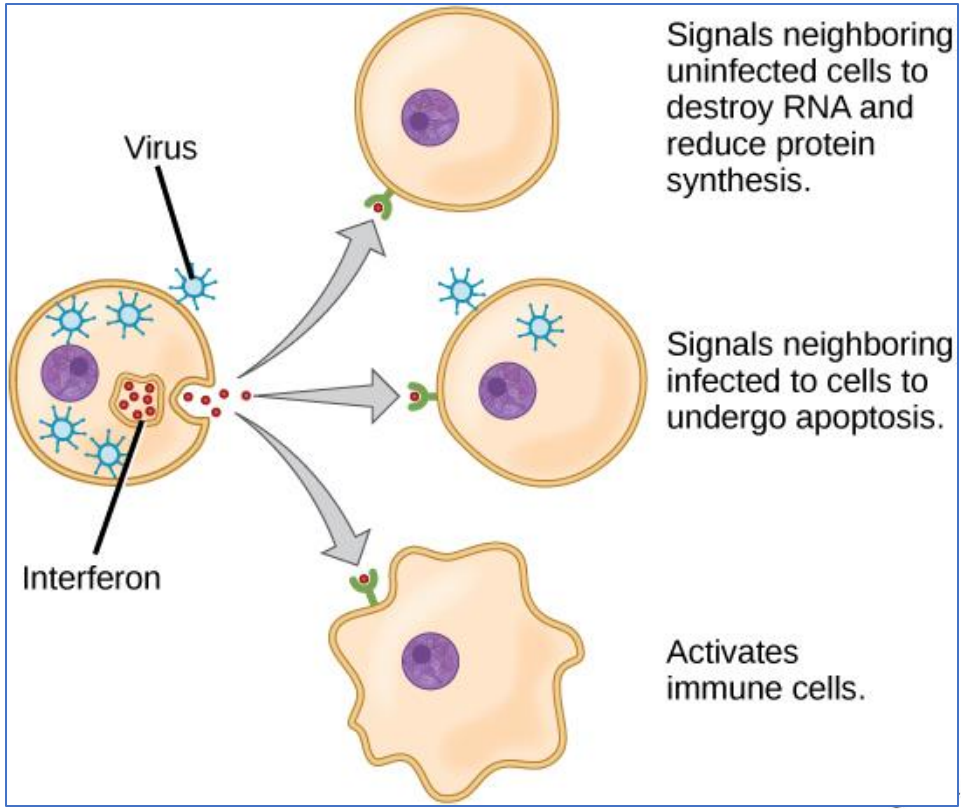
1. Abortive infection

- The virus infects the cell, but it cannot continue its replication cycle. Thus, no virus progeny is produced
- Replication cycle is not completed, so there is no production of new viruses
- Due to:
  - Mutation of Viral Genome
  - Defective Interfering Particles
  - Action of Interferons



Factors Involved in Viral Pathogenesis

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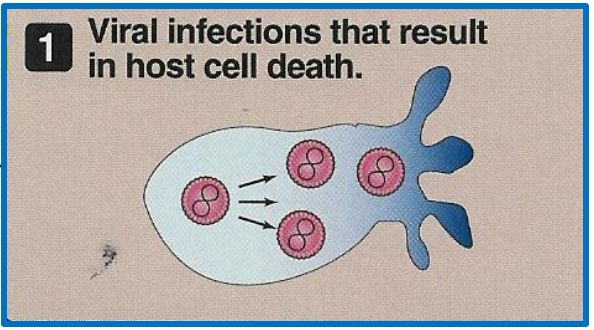
- Damage caused by the virus

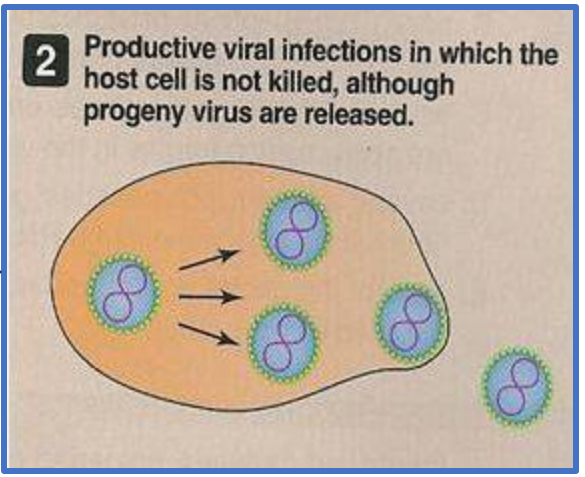
2. Productive infection

- Viruses replicate & produce progeny
- Two types:

1. Cytolytic infection → Affects (kills) the cell by 'cell lysis'
   - Results cell death & cytopathic effects (next slide)
   - The cell is destructed due to rupture of its membrane

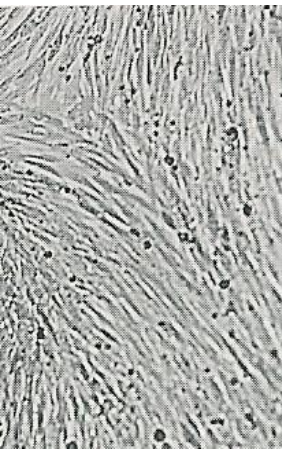


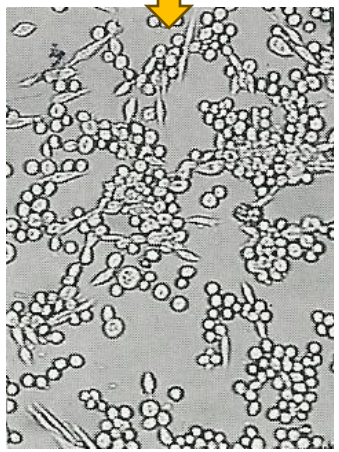
2. Non-cytolytic infection → Does not cause cell lysis
   - Virus released by cell budding & Little or no cytopathic effects
   - Usually, the cell is not destructed

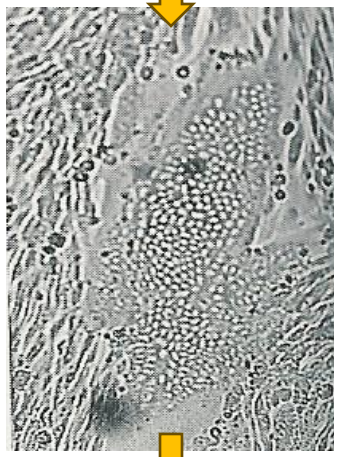


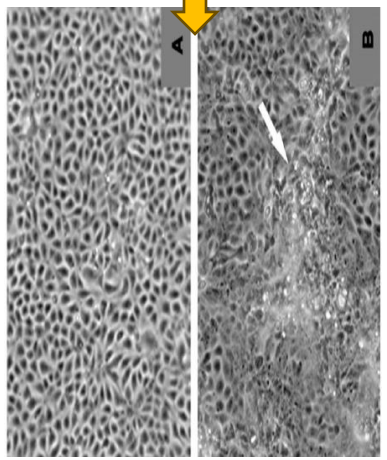
Features of CPE

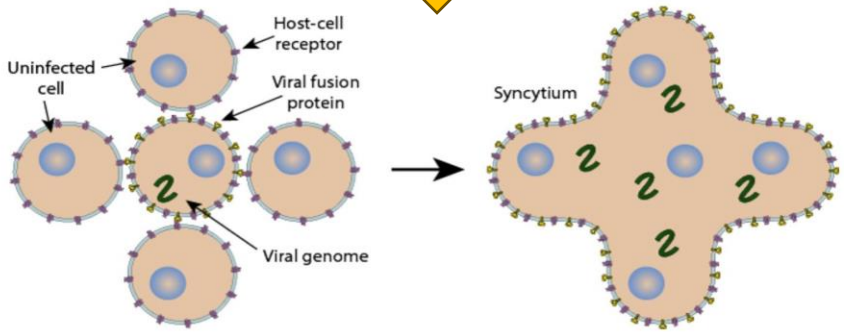
- Cell Rounding
- Syncytium formation (Cell Fusion)
- Cell Lysis (Disintegration)
- Inclusion Bodies Formation
  - Nucleus (intranuclear) → DNA viruses
  - Cytoplasm (intracytoplasmic) → RNA viruses









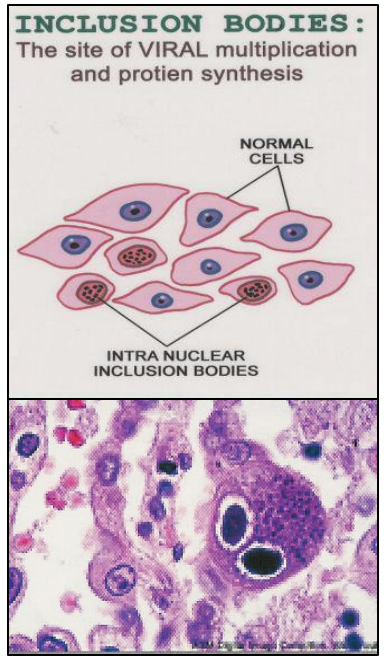


(single cell that contains multiple nuclei)

Formed by fusion of an infected cells with neighboring cells, resulting in a giant multinucleated cell.

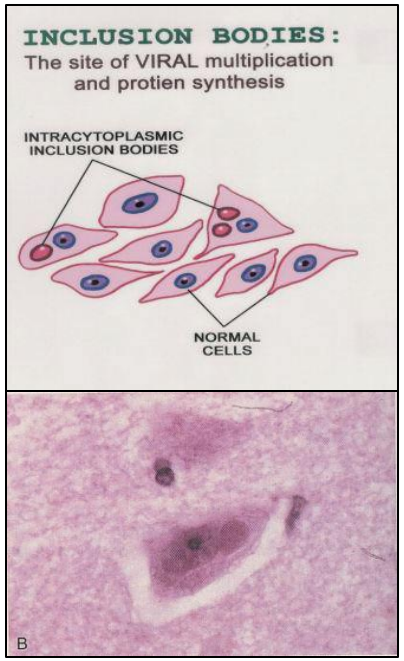
Common when cells are infected by respiratory syncytial virus (RSV)

E.g CMV



Owl's eye inclusions caused by CMV

E.g Rabies (Causes Negri Bodies)



Negri bodies

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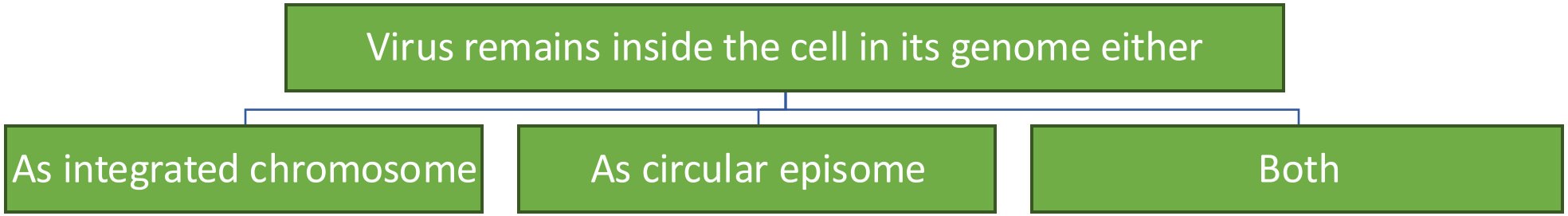
- Damage caused by the virus

3. Non-productive infection

- When the virus infects the cell, the virus cannot complete its replication cycle (because the cell lacks machinery to transcribe viral genes). Thus, no virus progeny produced.
- Viral genome is found either integrated into cell DNA or as a circular episome or both.



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3. Non-productive infection (cont)

Two types

- Latent Infection
  - The cell retains its normal properties
  - There is limited expression of viral genes e.g. HSV
  - Can reactivate under certain conditions
- Transformation
  - Cause tumor in animals & human and it can transform cell culture e.g. EBV, HPV
  - Viruses can stimulate uncontrolled cell growth causing transformation by alternating the balance between growth activators & growth suppressors gene products

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- **Viral pathogenesis at the host level (1)**
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Types of viral infections at host level:

A. Asymptomatic Infection (most common).

B. Symptomatic Infection

1. Acute infection (like common cold)
2. Persistent infection
    1. Latent
    2. Chronic
    3. Slow

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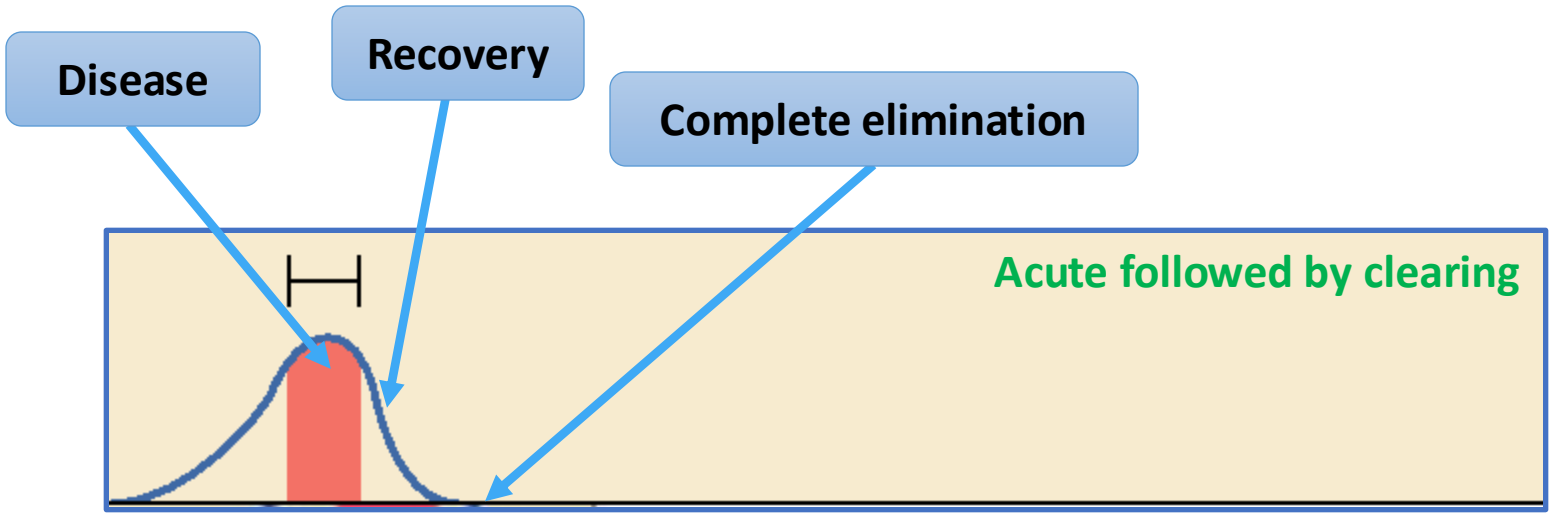
Acute infection

- An acute viral infection is a rapid-onset infection characterized by active viral replication and significant viral shedding, typically resolving within a short period.
- Generally, develop suddenly and last a short time, often only a few days or weeks.
- The patients become symptomatic → then the immune system kicks in
- The virus completely cleared from the body within 5-7 days OR could be fatal.
- This type of infection is cytocidal (Is it good or bad?).



Acute infection
- Rhinovirus
- Rotavirus
- Influenza virus

Acute : virus rapidly kills cells; rapid, self-limiting or fatal disease.

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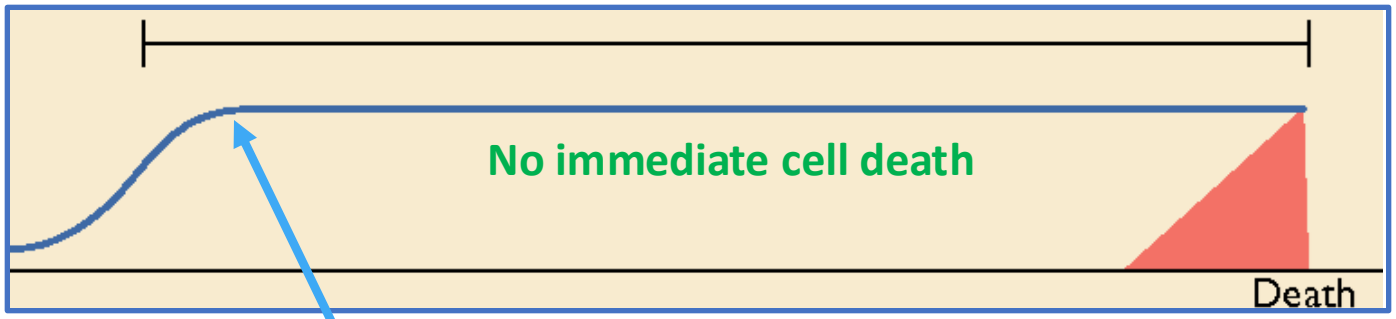
Chronic persistent infection

- They usually develop from acute infection.
- Host cells continue to survive despite a viral infection
- Then persists with no clearance (replication at slow rates with positive serological tests)
- Mild or no clinical symptoms may be evident.
- People may be able to transmit the virus to others.
- Serious signs may not appear until as long as 20 years after the infection began.
- For example: hepatitis B & C, which affects the liver is a chronic viral infection.



Hepatitis B (15% of cases)
Hepatitis C (85% of cases)

The end of acute stage, the immune system can't clear the virus

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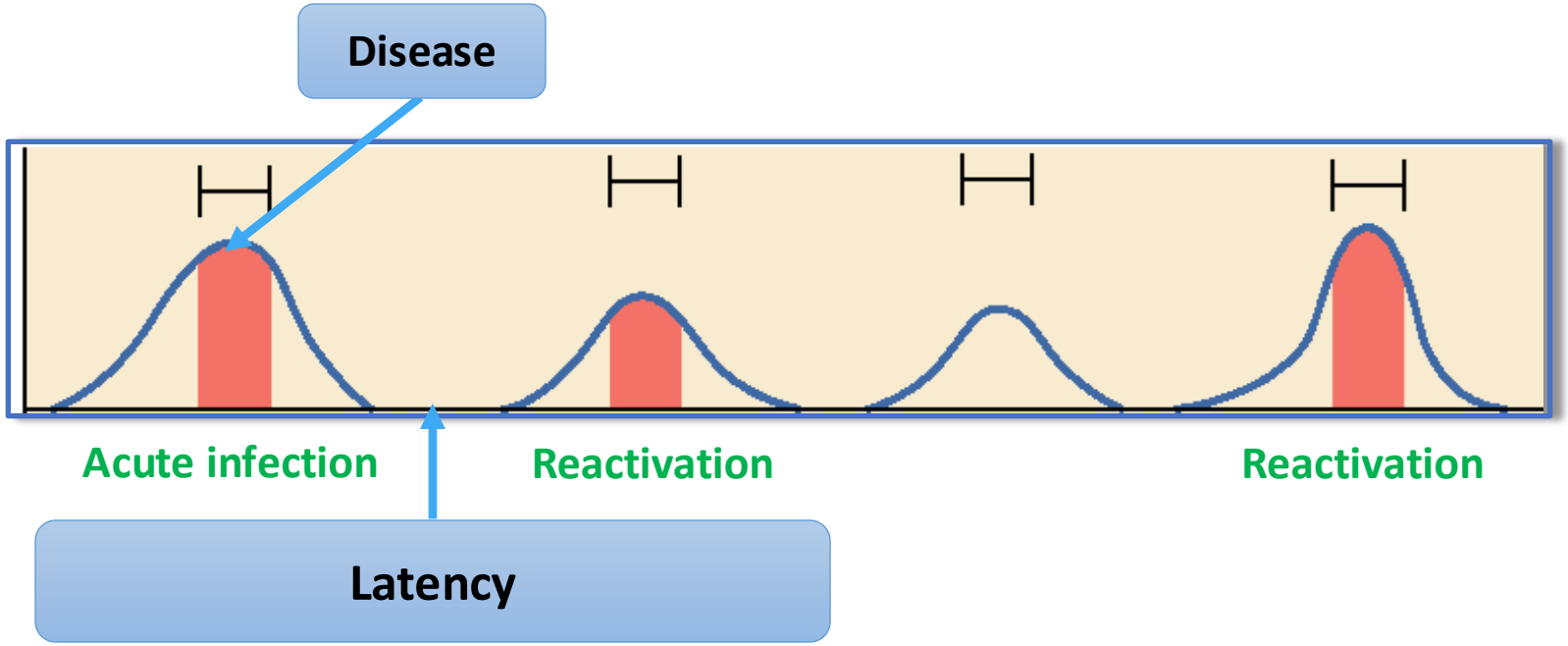
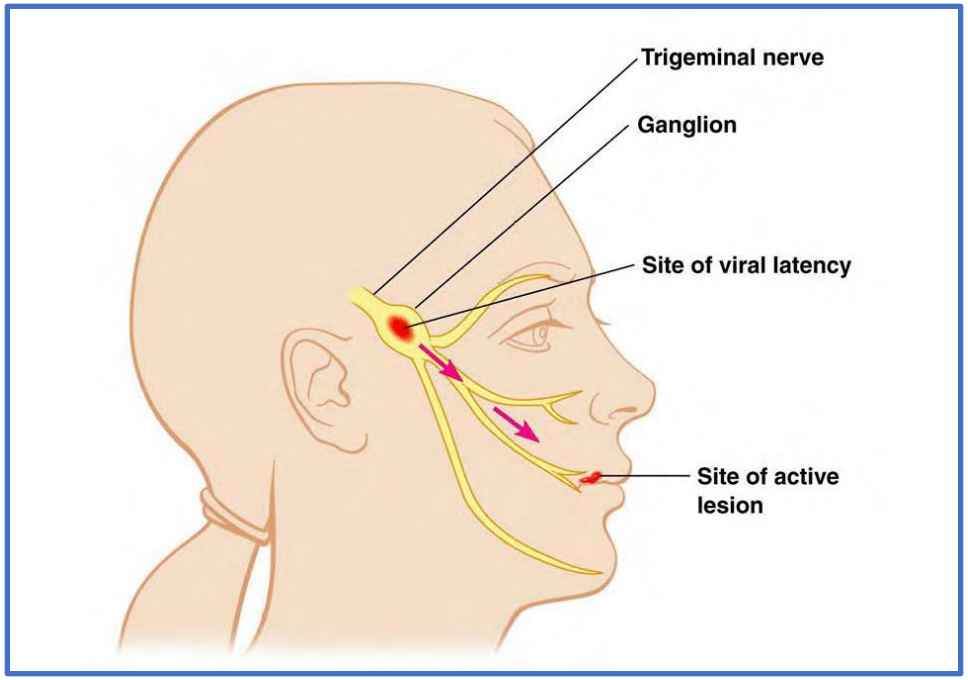
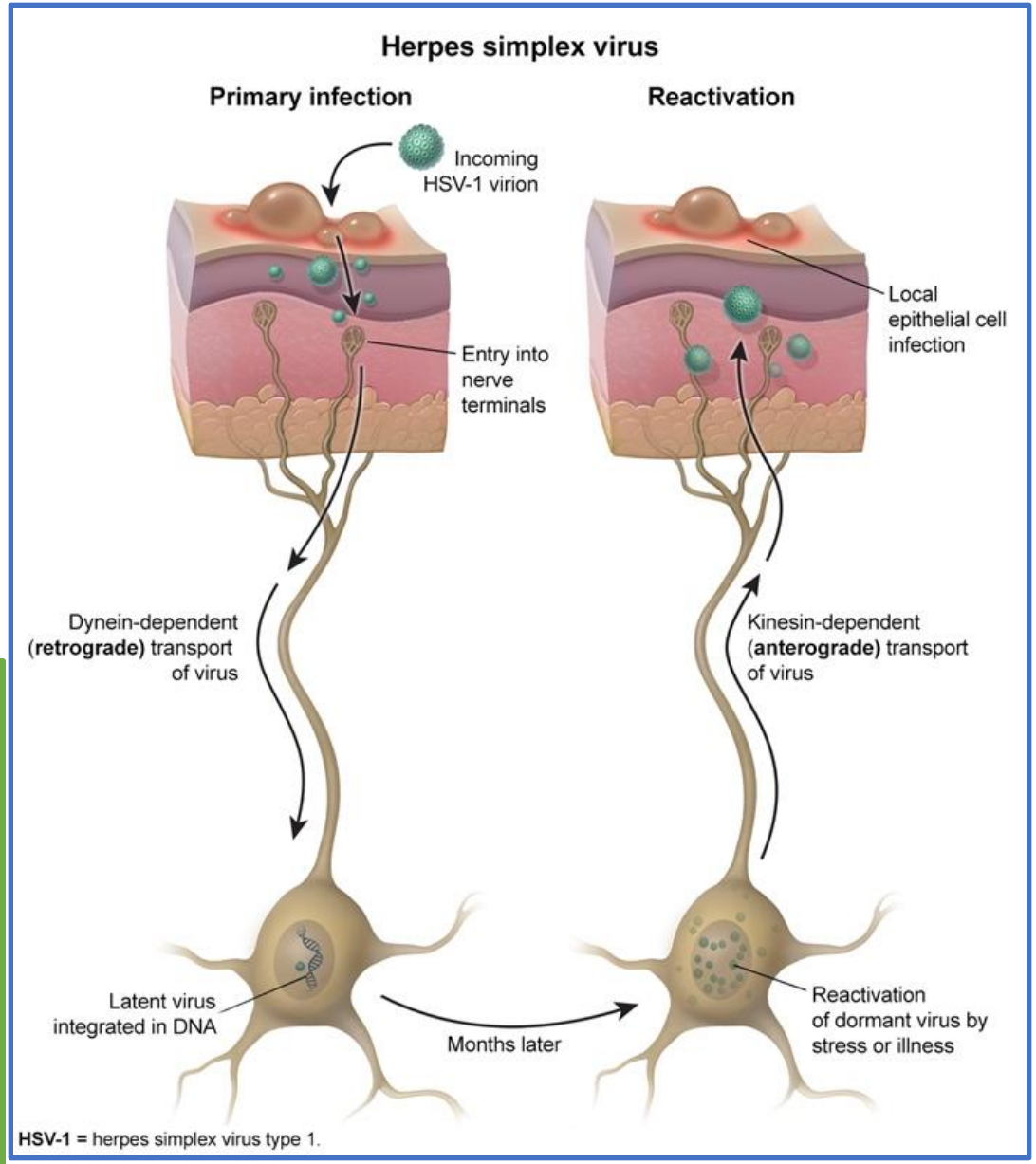
Latent persistent infections

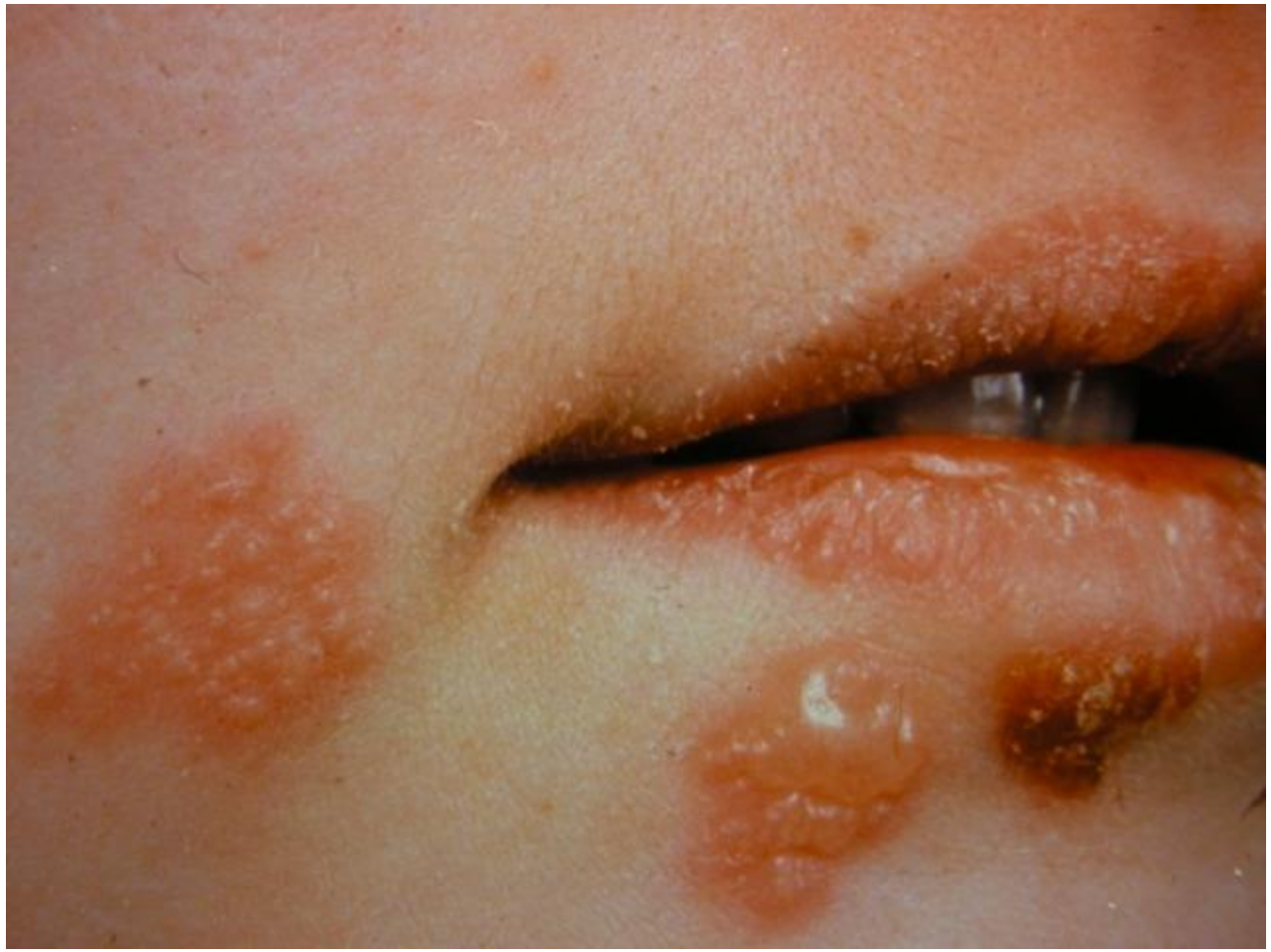
- Characterized by having acute periods between the latent periods.
- During the infection the viral titer peaks several times but in between the virus is in the latent phase.
- Eg: HSV1 (Oral infections), which periodically flares up to cause cold sores before going dormant again.
- What causes reactivation? 1) Drop in immunity 2) Stress





- Dynein is a microtubular motor protein that participates in retrograde axonal transport (ie, moving organelles toward the nucleus). Dynein is important in establishing the latent phase following primary HSV infection by transporting viral particles to the neural sensory ganglia.
- During reactivation, HSV particles rely on anterograde axonal transport to reach the skin and oral mucosa. Anterograde axonal transport is mediated by kinesin, a motor protein that moves intracellular cargo (eg, organelles, viral particles) away from the nucleus, down the axon, and toward the nerve terminal.





This patient is suffering from recurrent bouts of **herpes labialis** ("cold sores"), which is most commonly caused by ***herpes simplex virus 1*** **(*HSV-1*)**. Primary infection occurs following contact with an affected individual's saliva. Although it is often asymptomatic, infection can result in painful blister formation on the oral mucosa and surrounding skin of the mouth and lips.

Factors Involved in Viral Pathogenesis

- Transmission of the viruses
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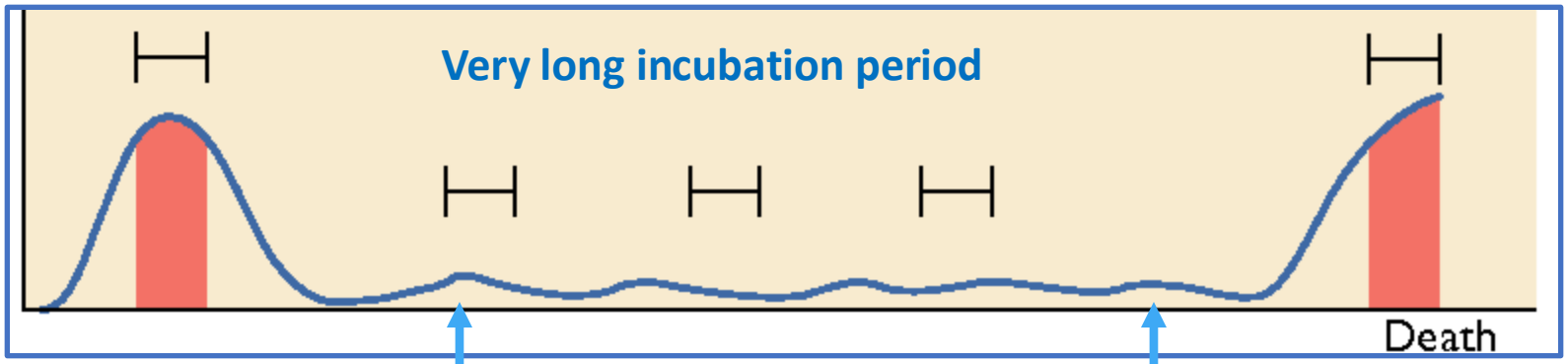
- Mode of viral spreading
- Viral pathogenesis at the cellular level
- **Viral pathogenesis at the host level (5)**
- Mechanisms of Viral Persistence
- Cell/Tissue Tropism
- Damage caused by the virus

Slow persistent infections

- Starts with acute infection.
- Then the symptoms subside but the amount of virus never goes to baseline.
- There is a struggle between the virus and the immune system.
- The virus is not dormant, it is replicating at a slow rate.
- Example: HIV



If the immune system drops the symptoms appear

Virus can be detected during the incubation period because it doesn't reach the base line

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Mechanisms of Viral Persistence

- Antigenic variation
- Molecular mimicry
- Restricted gene expression
- Down-regulation of MHC class I expression, resulting in lack of recognition of infected cells e.g. Adenoviruses
- Down-regulation of accessory molecules involved in immune recognition e.g. By EBV.
- Direct infection of the cells of the immune system itself e.g. retroviruses (HIV) - often resulting in immunosuppression

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- Mechanisms of Viral Persistence
- **Cell/Tissue Tropism**
- Damage caused by the virus

Cell Tropism

Viral affinity for specific body tissues (tropism) is determined by

- Cell receptors for virus.
- Cell transcription factors that recognize viral promoters and enhancer sequences.
- Ability of the cell to support virus replication.
- Physical barriers.
- Local temperature and pH.
- Digestive enzymes and bile in the gastrointestinal tract that may inactivate some viruses.

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- Cell/Tissue Tropism
- **Damage caused by the virus**

Damage caused by the virus

Viruses can destroy cells through a variety of mechanisms:

1. Direct cytopathic effects to disrupt cellular functions through releasing enzymes to degrade host metabolic precursors

   OR

2. Releasing proteins that inhibit the synthesis of important host factors, proteins, DNA and/or RNA

Thanks

- إن مرحلة العلم التي يغبط الناس عليها صاحبها لا تؤتى براحة الأبدان. قال تعالى (يا يحيى خذ الكتاب بقوة)
- تذكروا أنكم فرحة أهاليكم، حاولوا ما استطعتم أن تديموا الفرحة عليهم بنجاحكم
- تذكر أن مرحلة الامتحانات هي مرحلة مؤقتة، لكن ثمر النجاح يدوم