

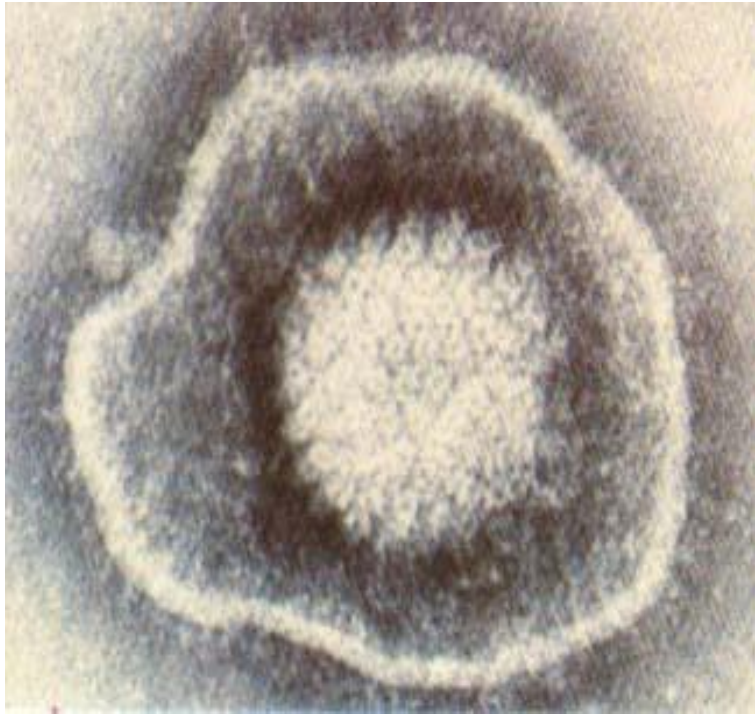
MBChB II

Herpesviruses – 06Nov2015

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Herpesviruses

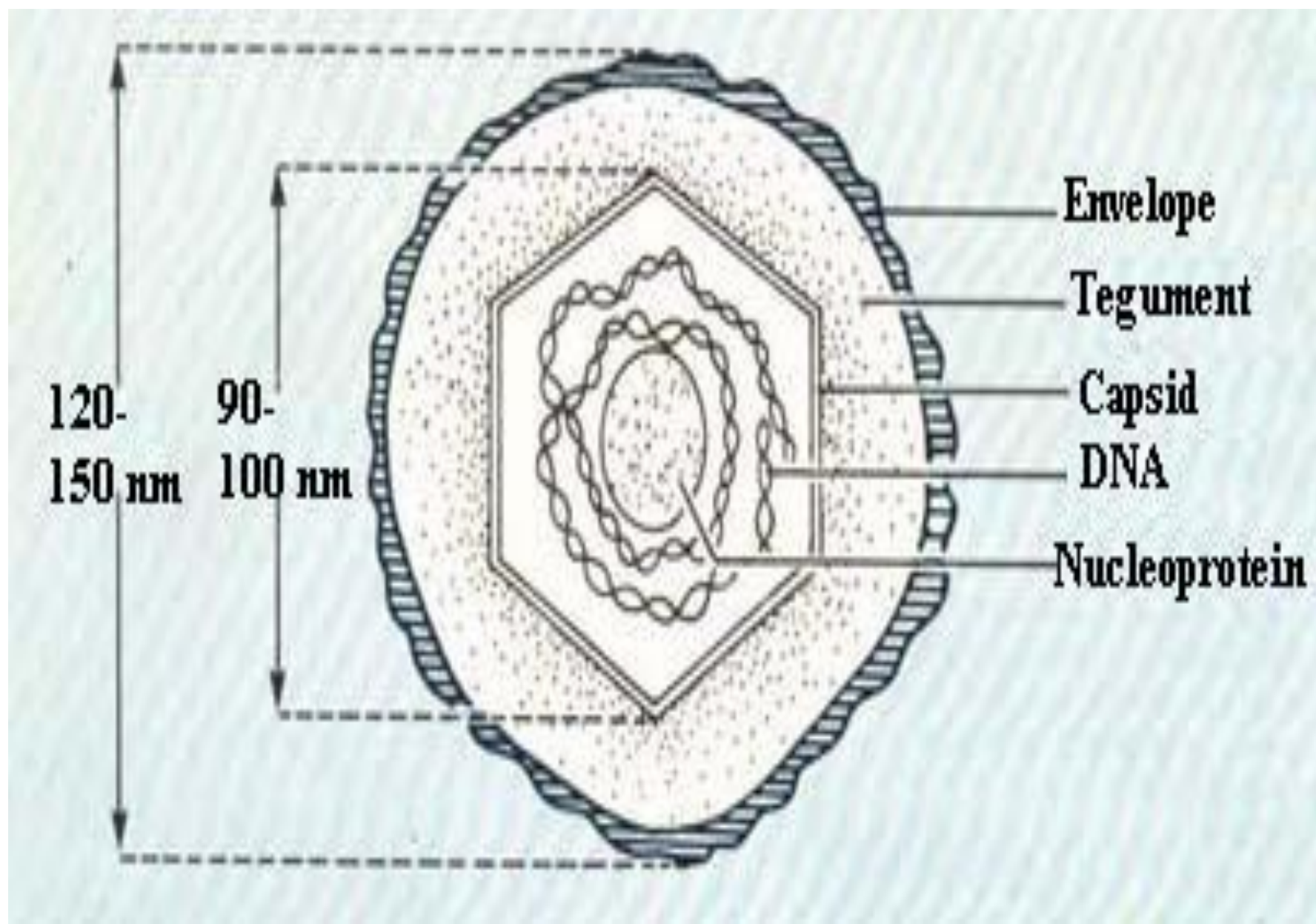
- > 130 herpesviruses
- Of these: 8 known to cause human disease as follows:
 1. **Herpes simplex I & II** (cold sores, genital herpes)
 2. **Varicella zoster** (chicken pox, shingles)
 3. **Cytomegalovirus** (microcephaly, infectious mono)
 4. **Epstein-Barr virus** (mononucleosis, Burkitt's lymphoma)
 5. **Human herpesvirus 6 & 7** (Roseola)
 6. **Human herpesvirus 8** (Kaposi's sarcoma)



Properties (Herpesviruses)

- dsDNA (Baltimore virus classification = class 1)
- Icosahedral capsid
- enveloped
- nuclear replication

Common and important herpesviruses of humans include HSV, VZV, Epstein-Barr (EB) virus, and cytomegalovirus (CMV).



Classification

1. Family: Herpesviridae
2. Subfamilies
 - a. Alpha herpesvirinae (HSV-1, HSV-2, VZV)
 - b. Beta herpesvirinae (CMV, HHV-6, HHV-7)
 - c. Gamma herpesvirinae (EBV, HHV-8 or KSHV)
3. Genus
 - a. Simplex virus (HSV1/2)
 - b. Varicelovirus (VZV or HHV3)
 - c. Lymphocryptovirus (EBV)
 - d. Cytomegalovirus (CMV)
 - e. Roseolovirus (HHV6, HHV7)
 - f. Rhadinovirus (HHV8 = KSHV)

Family: Herpesviridae

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 Recurr 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

HERPES SIMPLEX VIRUSES

Two types (HSV-1 & HSV-2)

-Infection is most often inapparent.

-Usual clinical manifestation:

1. Vesicular eruption of the skin or mucous membranes.
2. Sometimes seen as severe keratitis, meningoencephalitis, and a disseminated illness of the newborn.

Human Herpes Virus – 1 (HSV-1)

Prototype of group

Transmission of HSV-1 and HSV-2

- Via intimate contact (skin to skin contact)
- The virus does not penetrate intact skin
- Mild abrasion or chapping of skin can allow infection

Tissue tropism of HSV-1 and HSV-2

HSV-1:

- Causes 95% of orofacial herpes (remainder caused by HSV-2)
- Causes 10 - 30% of primary genital herpes (but seldom recurs there)

HSV-2:

- Causes primary and recurrent genital herpes infections
- May cause primary oral herpes but, like HSV-1 in genital area, it seldom recurs there

Pathogenesis of HSV-1

- **Asymptomatic infections** - young children (usually <5 yr old)
- **1° infection**
 - Oropharyngeal mucosal cells
 - Viremic spread (infection of different organs in the body).
- **Conditions include**
 - a. Acute gingivostomatitis,
 - b. Recurrent herpes labialis (cold sores)
 - c. Keratoconjunctivitis,
 - d. Encephalitis/meningitis,
 - e. Pharyngitis
 - f. Mucocutaneous lesions, herpetic whitlow etc

Herpes labialis – Cold Sore



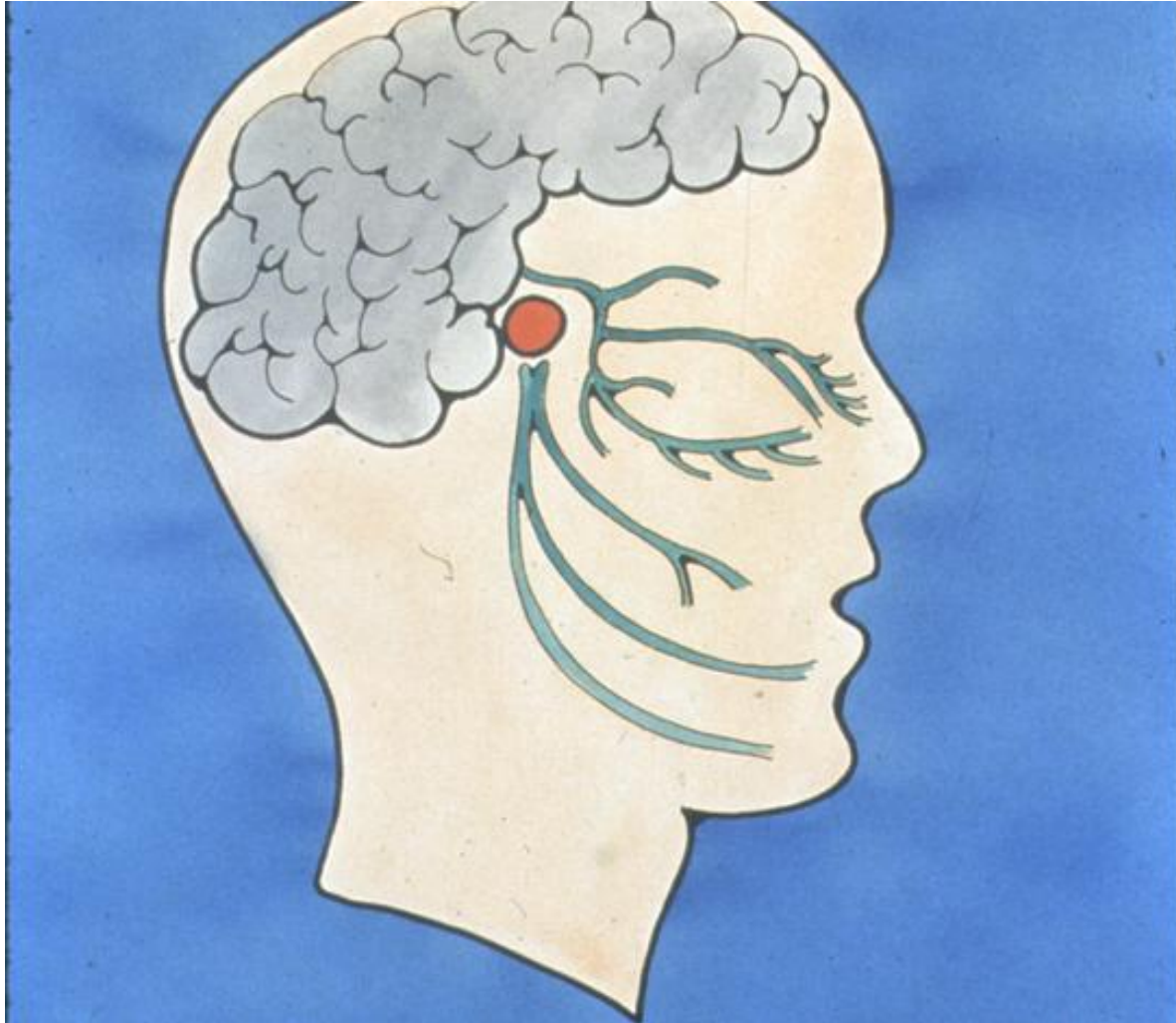
Cold Sores



Herpes labialis (cold sores, herpes febrilis).

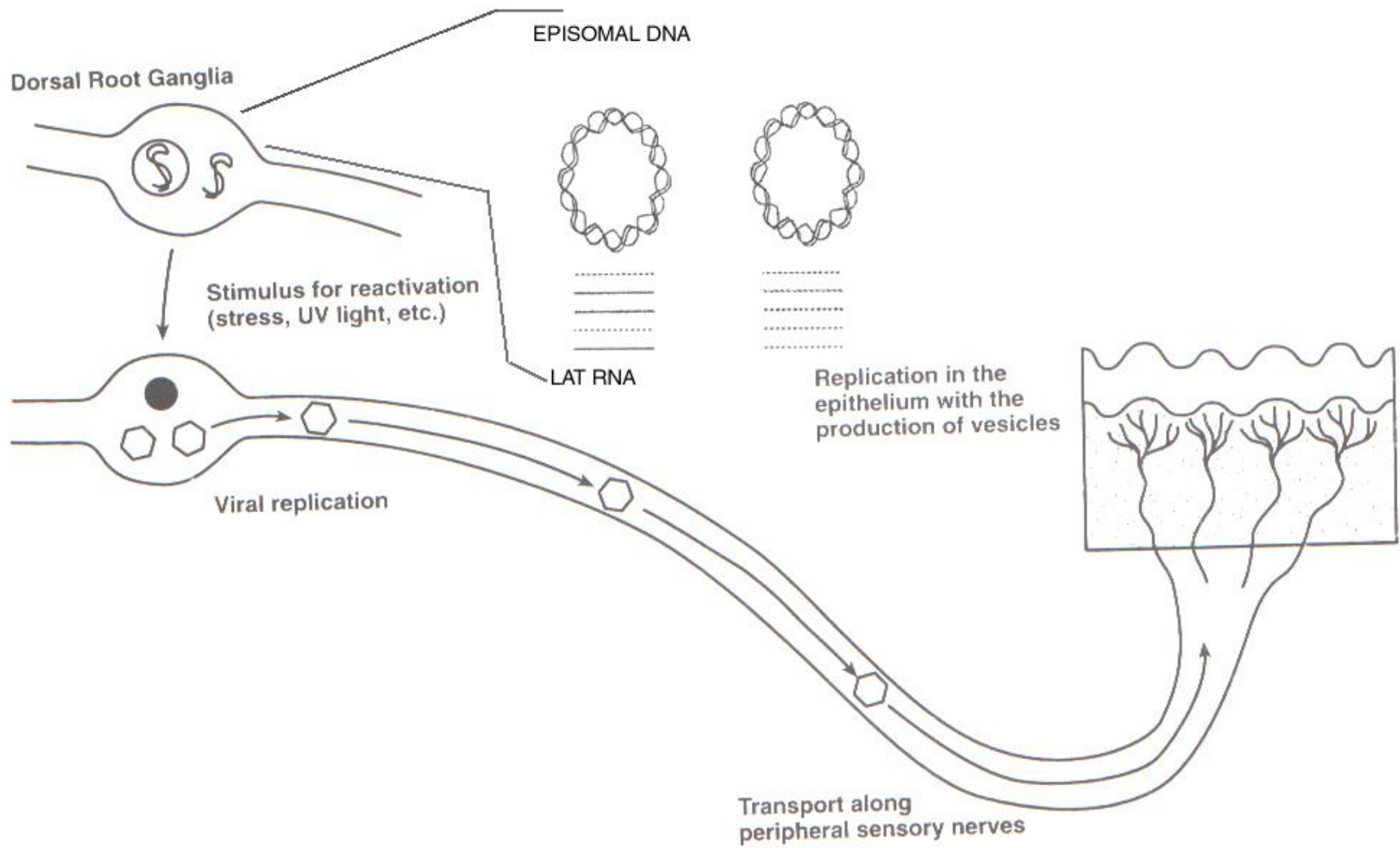
1. Most common recurrent disease (HSV-1)
2. Clusters of localized vesicles(lips)
3. Vesicles rupture (painful ulcer - heals without scarring)
4. Lesions may recur, repeatedly & at various intervals of time in same location
5. Permanent site of latent HSV = trigeminal ganglion

Life-long Latency



Viral latency (HSV)

- Primary infection
- Virus migration through PNS -> trigeminal ganglion
- Virus dormant (i.e. no replication) = latency
 - No viremia
 - Antiviral Abs in blood
- Reactivation of HSV
 - Stress to body (AIDS, immunosuppressive drugs, menses etc)
 - Disease & virus shedding (symptomatic or asymptomatic)



Three manifestations of HSV latency

Key Feature: there is a **wide spectrum** of clinical presentations

- Some individuals (5 - 10%) have frequent clinical reactivation
- Most individuals reactivation is clinically asymptomatic
- *In ALL cases, virus is shed*

Human Herpes Virus -2 (HSV-2)

Pathogenesis of HSV-2

- Sexually-transmitted virus (STI)
- Viremic spread to multiple body organs
- Conditions –
 - a. Genital herpes
 - b. Neonatal herpes,
 - c. Meningitis/encephalitis,
 - d. Keratoconjunctivitis
 - e. etc
- HSV disease ranges from mild illness (asymptomatic) in 1^o infection to sporadic, severe, & life-threatening disease in infants, children and adults.

Risk factors for HSV-2 infection

- Older age
- Female gender
- Poor socioeconomic status
- Low level of education
- Prior sexually transmitted disease
- Higher number of lifetime sexual partners

Genital herpes (HSV-2)



Healing recurrent HHV-2 lesions with crusts (Genital herpes)



Genital herpes (HSV-2)



Genital herpes (herpes progeneritalis).

1. Caused by HSV-2
2. Vesicles/lesions of the penis (male) or the cervix, vulva, vagina, and perineum of the female
3. Lesions more severe during primary infection (may be associated with fever, malaise, & lymphadenopathy).
4. Type 2 virus remains latent **in lumbar and sacral ganglia.**

Neonatal herpes.

1. HSV-2 may be transmitted to the newborn during birth by contact with herpetic lesions in the birth canal.
2. Disease = neonatal herpes
3. The spectrum of illness produced in the newborn appears to vary from subclinical or local to severe generalized disease with a fatal outcome.
4. Severely affected infants who survive may have permanent brain damage.

Specimen types for HSV

Examples - collected in transport media -> diagnostic lab

- Skin vesicles/lesions scrapings
- Cerebrospinal fluid (CSF)
- Ocular fluid
- Swabs from mucocutaneous lesions
- blood, stool, urine, throat, nasopharynx, conjunctivae and cornea, etc

Laboratory Diagnosis of HSV

- Virus isolation (main test)
- PCR (meningitis & encephalitis from CSF)
 - Rapid
 - High sensitivity & specificity etc
- Tzanck smear method
 - Cheap, rapid
 - Cannot distinguish HSV-1 from HSV-2
- Direct fluorescent antibody assay (DFA) technique
 - Can differentiate HSV-1/2
 - Rapid, inexpensive

Alpha Herpesviruses

Herpes Simplex Virus type 1

Site of Latency

Sensory neurons

Herpes Simplex Virus type 2

Sensory neurons

Varicella Zoster Virus

Sensory neurons

Beta Herpesviruses

Cytomegalovirus

Lymphocytes

Human Herpesvirus 6

CD4 T cells

Human Herpesvirus 7

CD4 T cells

Gamma Herpesviruses

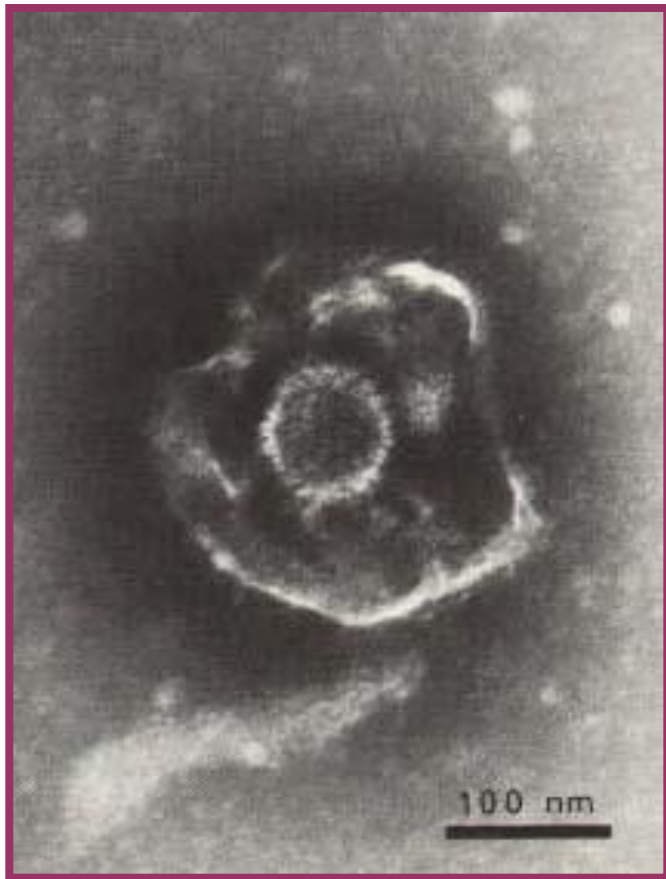
Epstein-Barr Virus

B lymphocytes

Human Herpesvirus 8

Sarcoma tissue

VARICELLA-ZOSTER VIRUS (Human Herpesvirus 3)



- a. Both diseases caused by the same virus.
- b. Varicella is the acute disease that follows primary contact with the virus,
- c. Zoster is the response of the partially immune host to a reactivation of varicella virus present in latent form in sensory ganglia.

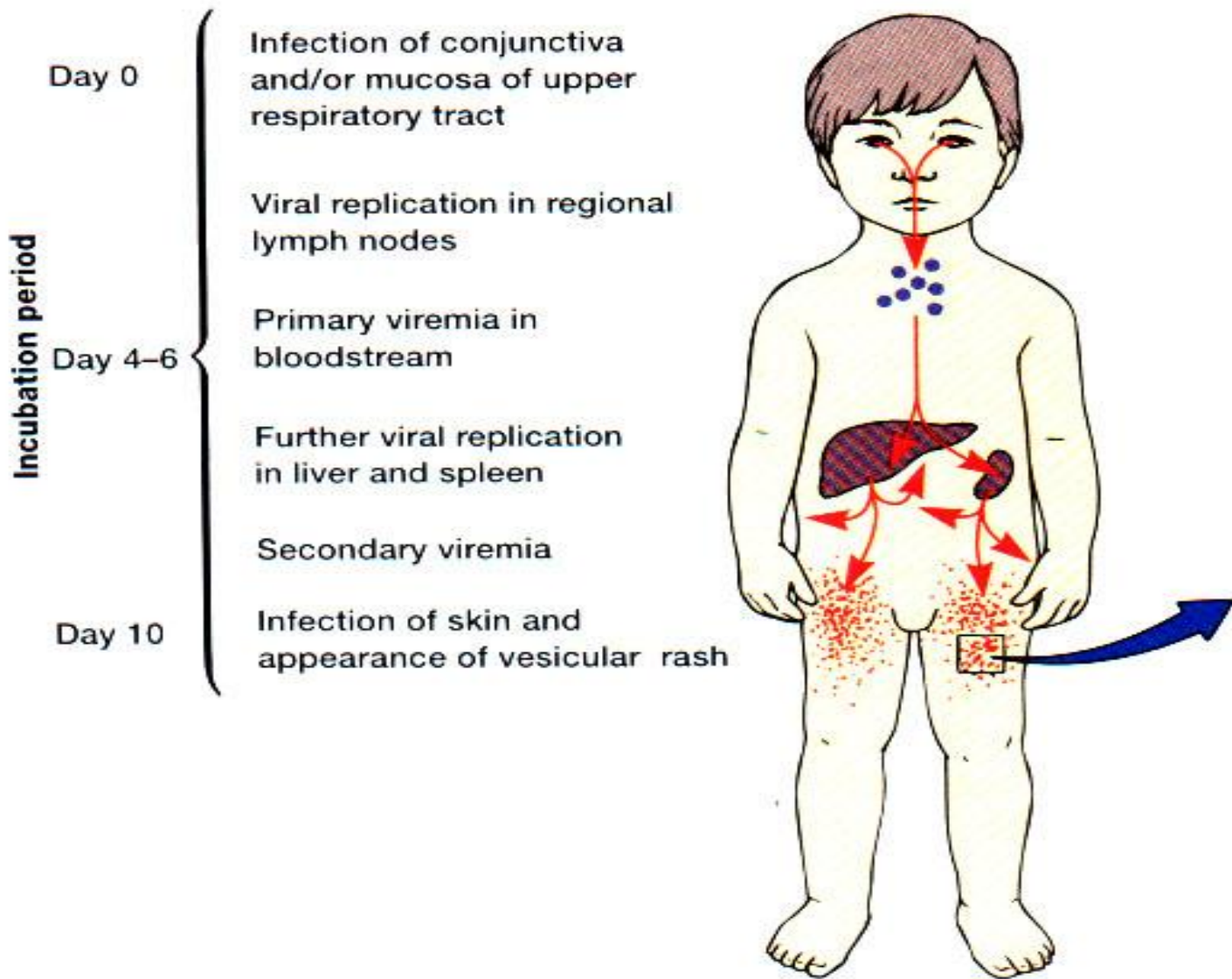
Two Unique Features of VZV:

- Airborne spread or skin to skin contact
- More severe infection if primary infection occurs as an adult

Pathogenesis of Varicella

- Highly contagious disease
- Transmission via aerosol (respiratory droplets/contact with infectious vesicular fluid)
- 1^o infection:
 - High tropism for T lymphocytes
 - viremic spread – dissemination to skin
 - Skin rash with: high fever & non-specific symptoms
- Most VZV infections in childhood (adult possible)
 - Adult: varicella pneumonia with fever, cough, tachypnea, dyspnea etc. Pneumonia transient, but interstitial pneumonitis -> respiratory failure
- Viral latency (like HSV)

Varicella virus, pathogenesis

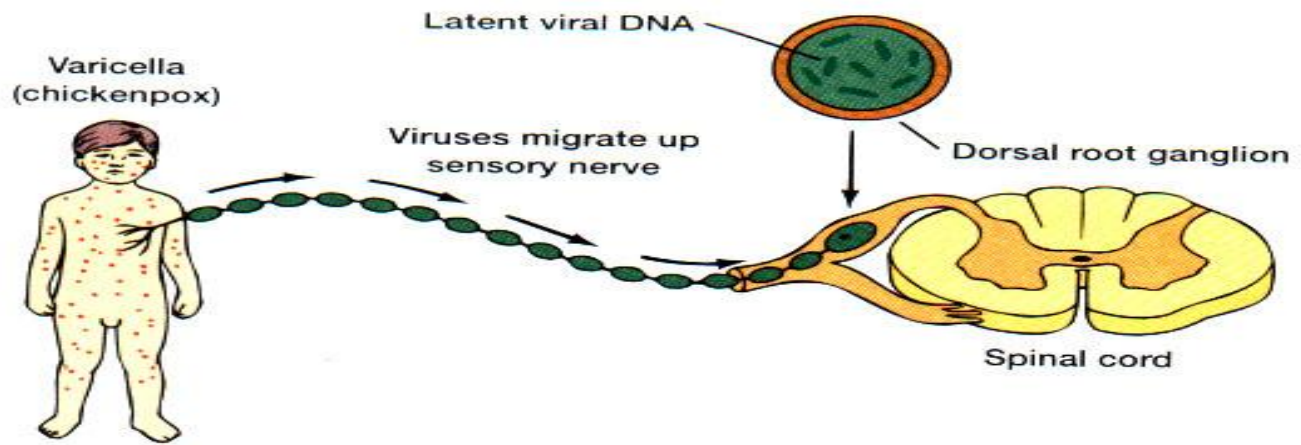




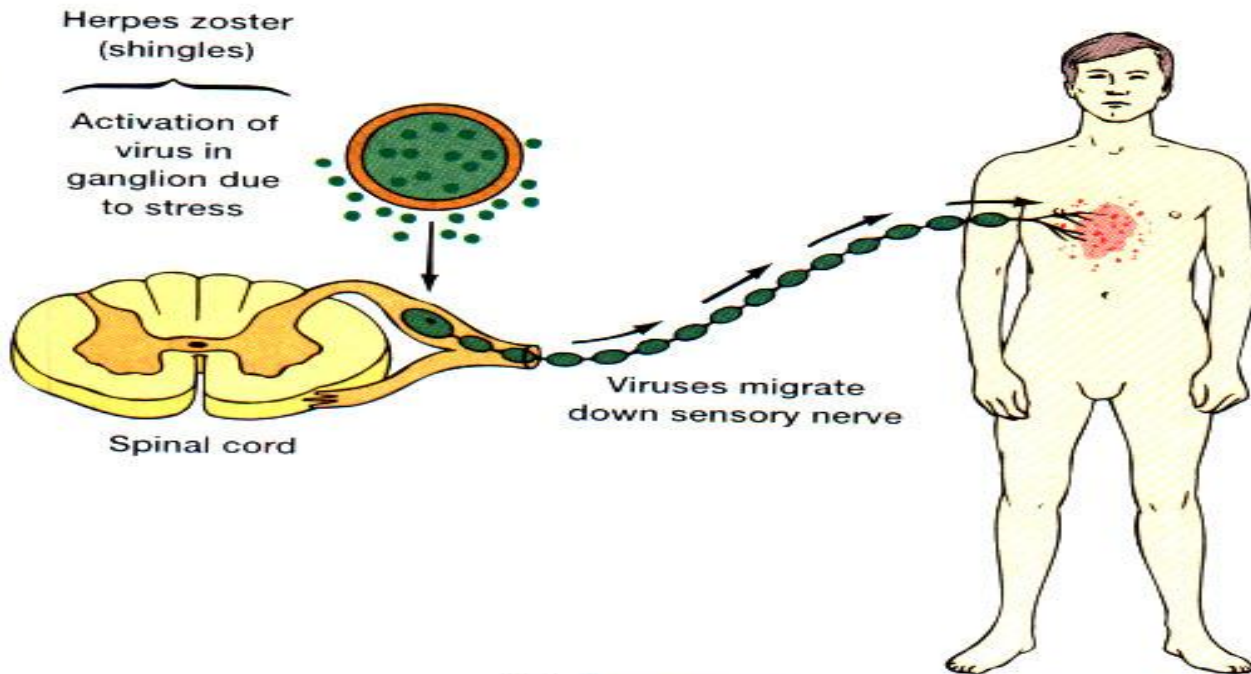
Varicella

Chickenpox





(a) Primary infection



(b) Recurrence

Pathogenesis & Pathology.

Zoster:

- a. In addition to skin lesions — histopathologically identical with those of varicella — there is an inflammatory reaction of the dorsal nerve roots and sensory ganglia.
- b. Often only a single ganglion may be involved. As a rule, the distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion.
- c. There is cellular infiltration, necrosis of nerve cells, and inflammation of the ganglion sheath.

Zoster/Shingles



Zoster



Shingles



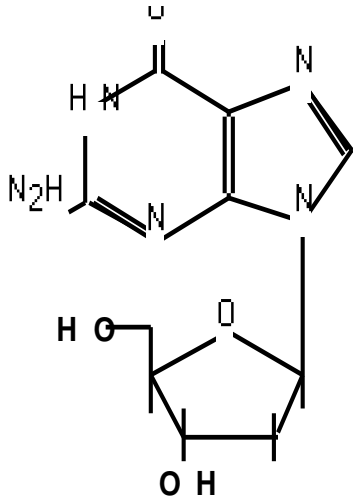
VARICELLA-ZOSTER VIRUS (Summary)

Same virus - two diseases

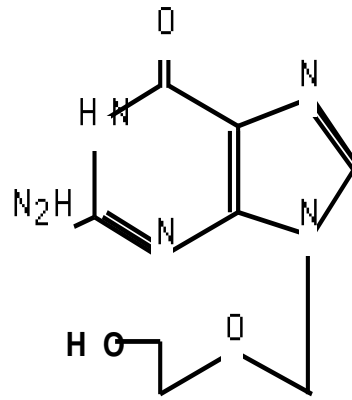
a. Varicella (chickenpox) is a mild, highly infectious disease, chiefly of children, characterized clinically by a vesicular eruption of the skin and mucous membranes. The causative agent is indistinguishable from the virus of zoster.

b. Zoster (shingles) is a sporadic, incapacitating disease of adults (rare in children) that is characterized by an inflammatory reaction of the posterior nerve roots and ganglia, accompanied by crops of vesicles (like those of varicella) over the skin supplied by the affected sensory nerves.

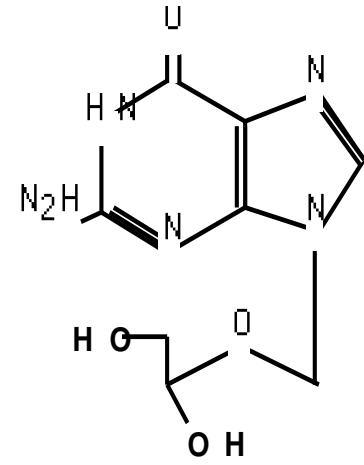
Antiviral therapy



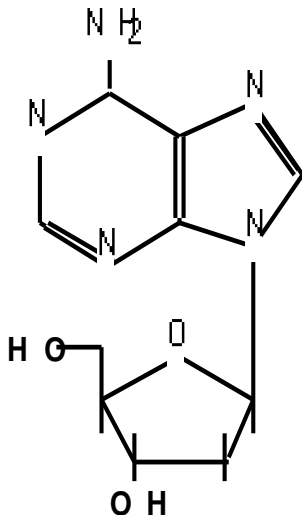
Deoxyguanosine



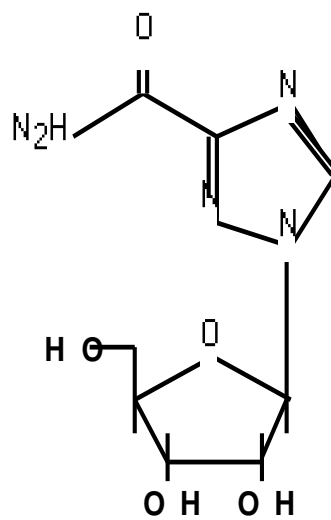
Acyclovir



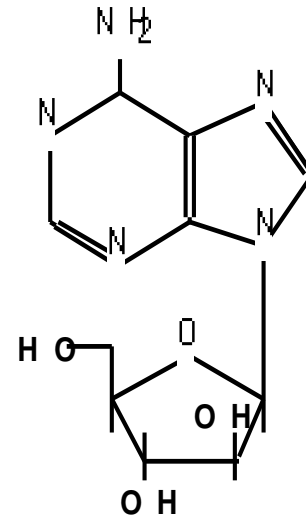
Ganciclovir



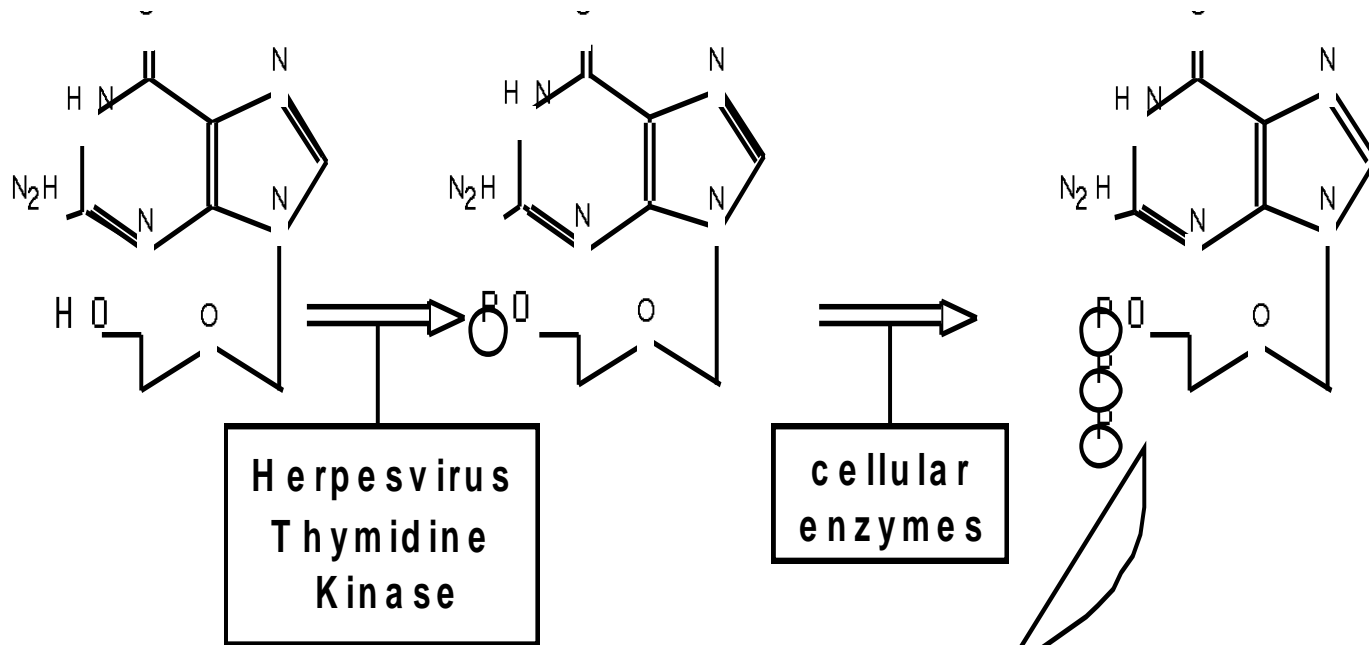
Deoxyadenosine



Ribavirin

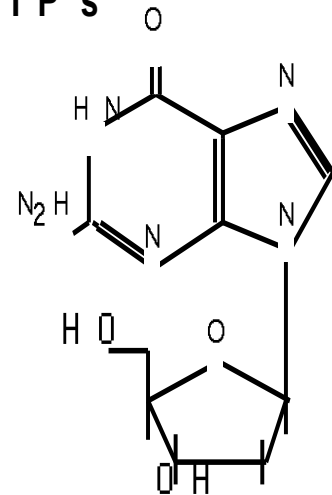


Vidarabine



DNA replication

XTP's



Deoxyguanosine

Acyclovir

- 1) Blocks Viral DNA Polymerase
- 2) Chain Terminates

Alpha Herpesviruses

Site of Latency

Herpes Simplex Virus type 1

Sensory neurons

Herpes Simplex Virus type 2

Sensory neurons

Varicella Zoster Virus

Sensory neurons

Beta Herpesviruses

Cytomegalovirus

Lymphocytes

Human Herpesvirus 6

CD4 T cells

Human Herpesvirus 7

CD4 T cells

Gamma Herpesviruses

Epstein-Barr Virus

B lymphocytes

Human Herpesvirus 8

Sarcoma tissue

Transmission of CMV

- In utero
- Early childhood (saliva, etc.)
- Venereal in young adults
- Blood transfusion
- Organ transplantation

Clinical Manifestations.

Normal individuals - Asymptomatic in majority of cases

Three distinct clinical syndromes.

- 1. Congenital cytomegalovirus infection:**
 - Primary CMV infection in 3rd trimester of pregnancy of a seronegative mother
 - Hepatospleno-megaly, retinitis, skin rash, CNS etc).
- 2. Mononucleosis syndrome** (fever, malaise, atypical lymphocytosis, pharyngitis etc)
- 3. CMV infection in severely immunocompromised individuals.** Infection can involve the lungs, GIT tract, liver, retina, and CNS

Summary - CMV

- Immunity
 - IgM, IgG, IgA
 - Virus becomes latent with episodes of recurrence
- Laboratory diagnosis
 - PCR is method of choice
 - Virus isolation is slow - two to three weeks before CPE
 - Serology
- Epidemiology
 - Worldwide
 - Humans are only known host
 - Transmission through close contact (oral/respiratory routes)
- Treatment
 - Gancyclovir for life-threatening infections

Alpha Herpesviruses

Site of Latency

Herpes Simplex Virus type 1

Sensory neurons

Herpes Simplex Virus type 2

Sensory neurons

Varicella Zoster Virus

Sensory neurons

Beta Herpesviruses

Cytomegalovirus

Lymphocytes

Human Herpesvirus 6

CD4 T cells

Human Herpesvirus 7

CD4 T cells

Gamma Herpesviruses

Epstein-Barr Virus

B lymphocytes

Human Herpesvirus 8

Sarcoma tissue

EB HERPESVIRUS

(Human Herpesvirus 4).



- a. EB (Epstein-Barr) virus is the causative agent of infectious mononucleosis
- b. Also associated with Burkitt's lymphoma and nasopharyngeal carcinoma.

Epidemiology. Epstein-Barr virus is transmitted by intimate contact.

Pathogenesis. Epstein-Barr virus is tropic for B-lymphocytes.



**Nasopharyngeal
carcinoma**

Burkitt's Lymphoma



Burkitt's lymphoma



Summary - EBV

- Laboratory diagnosis
 - PCR
 - Virus isolation (slow)
 - Serology
- Epidemiology
 - Worldwide
 - Transmitted via intimate contact
- Prevention and control
 - No vaccine available
 - Acyclovir has no effect

Herpesvirus Diseases

- Other herpesviruses
 - HHV-6
 - Infects T cells
 - Causes roseola
 - Only a problem in immunocompromised patients
 - HHV-7
 - Infects T cells
 - No known disease
 - HHV-8
 - Kaposi's sarcoma virus
 - Before HIV disease, only known to cause disease in men of Mediterranean descent and chemotherapy patients
 - Isolated from HIV patients



Kaposi Sarcoma





HHV-6: Roseola Infantum

