Introduction to Microbiology

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Pathogenesis of Viral Diseases

- The outcome of a viral infection is determined by the nature of the **virus-host interaction**.
- Viruses encode activities **(virulence factors)** that promote the efficiency of viral **replication**, viral **transmission**, access and **binding** of the virus to target tissue, or **escape** of the virus from host defences and immune resolution.
- Host factors affecting viral disease include immunocompetence, age, previous infection,…

Pathogenesis of Viral Diseases

- A particular disease may be **caused by several viruses** that have a common tissue preference. (hepatitis—liver, encephalitis—CNS)

- A particular virus may cause **several different diseases** herpes simplex virus type 1 (HSV-1) can cause gingivostomatitis, pharyngitis, herpes labialis (cold sores), genital herpes.

- A particular virus **may cause no symptoms at all**. Which is a major source of contagion.

The outcome of a viral infection is determined by the nature of the **virus-host interaction** and the **host's response** to the infection.

Nature of the Disease

Target tissue
Portal of entry of virus
Access of virus to target tissue
Tissue tropism of virus
Permissiveness of cells for viral replication
Pathogenic activity (strain)

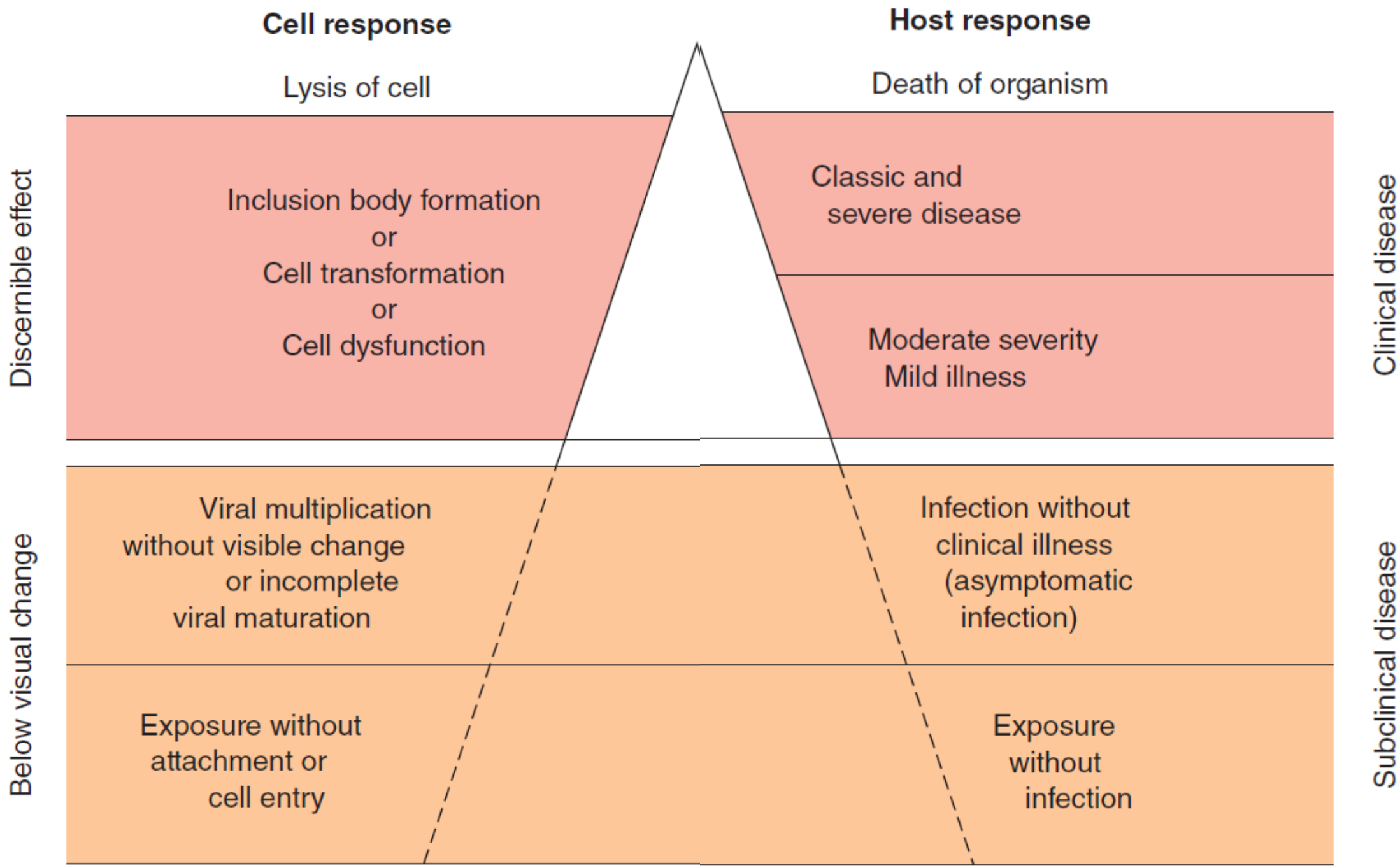
Severity of Disease

Cytopathic ability of virus
Immune status (naïve or immunized)
Competence of the immune system
Prior immunity to the virus
Immunopathology
Virus inoculum size
Length of time before resolution of infection
General health of the person
Nutrition
Other diseases influencing immune status
Genetic makeup of the person
Age

Pathogenesis of Viral Diseases

- The relative susceptibility of a person and the severity of the disease depend on the following factors:

1. The mechanism of exposure and site of infection
2. The immune status, age, and general health of the person
3. The viral dose
4. The genetics of the virus and the host


Cell response
Lysis of cell
Host response
Death of organism
Discernible effect
Below visual change
Inclusion body formation
or
Cell transformation
or
Cell dysfunction
Classic and
severe disease
Moderate severity
Mild illness
Viral multiplication
without visible change
or incomplete
viral maturation
Infection without
clinical illness
(asymptomatic
infection)
Exposure without
attachment or
cell entry
Exposure
without
infection
Clinical disease
Subclinical disease

Steps in Viral Pathogenesis

Box 37-2 Progression of Viral Disease

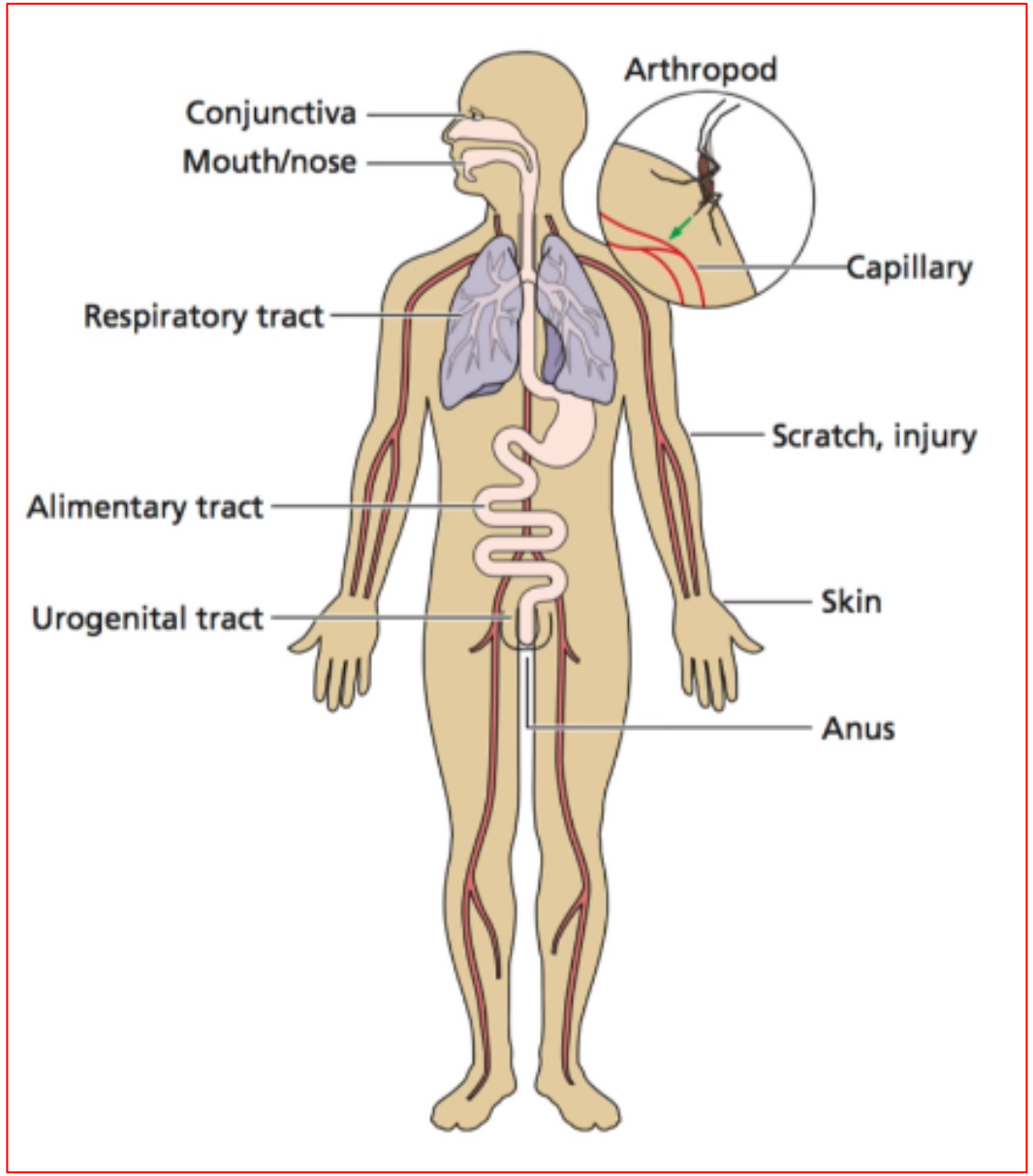
1. **Acquisition** (entry into the body)
2. Initiation of infection at a primary site
3. Activation of innate protections
4. An **incubation period,** when the virus is amplified and may spread to a secondary site
5. Replication in the **target tissue,** which causes the characteristic disease signs
6. **Host responses** that limit and contribute (immunopathogenesis) to the disease
7. Virus production in a tissue that releases the virus to other people for **contagion**
8. **Resolution** or **persistent infection/chronic disease**

A. Entry and Primary replication

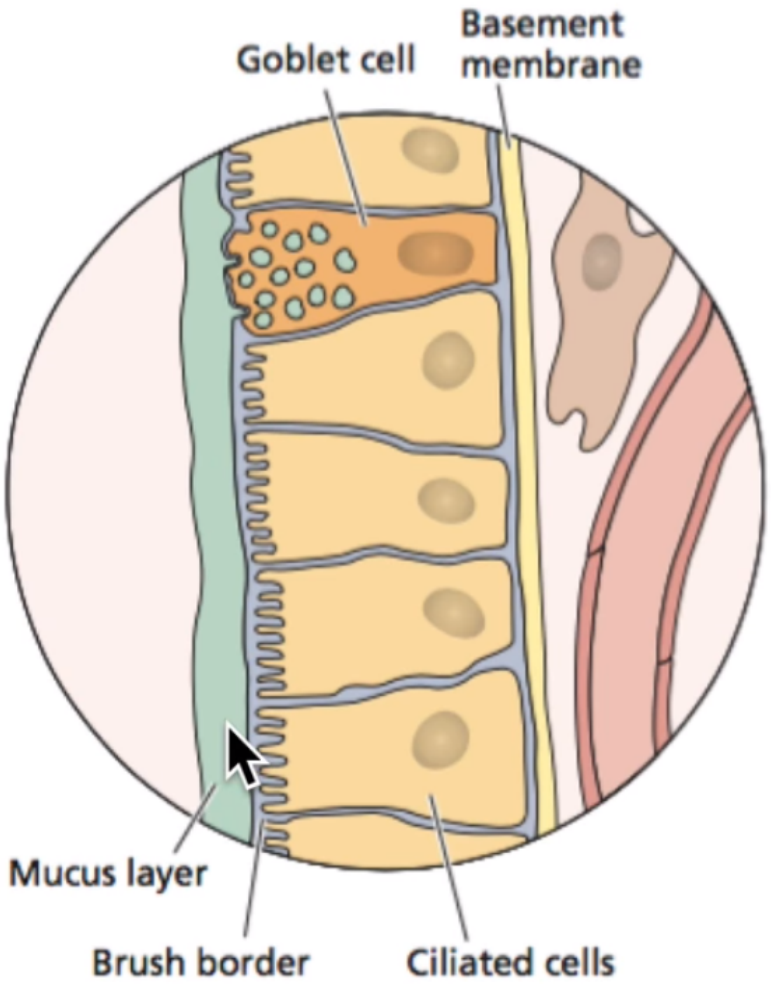
- The virus gains **entry into the body** through breaks in the **skin** (cuts, bites, injections) or across the **mucoepithelial membranes** that line the orifices of the body (eyes, respiratory tract, mouth, genitalia, and gastrointestinal tract). ***Inhalation*** *is probably the most common route of viral infection*.

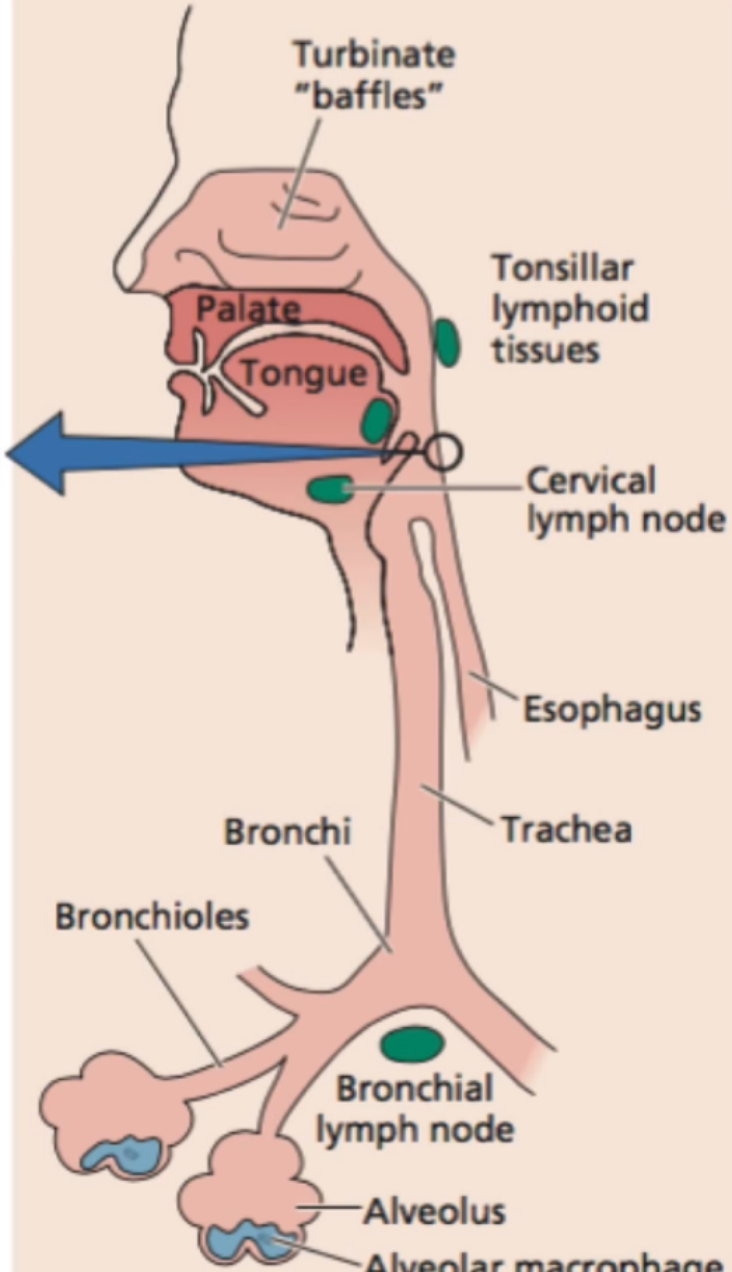
- Viruses usually **replicate at the primary site of entry**. Some, such as influenza viruses (respiratory infections) and noroviruses (gastrointestinal infections), produce disease at the portal of entry and likely have no necessity for further systemic spread.

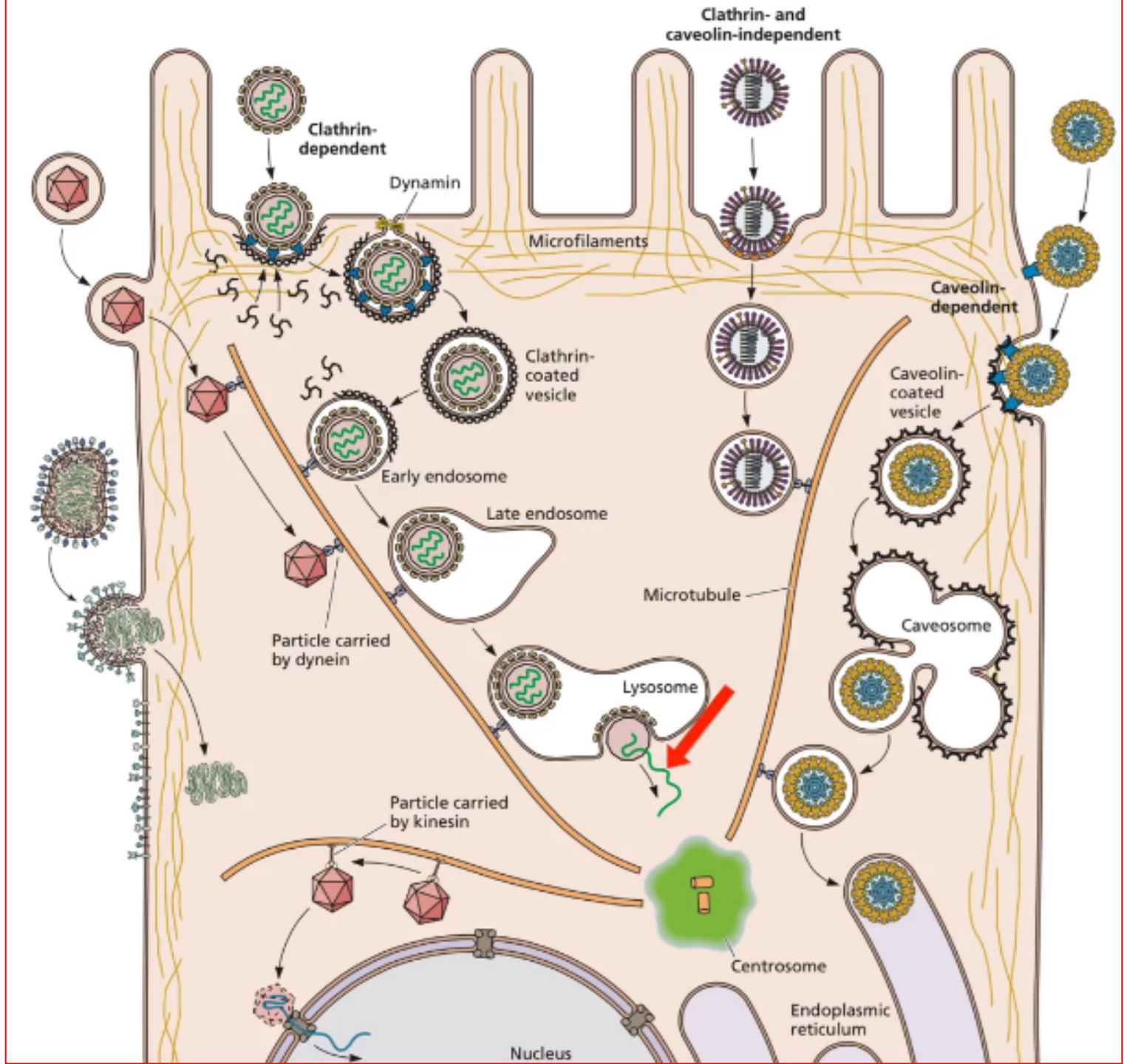
- Some viruses are introduced **directly** into the **bloodstream** by needles (hepatitis B, human immunodefi ciency virus [HIV]), by blood transfusions, or by insect vectors (arboviruses).



Route of Entry	Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Respiratory tract	Parvovirus		B19
	Adenovirus	Most types	
	Herpesvirus	Epstein-Barr virus, herpes simplex virus	Varicella virus
	Poxvirus		Smallpox virus
	Picornavirus	Rhinoviruses	Some enteroviruses
	Togavirus		Rubella virus
	Coronavirus	Most types	
	Orthomyxovirus	Influenza virus	
	Paramyxovirus	Parainfluenza viruses, respiratory syncytial virus	Mumps virus, measles virus
Mouth, intestinal tract	Adenovirus	Some types	
	Calicivirus	Noroviruses	
	Herpesvirus	Epstein-Barr virus, herpes simplex virus	Cytomegalovirus
	Picornavirus		Some enteroviruses, including poliovirus, and hepatitis A virus
	Reovirus	Rotaviruses	
Skin			
Mild trauma	Papillomavirus	Most types	
	Herpesvirus	Herpes simplex virus	
	Poxvirus	Molluscum contagiosum virus, orf virus	
Injection	Hepadnavirus		Hepatitis B
	Herpesvirus		Epstein-Barr virus, cytomegalovirus
	Retrovirus		Human immunodeficiency virus
Bites	Togavirus		Many species, including eastern equine encephalitis virus
	Flavivirus		Many species, including yellow fever virus
	Rhabdovirus		Rabies virus



Site of reproduction	Clinical manifestation	Virus
	Rhinitis (common cold) Pharyngitis Laryngitis Tracheitis Bronchitis Bronchiolitis Bronchopneumonia	Rhinovirus Coronavirus Parainfluenza virus Respiratory syncytial virus Influenza virus Adenovirus Herpes simplex virus Epstein-Barr virus Parainfluenza virus Respiratory syncytial virus Influenza virus Adenovirus Measles SARS MERS


Clathrin- and caveolin-independent
Clathrin-dependent
Dynamin
Microfilaments
Caveolin-dependent
Clathrin-coated vesicle
Caveolin-coated vesicle
Early endosome
Late endosome
Microtubule
Particle carried by dynein
Caveosome
Lysosome
Particle carried by kinesin
Centrosome
Endoplasmic reticulum
Nucleus

Box 36-4 Virion Structure: Naked Capsid

Component

Protein

Properties*

Is environmentally stable to the following:
- Temperature
- Acid
- Proteases
- Detergents
- Drying

Is released from cell by lysis

Consequences*

Can be spread easily (on fomites, from hand to hand, by dust, by small droplets)
Can dry out and retain infectivity
Can survive the adverse conditions of the gut
Can be resistant to detergents and poor sewage treatment
Antibody may be sufficient for immunoprotection

*Exceptions exist.

Box 36-5 Virion Structure: Envelope

Components

Membrane
Lipids
Proteins
Glycoproteins

Properties*

Is environmentally labile—disrupted by the following:
- Acid
- Detergents
- Drying
- Heat

Modifies cell membrane during replication
Is released by budding and cell lysis

Consequences*

Must stay wet
Cannot survive the gastrointestinal tract
Spreads in large droplets, secretions, organ transplants, and blood transfusions
Does not need to kill the cell to spread
May need antibody and cell-mediated immune response for protection and control
Elicits hypersensitivity and inflammation to cause immunopathogenesis

*Exceptions exist.

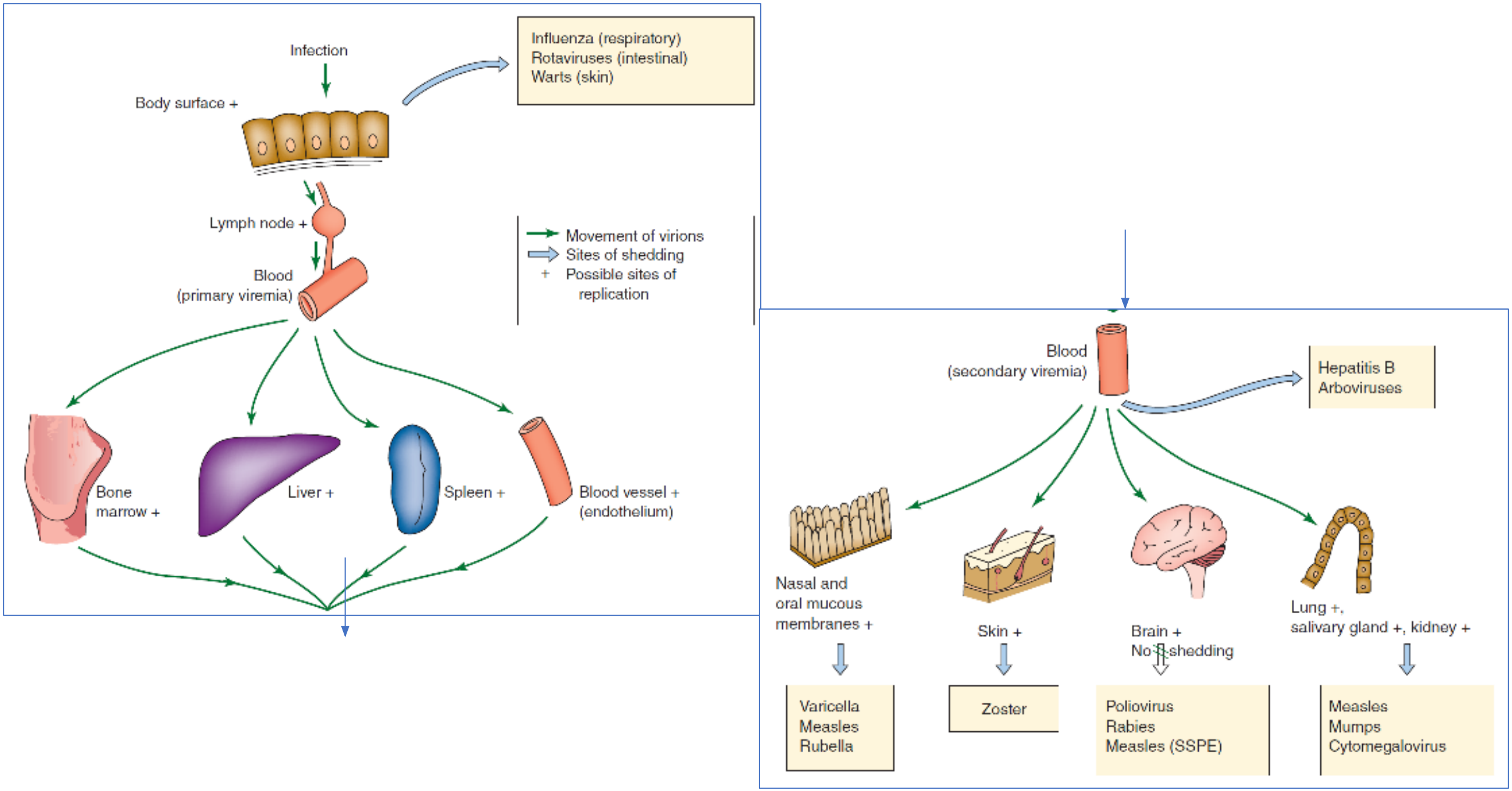
B. Viral Spread and Cell Tropism

Many viruses produce disease at sites **distant** from their point of entry, the most common route is via the **bloodstream** or **lymphatics**. The presence of virus in the blood is called **viremia** . Virions may be **free** in the plasma (eg, enteroviruses, togaviruses) or associated with **particular cell types** (eg, measles virus)

Viruses tend to exhibit organ and cell specificities. Thus, **tropism** determines the pattern of systemic illness produced during a viral infection. (e.g. hepatitis B virus has a tropism for liver hepatocytes).

Tissue tropism depends mainly on **cell receptors** for attachment and internalization of the virus. Also **cellular enzymes** can be needed to modify viral proteins and initiate infection, and thus affect tropism.

For example, the JC polyomavirus enhancer is much more active in glial cells than in other cell types.


Infection
Body surface +
Influenza (respiratory)
Rotaviruses (intestinal)
Warts (skin)
Lymph node +
Blood
(primary viremia)
Movement of virions
Sites of shedding
+ Possible sites of replication
Bone marrow +
Liver +
Spleen +
Blood vessel + (endothelium)
Blood
(secondary viremia)
Hepatitis B
Arboviruses
Nasal and oral mucous membranes +
Skin +
Brain +
No shedding
Lung +, salivary gland +, kidney +
Varicella
Measles
Rubella
Zoster
Poliovirus
Rabies
Measles (SSPE)
Measles
Mumps
Cytomegalovirus

C. Cell Injury and Clinical Illness

- **Destruction of virus-infected cells** in the target tissues and **physiologic alterations** produced in the host by the tissue injury are partly responsible for the development of disease.

- General symptoms associated with many viral infections, such as **malaise** and **anorexia**, may **result from host response** functions such as cytokine production.

- **Inapparent infections** by viruses are very common.

Table 37-2 Mechanisms of Viral Cytopathogenesis

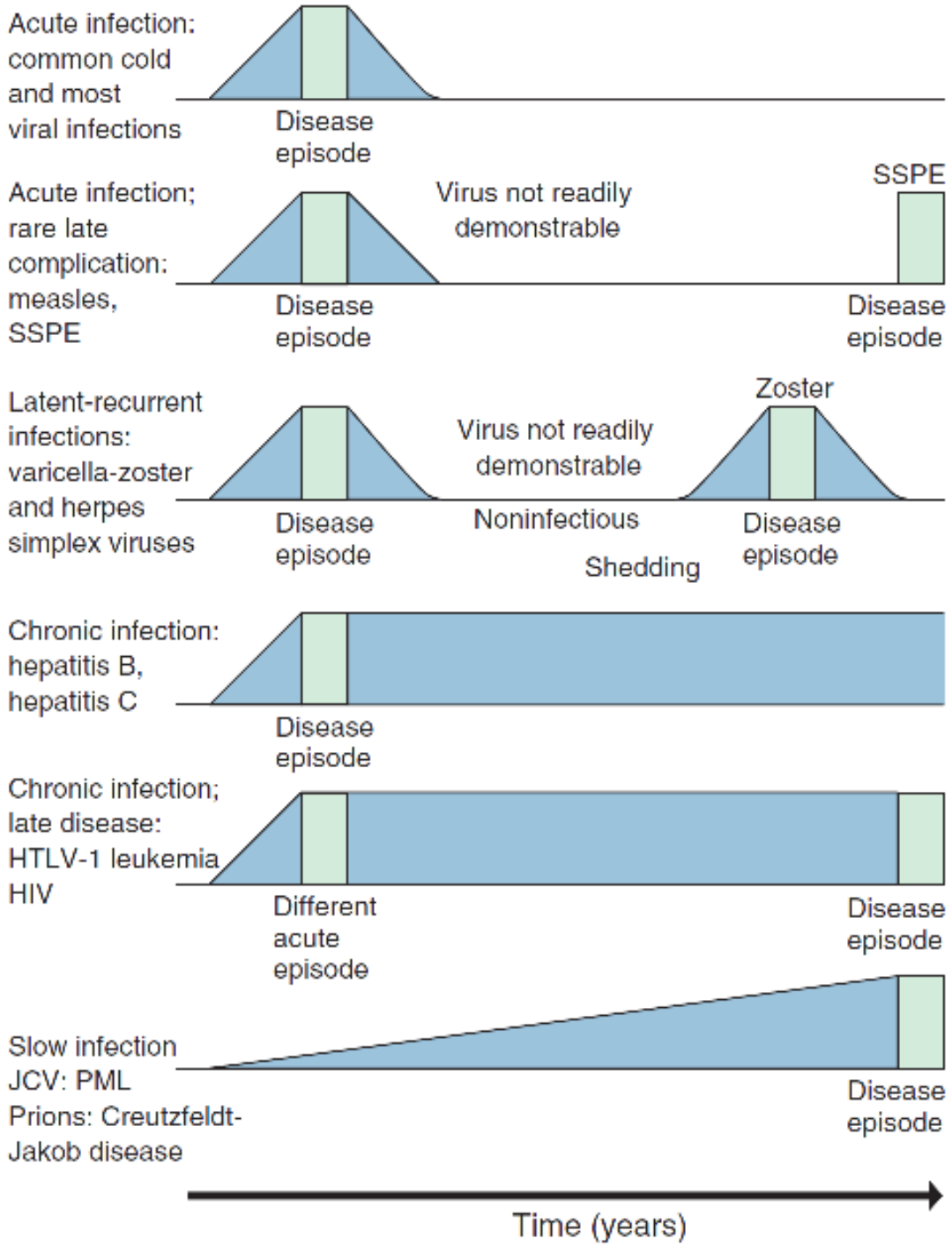
Mechanism	Examples
Inhibition of cellular protein synthesis	Poliovirus, herpes simplex virus (HSV), togaviruses, poxviruses
Inhibition and degradation of cellular DNA	Herpesviruses
Alteration of cell membrane structure	Enveloped viruses
Viral glycoprotein insertion	All enveloped viruses
Syncytia formation	HSV, varicella-zoster virus, paramyxoviruses, human immunodeficiency virus
Disruption of cytoskeleton	Nonenveloped viruses (accumulation), HSV
Permeability	Togaviruses, herpesviruses
Toxicity of virion components	Adenovirus fibers, reovirus NSP4 protein

D. Recovery from Infection

- The host either succumbs or recovers from viral infection.

- Recovery mechanisms include both innate and adaptive immune responses. **Interferon** (IFN) and other cytokines, humoral and cell-mediated immunity, and possibly other host defense factors are involved.

- In acute infections, recovery is associated with viral **clearance**. However, there are times when the host remains **persistently** infected with the virus.



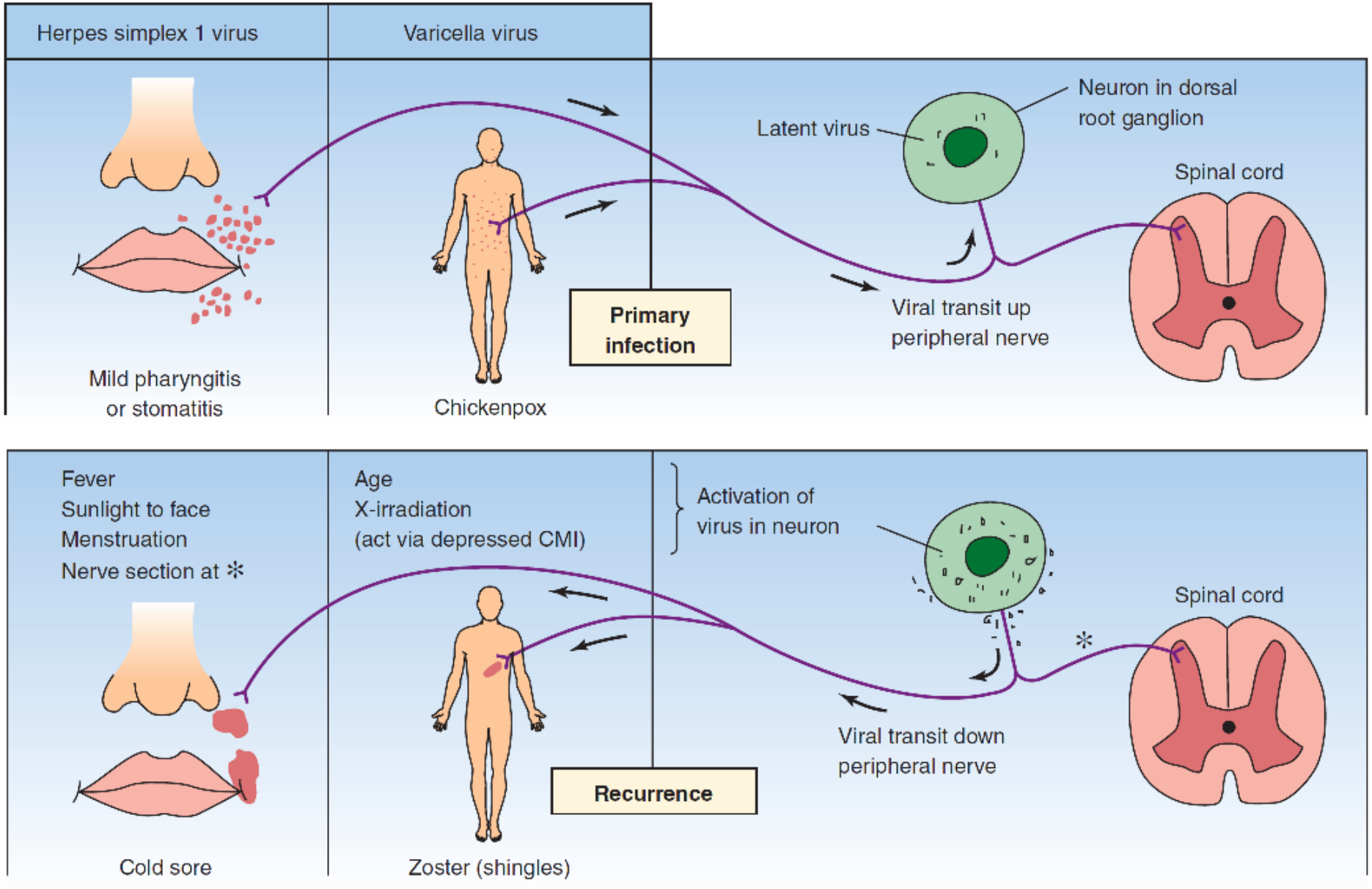
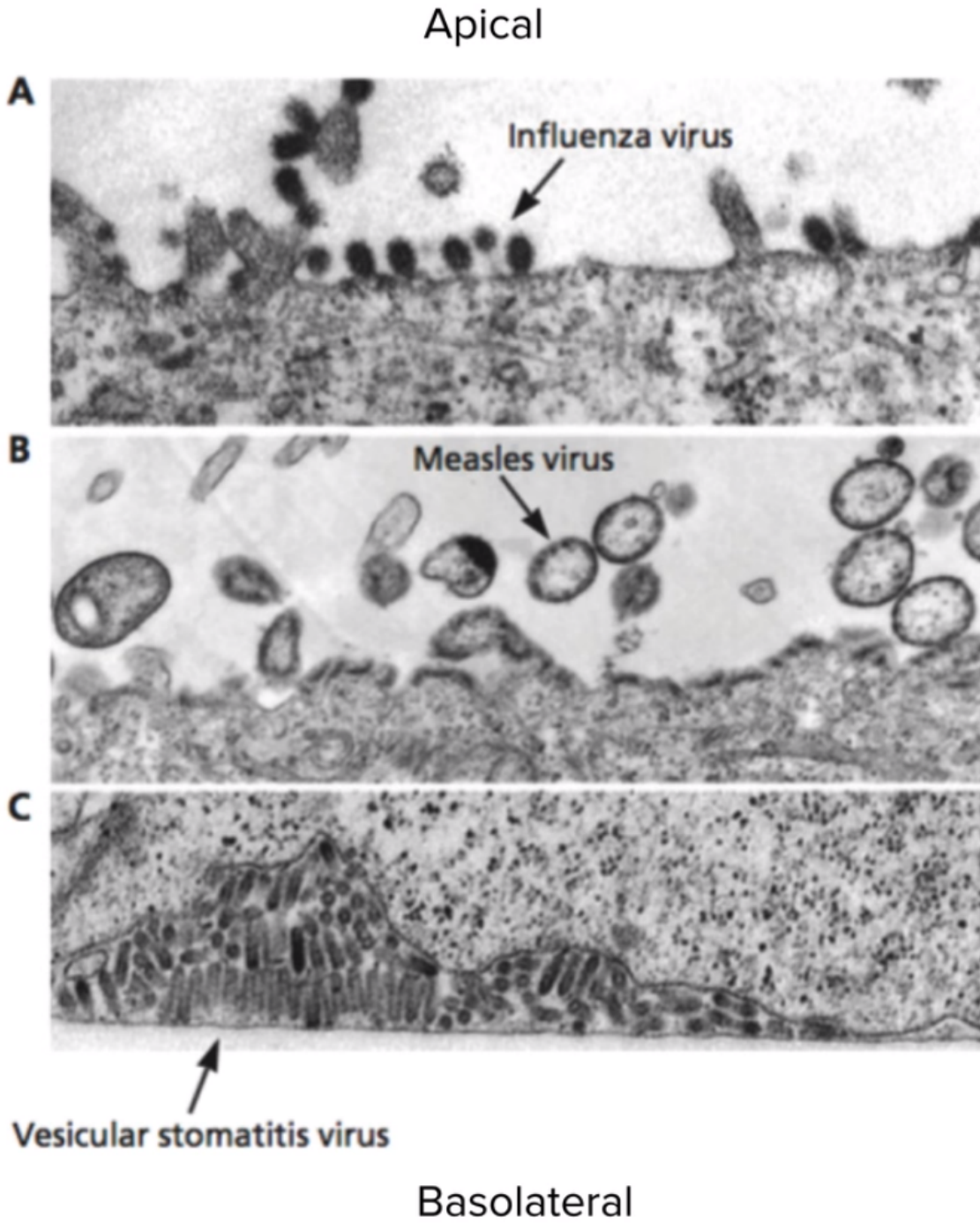


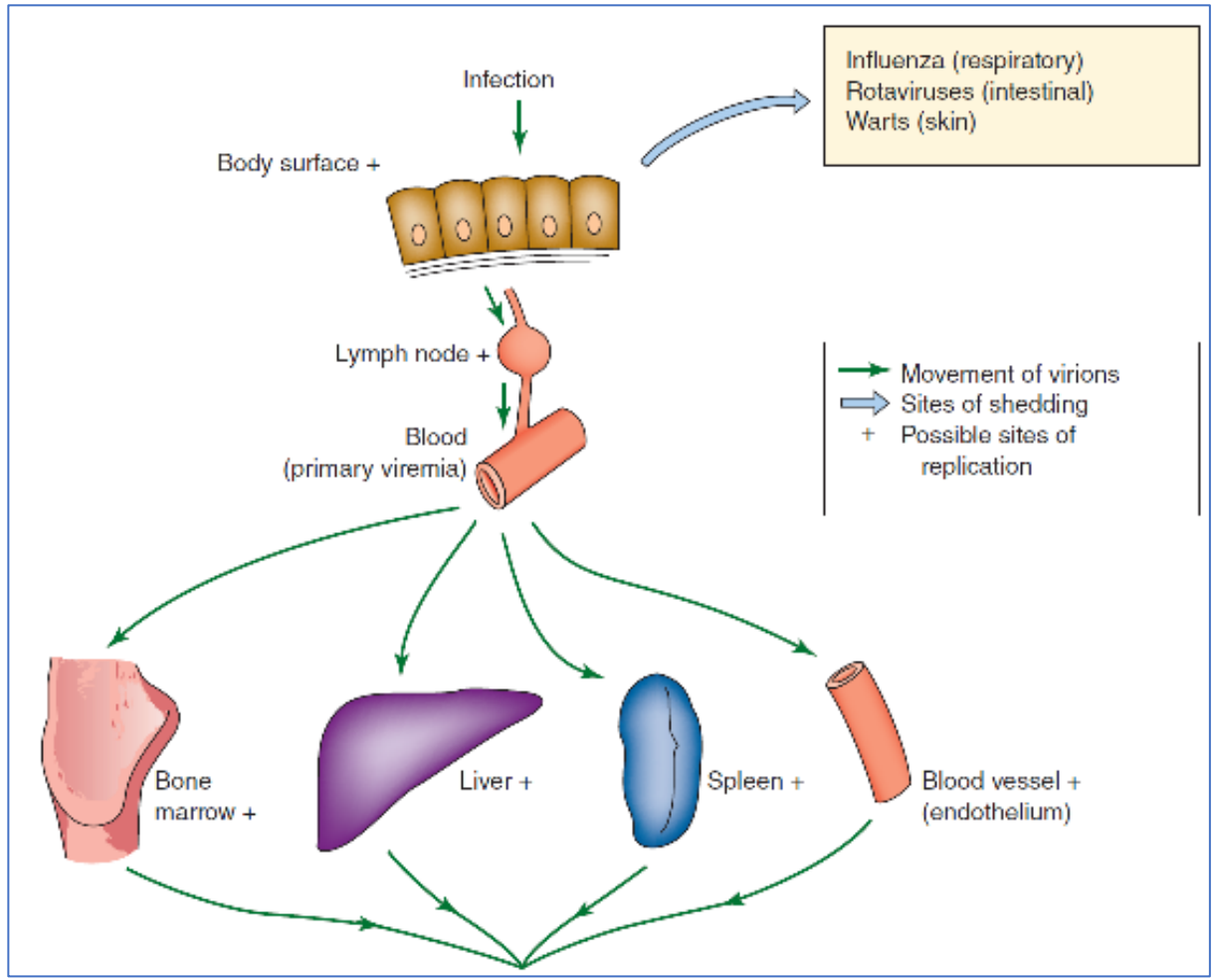
FIGURE 30-4 Latent infections by herpesviruses. Examples are shown for both herpes simplex and varicella-zoster viruses. Primary infections occur in childhood or adolescence, followed by establishment of latent virus in the cerebral or spinal ganglia. Later activation causes recurrent herpes simplex or zoster. Recurrences are rare for zoster. CMI, cell-mediated immunity. (Reproduced with permission from Mims CA, White DO: *Viral Pathogenesis and Immunology.* Blackwell, 1984.)

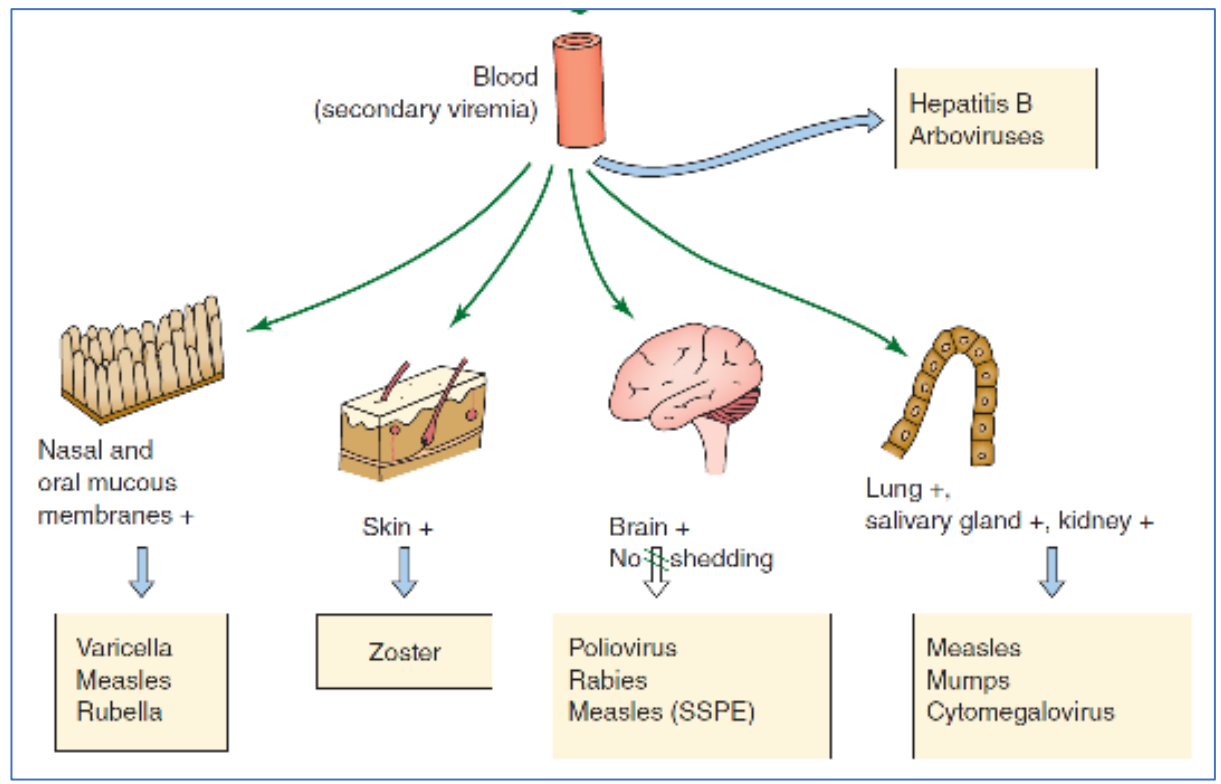
E. Virus Shedding

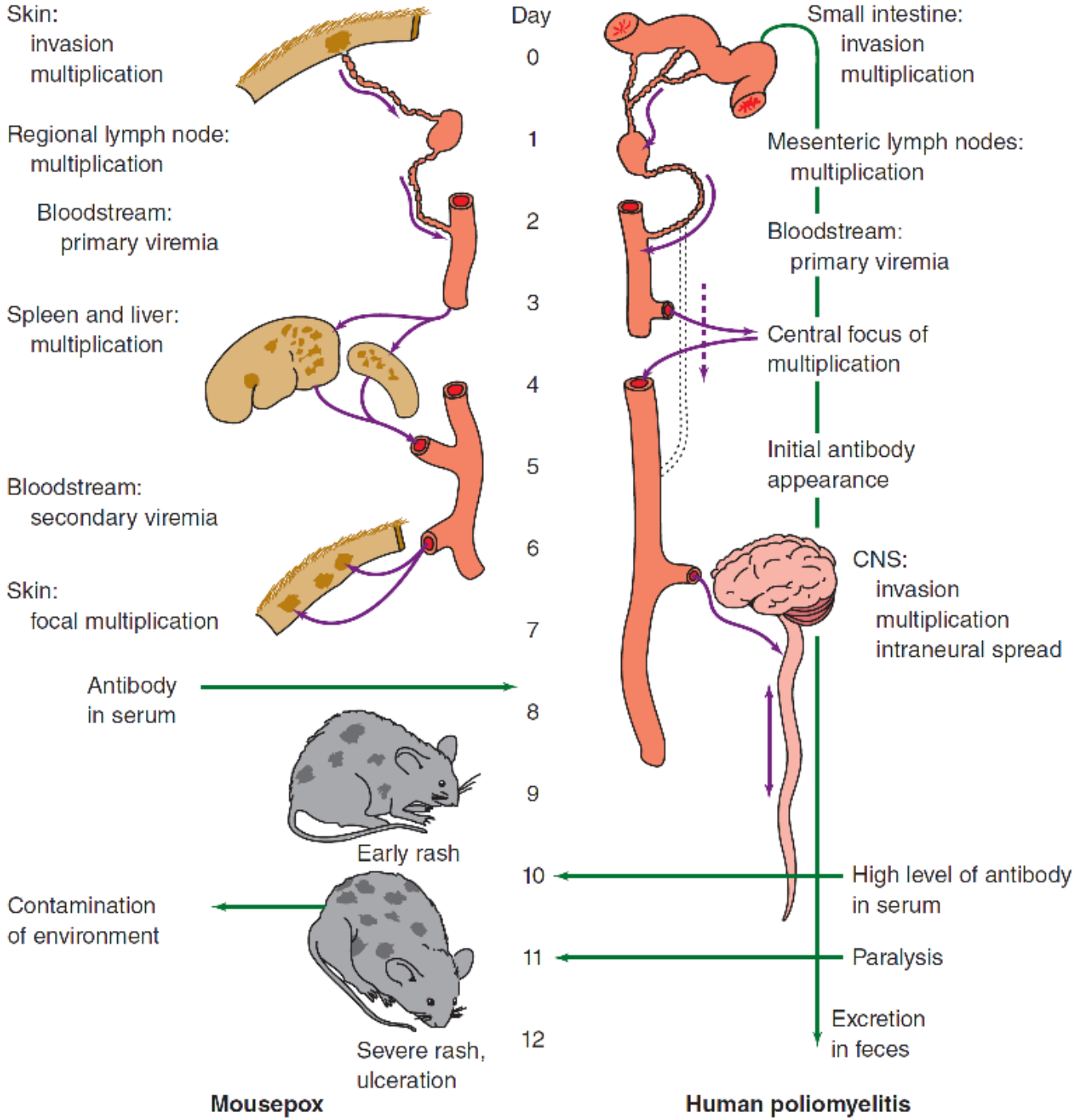
- Shedding occurs at different stages of disease depending on the particular agent involved, It represents the time at which an infected individual is infectious to contacts.

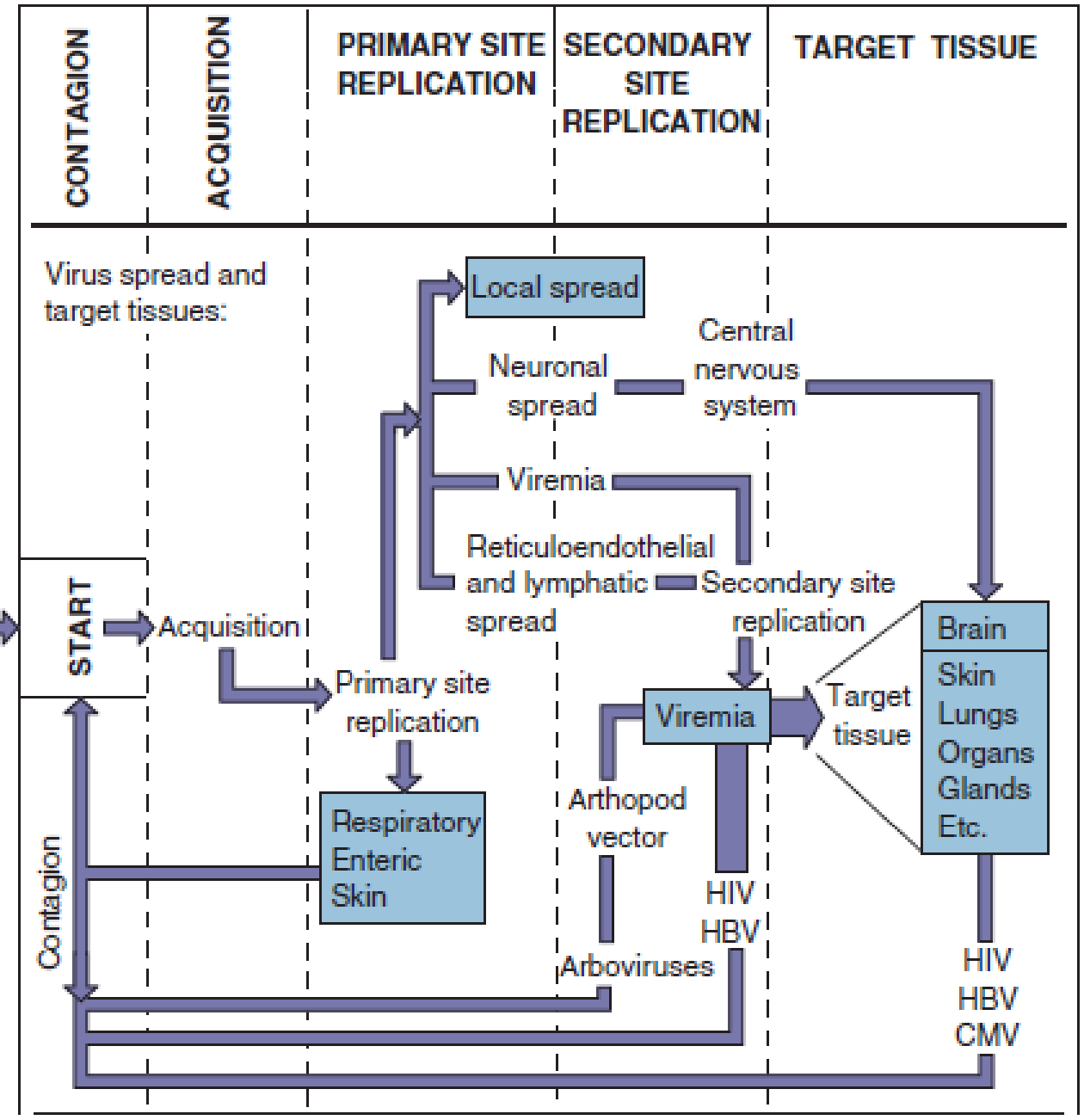
- Shedding is important to maintain a viral infection in populations of hosts. In some viral infections, such as rabies, humans represent dead-end infections, and shedding does not occur.

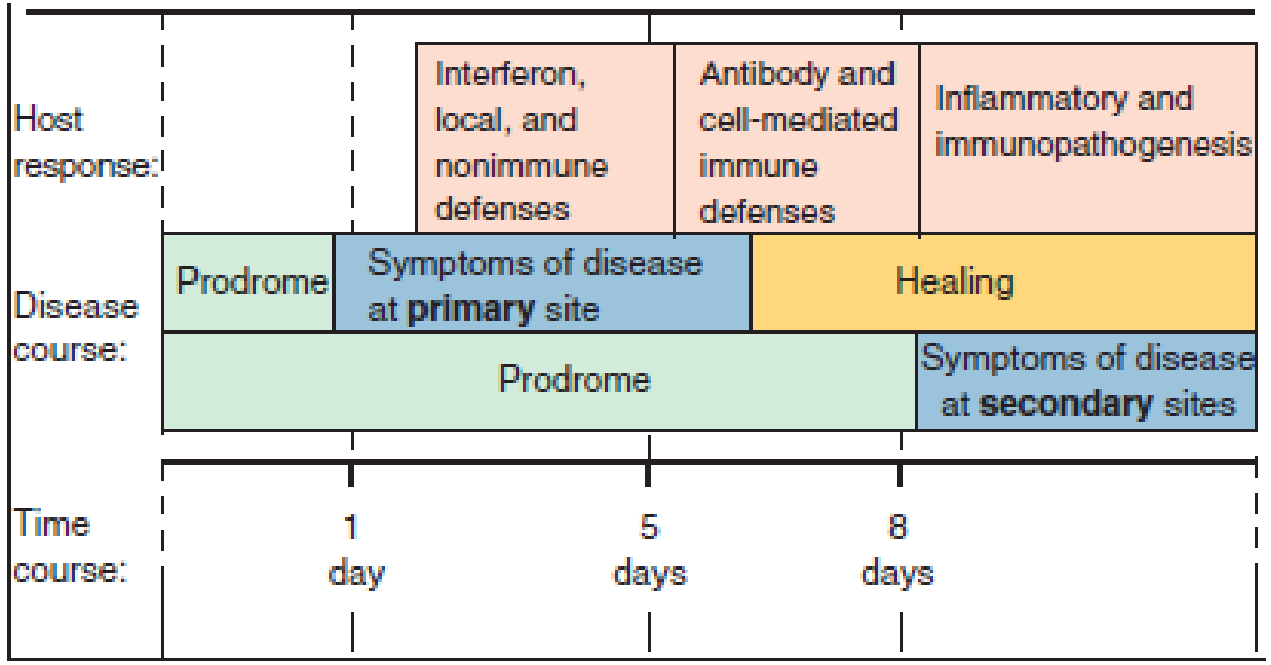



Infection
Body surface +
Influenza (respiratory)
Rotaviruses (intestinal)
Warts (skin)
Lymph node +
Blood
(primary viremia)
Movement of virions
Sites of shedding
+ Possible sites of replication
Bone
marrow +
Liver +
Spleen +
Blood vessel +
(endothelium)


Blood
(secondary viremia)
Hepatitis B
Arboviruses
Nasal and
oral mucous
membranes +
Skin +
Brain +
No shedding
Lung +,
salivary gland +, kidney +
Varicella
Measles
Rubella
Zoster
Poliovirus
Rabies
Measles (SSPE)
Measles
Mumps
Cytomegalovirus


Skin:
invasion
multiplication
Regional lymph node:
multiplication
Bloodstream:
primary viremia
Spleen and liver:
multiplication
Bloodstream:
secondary viremia
Skin:
focal multiplication
Antibody
in serum
Early rash
Contamination
of environment
Severe rash,
ulceration
Mousepox
Day
0
1
2
3
4
5
6
7
8
9
10
11
12
Small intestine:
invasion
multiplication
Mesenteric lymph nodes:
multiplication
Bloodstream:
primary viremia
Central focus of
multiplication
Initial antibody
appearance
CNS:
invasion
multiplication
intraneural spread
High level of antibody
in serum
Paralysis
Excretion
in feces
Human poliomyelitis


CONTAGION
ACQUISITION
PRIMARY SITE REPLICATION
SECONDARY SITE REPLICATION
TARGET TISSUE
Virus spread and target tissues:
Local spread
Neuronal spread
Central nervous system
Viremia
Reticuloendothelial and lymphatic spread
Secondary site replication
START
Acquisition
Primary site replication
Brain
Skin
Lungs
Organs
Glands
Etc.
Target tissue
Viremia
Arthopod vector
Respiratory
Enteric
Skin
Contagion
HIV
HBV
Arboviruses
HIV
HBV
CMV


Host response:
Interferon, local, and nonimmune defenses
Antibody and cell-mediated immune defenses
Inflammatory and immunopathogenesis
Disease course:
Prodrome
Symptoms of disease at primary site
Healing
Prodrome
Symptoms of disease at secondary sites
Time course:
1 day
5 days
8 days

Further reading and material:

- Murray - Medical Microbiology 8th Edition
  Section 5: Virology
    Chapter 37
    Chapter 38
- Jawetz, Melnick & Adelberg's Medical Microbiology, 26th edition-
  Section 4: Virology
      Chapter 30

- Youtube:

Channel: Vincent Racaniello
Videos : Virology Lectures 2018 #11 + #12 + # 15