Pathogenesis of viral infection

Lecturer
Dr Ashraf Khasawneh
Department of Biomedical Sciences

Viral epidemiology

- Endemic: Disease present at fairly low but constant level
- Epidemic: Infection greater than usually found in a population
- Pandemic: Infections that are spread worldwide
- Infectivity: The frequency with which an infection is transmitted when contact between a virus and host occurs
- Disease index: # persons develop disease/ total infected
- Virulence: # fatal cases/ total # of cases
- Incidence: # of new cases within a specific period of time %
- Prevalence: # of cases of a disease that are present in a particular population at a given time

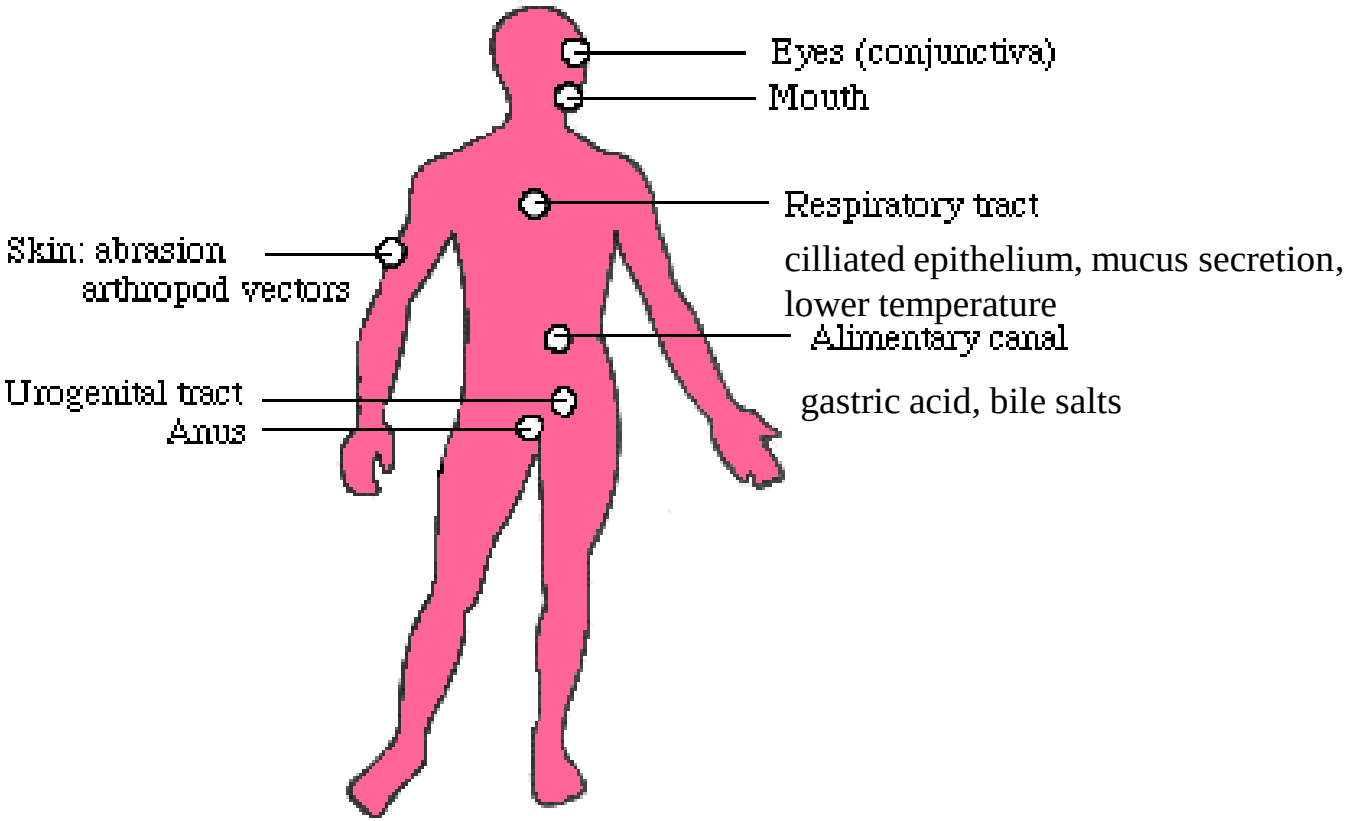
What does a pathogen have to do?

- **Infect (infest) a host**
- **Reproduce (replicate) itself**
- **Ensure that its progeny are transmitted to another host**

Virus route of entry

1. **Horizontal: (person to person)**
   a) **Inhalation- via the respiratory tract ex.** RSV, MMR, VZV, Rhinovirus
   b) **Ingestion- via the gastrointestinal tract ex.** Hep A, Rota, Astroviruses, Caliciviruses
   c) **Inoculation- through skin abrasions; mucous membranes (e.g. sexual transmission); transfusion; injections (e.g. by doctors or via shared syringes in drug abuse); transplants**
2. **Vertical : i.e. from mother to fetus**
   a) **Transplacental ex.** CMV, rubella, HIV
   b) **Delivery ex.** Hep B, Hep C, HSV, HIV, HPV
   c) **Breast feeding ex.** CMV, Hep B, HIV
3. **Zoonotic (animal to human)**
   a) **Animal bite ex.** Rabies
   b) **Insect bite ex.** Dengue, West Nile
   c) **Animal excreta ex.** Hanta, Arena

Sites of virus entry



Terminology

- Incubation period: Time between exposure and first symptom

Influenza	1-2d	Chickenpox	13-17d
Common cold	1-3d	Mumps	16-20d
Bronchiolitis,croup	3-5d	Rubella	17-20d
Acute respiratory disease	5-7d	Mononucleosis	30-50d
Dengue	5-8d	Hepatitis A	15-40d
Herpes simplex	5-8d	Hepatitis B	50-150d
Enteroviruses	6-12d	Rabies	30-100d
poliomyelitis	5-20d	Papilloma	50-150d
Measles	9-12d	HIV	1-10y

Terminology

- Communicability: Ability of virus to shed into secretions
- Localized infection: infection limited to site of entry
- Disseminated infection: spread throughout the body
- Primary viremia: site of entry > regional LN > blood
- Secondary viremia: site of entry > regional LN > blood > organs (liver, spleen) > blood

Primary Replication

- **Having gained entry to a potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection will remain localized at the site of entry or spread to become a systemic infection**

Secondary Replication

- Occurs in systemic infections when a virus reaches other tissues in which it is capable of replication, e.g. Poliovirus (gut epithelium - neurons in brain & spinal cord) or Lentiviruses (macrophages - CNS + many other tissues). If a virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results.

Localized Infections:		
Virus:	**Primary Replication:**	
Rhinoviruses	U.R.T.	
Rotaviruses	Intestinal epithelium	
Papillomaviruses	Epidermis	
Systemic Infections:		
Virus:	**Primary Replication:**	**Secondary Replication:**
Enteroviruses	Intestinal epithelium	Lymphoid tissues, C.N.S.
Herpesviruses	Oropharynx or G.U.tract	Lymphoid cells, C.N.S.

Spread Throughout the Host

- Apart from direct cell-cell contact, there are 2 main mechanisms for spread throughout the host:
- via the bloodstream
- via the nervous system

via the bloodstream

- Virus may get into the bloodstream by direct inoculation - e.g. Arthropod vectors, blood transfusion or I.V. drug abuse. The virus may travel free in the plasma (Togaviruses, Enteroviruses), or in association with red cells (Orbiviruses), platelets (HSV), lymphocytes (EBV, CMV) or monocytes (Lentiviruses). Primary viraemia usually proceeds and is necessary for spread to the blood stream, followed by more generalized, higher titre secondary viraemia as the virus reaches other target tissues or replicates directly in blood cells

via the nervous system

- spread to nervous system is preceded by primary viraemia. In some cases, spread occurs directly by contact with neurons at the primary site of infection, in other cases via the bloodstream. Once in peripheral nerves, the virus can spread to the CNS by axonal transport along neurons (classic - HSV). Viruses can cross synaptic junctions since these frequently contain virus receptors, allowing the virus to jump from one cell to another

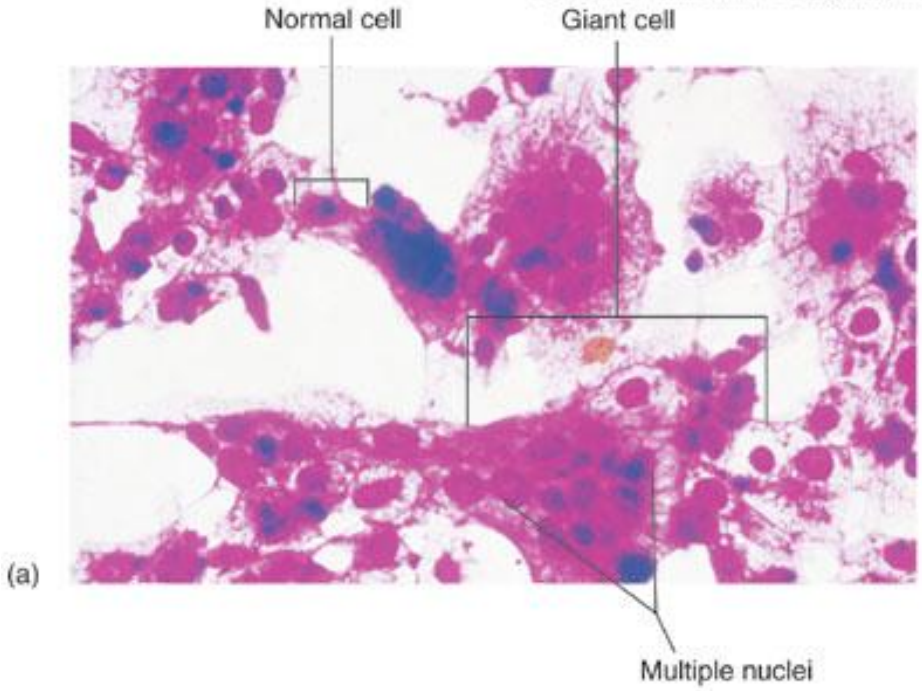
Virulence and cytopathogenicity

- Virulence: the ability of the virus to cause disease in infected cell
- Persistent infection
  - Latent infection, lysogeny
  - Chronic infection
- Permissive cells allow production of virions and/or transformation
- Virulent viruses Kill target cell and cause disease (productive response)
- Nonpermissive cells permits cell transformation only
- Abortive infection no virus replication, early viral proteins cause cell death
- Cytopathic effect

Cytopathic effects- virus-induced damage to cells

1. Changes in size & shape
2. Cytoplasmic inclusion bodies
3. Nuclear inclusion bodies
4. Cells fuse to form multinucleated cells
5. Cell lysis
6. Alter DNA
7. Transform cells into cancerous cells
8. Virokines and viroreceptors: DNA viruses; cell proliferate and avoid host defenses

Cytopathic changes in cells



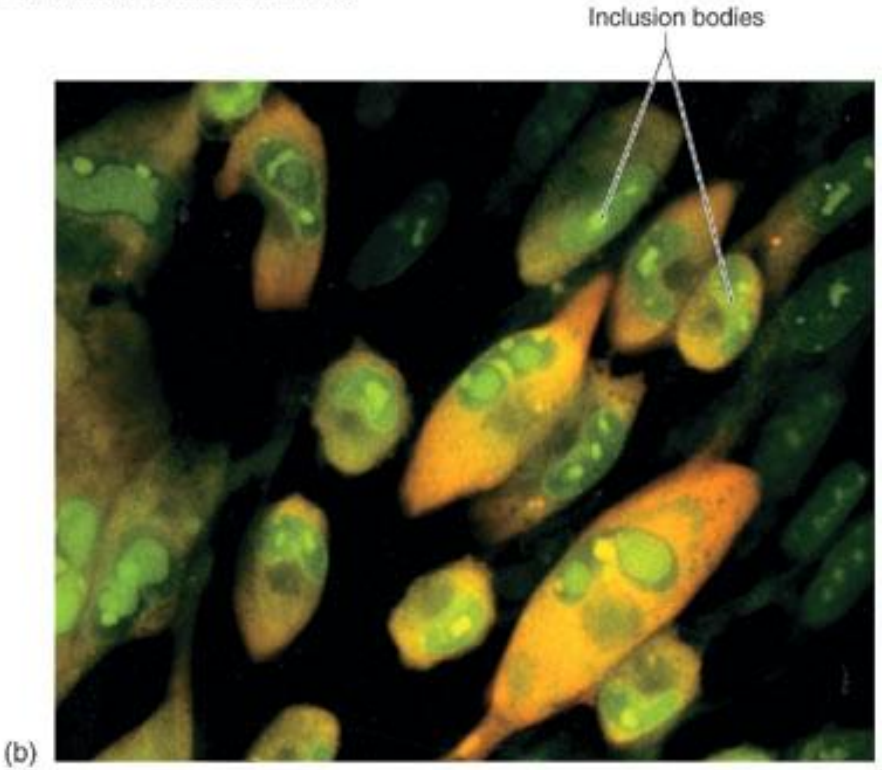


TABLE 6.4

Cytopathic Changes in Selected Virus-Infected Animal Cells

Virus	Response in Animal Cell
Smallpox virus	Cells round up; inclusions appear in cytoplasm
Herpes simplex	Cells fuse to form multinucleated giant cells; nuclear inclusions
Adenovirus	Clumping of cells; nuclear inclusions
Poliovirus	Cell lysis; no inclusions
Reovirus	Cell enlargement; vacuoles and inclusions in cytoplasm
Influenza virus	Cells round up; no inclusions
Rabies virus	No change in cell shape; cytoplasmic inclusions (Negri bodies)
HIV	Giant cells with numerous nuclei (multinucleate)

Patterns of viral infection

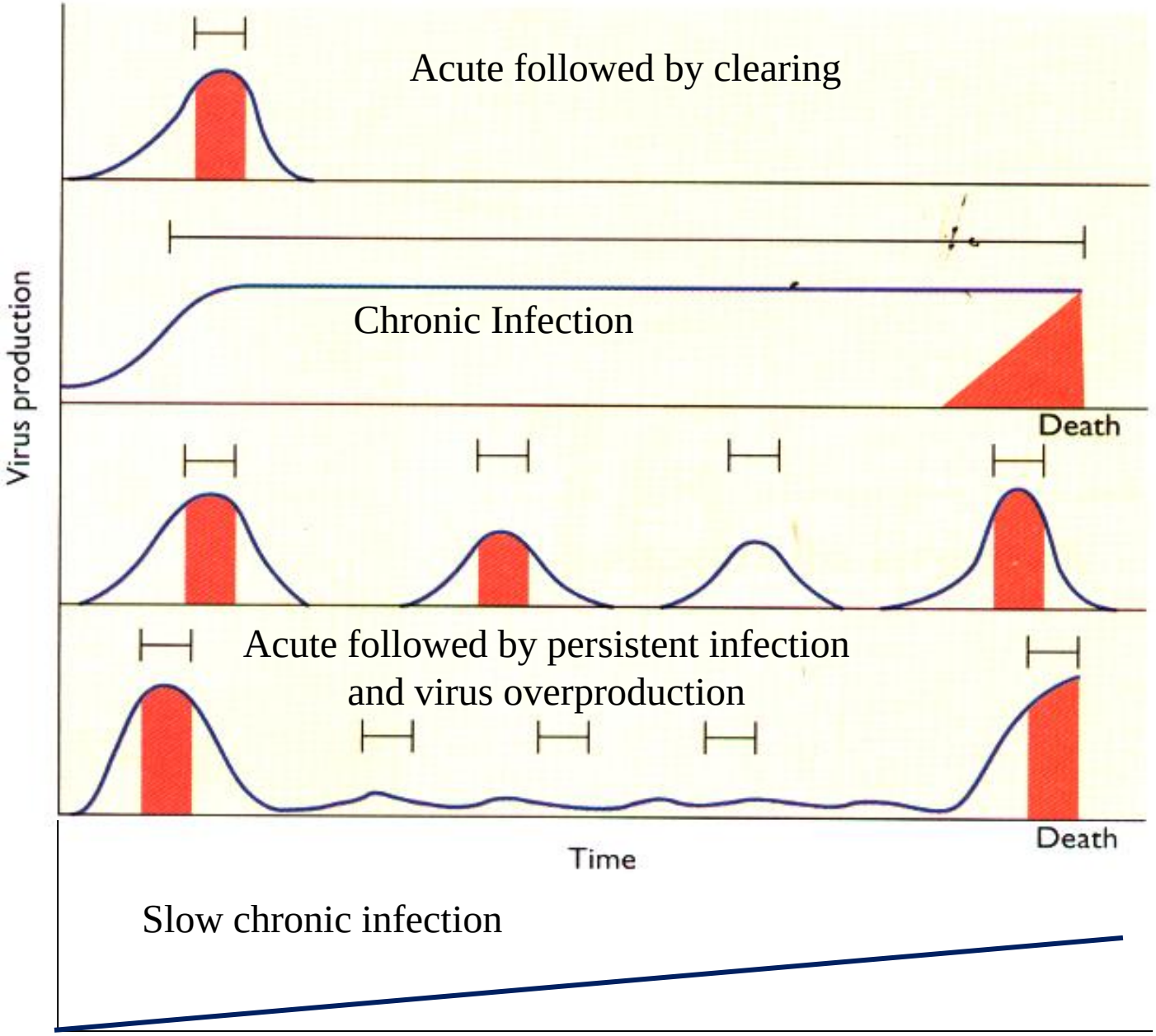
- **Inapparent infection(Subclinical infection) .**
- **Apparent infection:**
- **Acute infection**
- **Persistent Infection**

Chronic infections

Latent Infection

Slow virus infections

Patterns of viral infection



Acute infection
- Rhinovirus
- Rotavirus
- Influenza virus

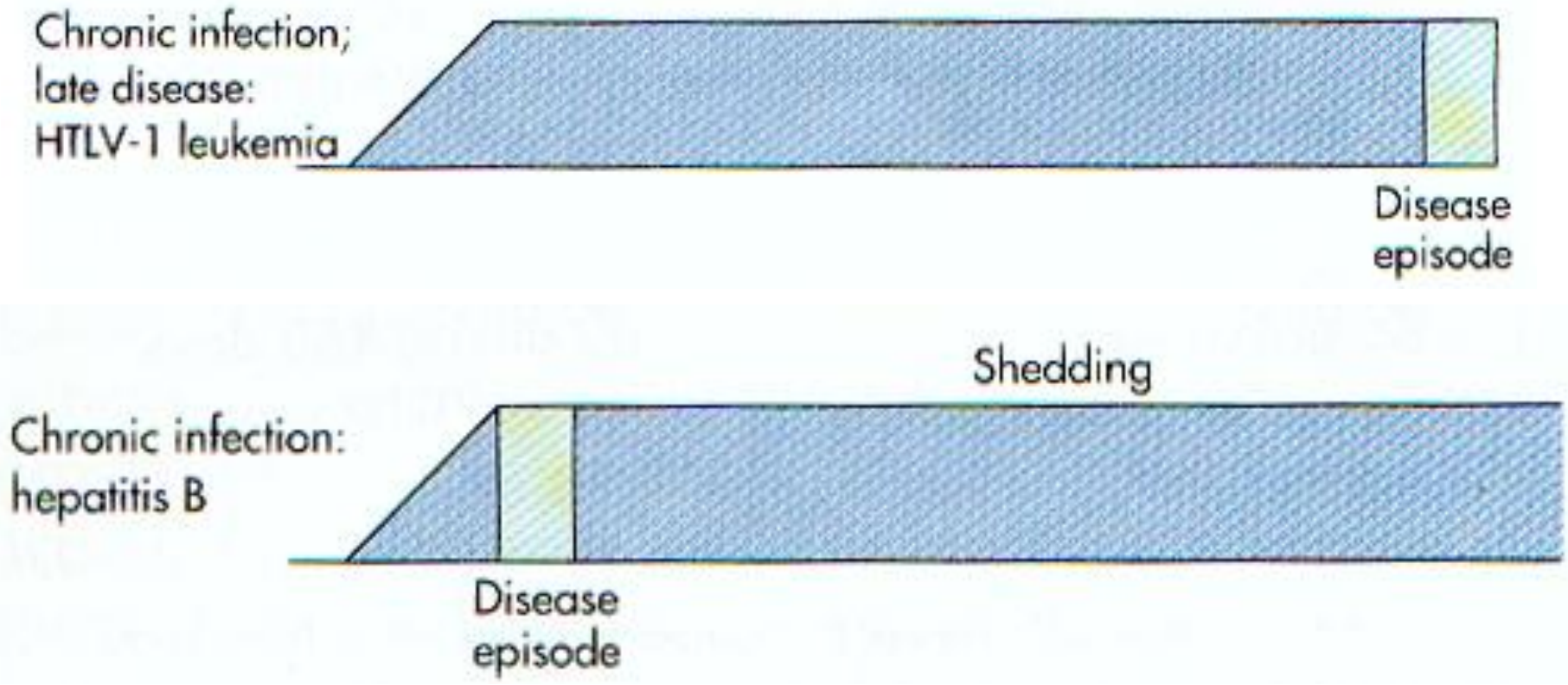
Persistent infection
- Lymphocytic choriomeningitis virus

Latent, reactivating infection
- Herpes simplex virus

Slow virus infection
- Measles virus SSPE
- Human immunodeficiency virus

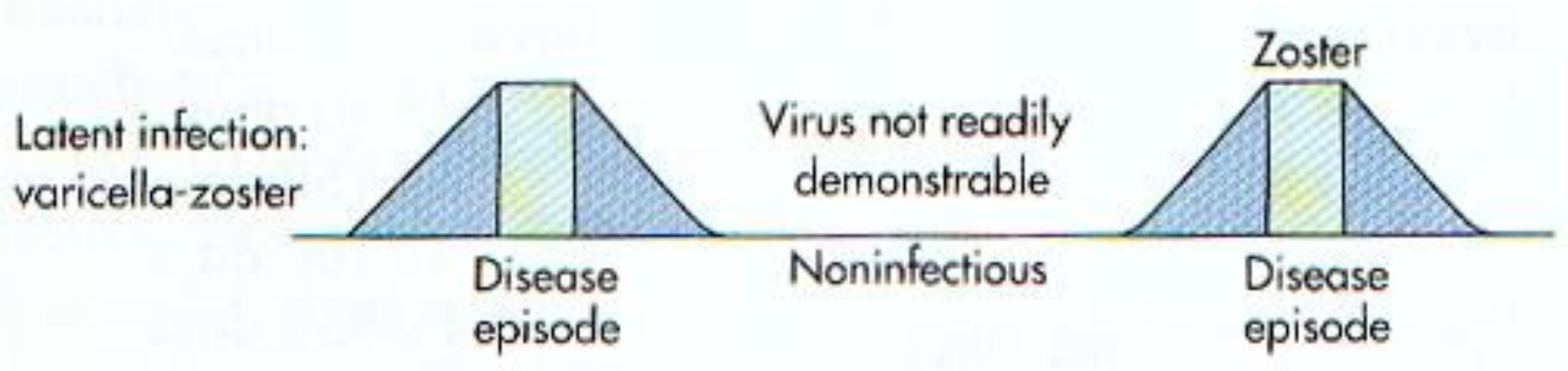
Chronic Infection

- Virus can be continuously detected ; mild or no clinical symptoms may be evident.



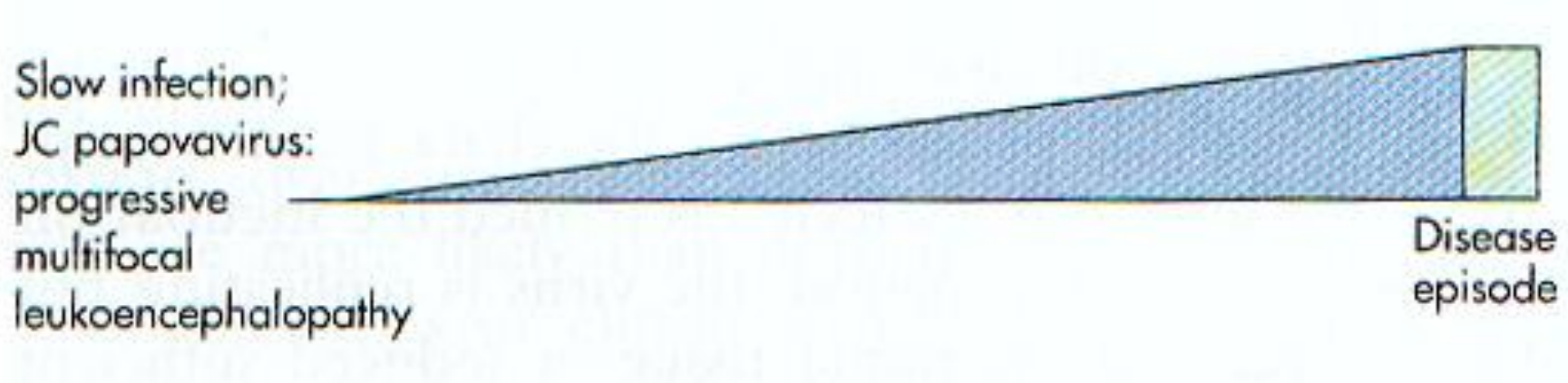
Latent infection

The Virus persists in an occult, or cryptic, from most of the time. There will be intermittent flare-ups of clinical disease , Infectious virus can be recovered during flare-ups . Latent virus infections typically persist for the entire life of the host



Slow virus infection

- A prolonged incubation period, lasting months or years, during which virus continues to multiply. Clinical symptoms are usually not evident during the long incubation period .



Overall fate of the cell

- The cell dies in **cytocidal** infections
  this may be **acute** (when infection is brief and self-limiting) or **chronic** (drawn out, only a few cells infected while the rest proliferate)-Cytocidal effect
- The cell lives in **persistent** infections
  this may be **productive** or **nonproductive** (refers to whether or not virions are produced) or it may alternate between the two by way of **latency** and **reactivation -** Steady state infection

- **Transformation-**Integrated infection (Viruses and Tumor)
  - RNA tumor viruses usually transform cells to a malignant phenotype by integrating their own genetic material into the cellular genome and may also produce infectious progeny.
  - Retroviruses:
    - Acute transforming viruses: *v-src* oncogene mimic cellular genes (proto-oncogene)
    - Insertional mutagenesis: inappropriate expression of a proto-oncogene adjacent to integrated viral genome
    - Transactivating factors: *tax gene in HTLV-1; turns on cellular genes causing cellular proliferation*
  - DNA tumor virus infections are often cytocidal; thus transformation is associated with abortive or restrictive infections in which few viral genes are expressed. The persistence of at least part of the viral genome within the cell is required for cell transformation. This is accompanied by the continual expression from a number of viral genes.
  - P53: regulates the cell cycle; functions as a tumor suppressor that is involved in preventing cancer. HPV
  - pRb: prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide. HPV
- **Apoptosis**
  - P53: initiate apoptosis, programmed cell death, if DNA damage proves to be irreparable

Types of Viral infections at the cellular level

Type	Virus production	Fate of cell
Abortive	-	No effect
Cytolytic	+	Death
Persistent		
Productive	+	Senescence
Latent	-	No effect
Transforming		
DNA viruses	-	Immortalization
RNA viruses	+	Immortalization

Mechanisms of viral cytopathogenesis

Inhibition of cellular protein synthesis	**Polioviruses, HSV, poxviruses, togaviruses**
Inhibition and degradation of cellular DNA	**herpesviruses**
Alteration of cell membrane structure **Glycoprotein insertion** **Syncytia formation** **Disruption of cytoskeleton permeability**	**All enveloped viruses** **HSV, VZ virus, HIV** **HSV, HIV, RSV** **Togaviruses, herpesviruses**
Inclusion bodies	**Rabies**
Toxicity of Virion components	**Adenovirus fibers**

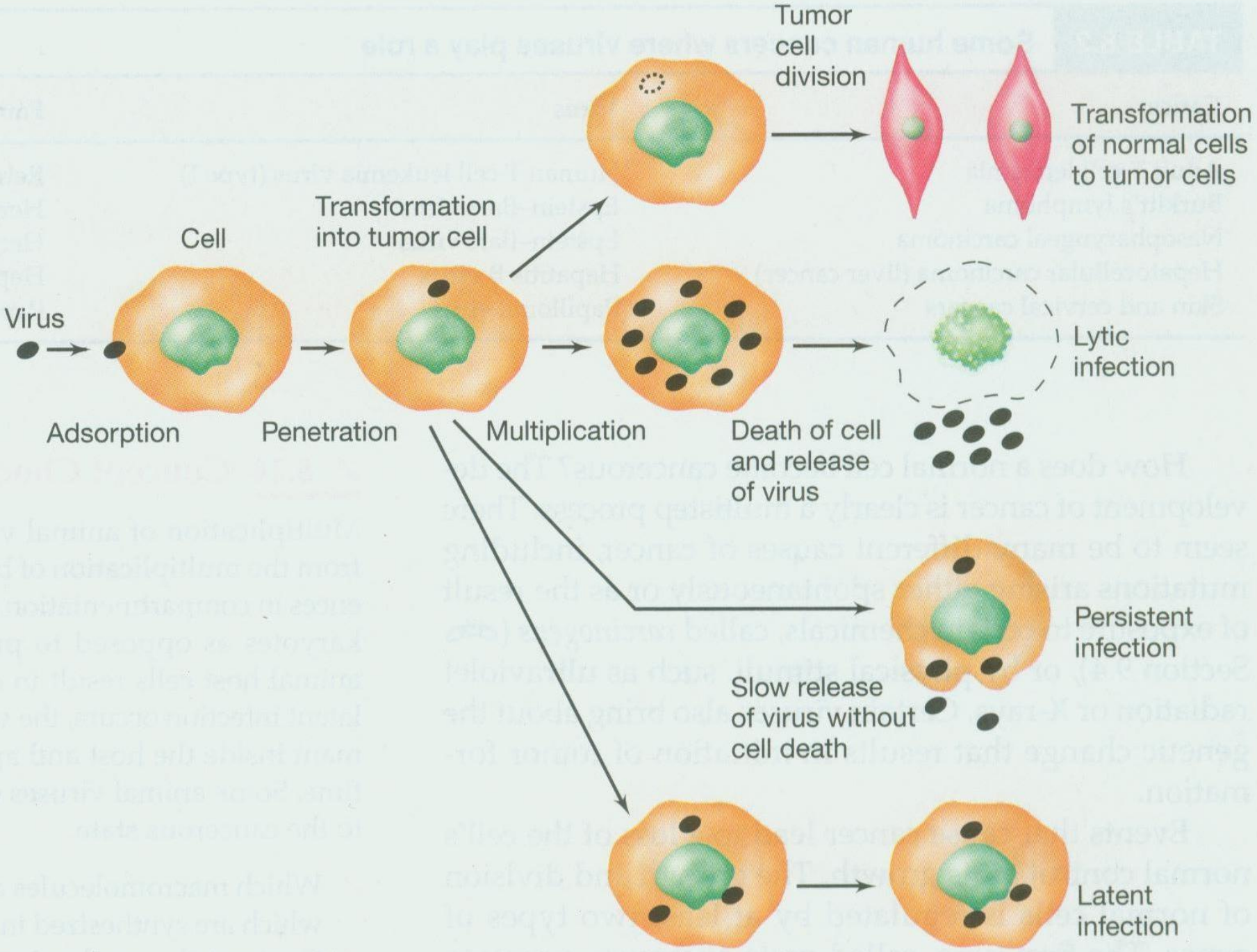
Possible consequences to a cell that is infected by a virus

- **Lytic infections: Result in the destruction of the host cell; are caused by virulent viruses, which inherently bring about the death of the cells that they infect.**

- **persistent infections: Infections that occur over relatively long periods of time, Where the release of the viral particles may be slow and the host cell may not be lysed.**

- **latent infections: Delay between the infection by the virus and the appearance of symptoms.**

- **Transformation: Some animal viruses have the potential to change a cell from a normal cell into a tumor cell which grows without restraint.**


Tumor cell division
Transformation of normal cells to tumor cells
Transformation into tumor cell
Cell
Virus
Lytic infection
Adsorption
Penetration
Multiplication
Death of cell and release of virus
Persistent infection
Slow release of virus without cell death
Latent infection