Chapter 37

DNA viruses

Herpes viruses

-- There are more than **100** known **herpesviruses**.

-- Human pathogens include **herpes simplex virus types 1 and 2**, **varicella-zoster virus, cytomegalovirus,** and **Epstein-Barr virus**.

-- All **herpesviruses** can establish **latent infection within specific tissues**, which are characteristic for each virus.

The human **herpesviruses** share **four significant biologic properties:**

-- All of the **herpesviruses** code for **unique enzymes** involved in the biosynthesis of viral nucleic acids.

-- Secondly, the **synthesis and assembly of viral DNA is initiated in the nucleus**. **Assembly of the capsid is also initiated in the nucleus.**

-- **Release of progeny virus** from the infected cell is **accompanied by cell death**.

-- All **herpesviruses** establish **latent infection within tissues that are characteristic for each virus**, reflecting the unique tissue tropism of each member of this family.

Structure

-- These viruses contain **double-stranded DNA** surrounded by a capsid which consists of **162 capsomers**, arranged in **icosapentahedral symmetry**.

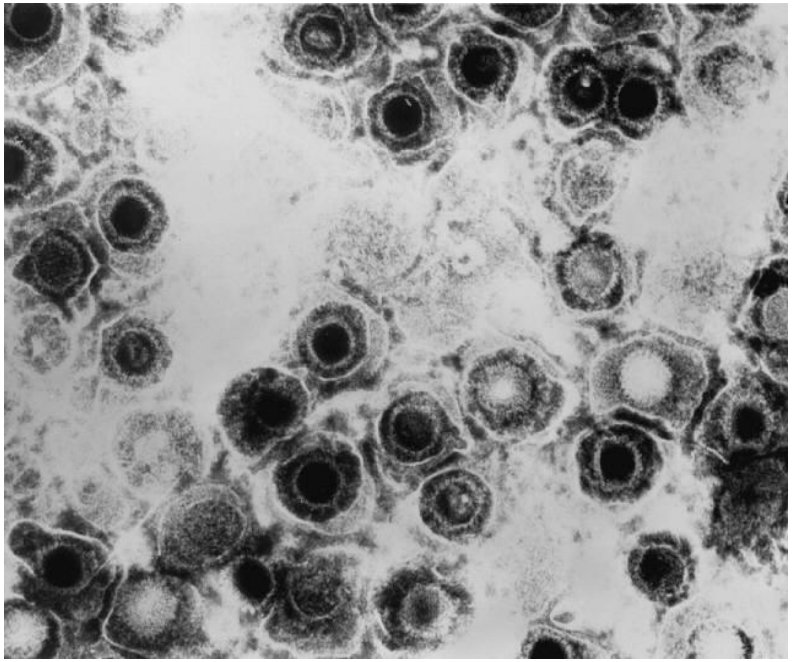
-- The capsid is approximately **100 to 110 nanometers** in diameter.

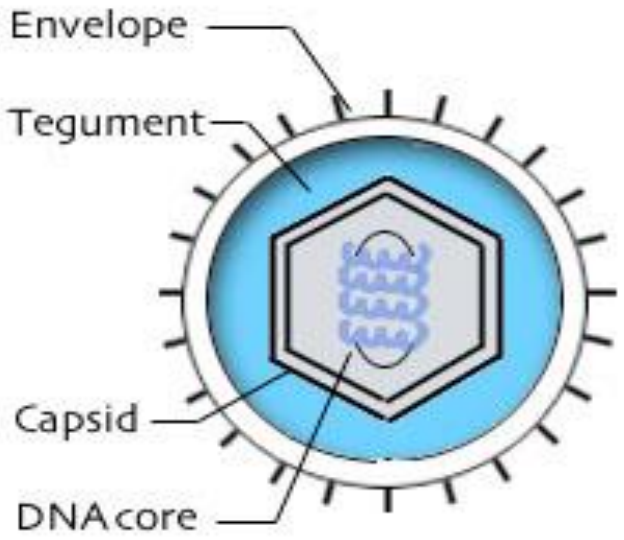
-- Tightly adherent to the capsid is the **tegument,** which appears to consist of amorphous material.

-- Loosely surrounding the capsid and tegument is a **lipid bilayer envelope derived from host cell membranes.**

The envelope consists of **polyamines, lipids,** and **glycoproteins**.

These **glycoproteins** confer distinctive properties to each virus and provide unique antigens to which the host is capable of responding.





There are **three** subfamilies:

Alpha herpesviruses

-- These **herpesviruses** are characterized by an **extremely short reproductive cycle (hours)**, **prompt destruction of the host cell**, and the ability to replicate in a **wide variety of host tissues**.

-- They characteristically establish **latent infection** in **sensory nerve ganglia**.

-- This sub-family consists of **herpes simplex virus 1 and 2** and **varicella-zoster** virus.

Beta herpesviruses

-- **Beta herpesviruses** have a restricted host range.

-- Their reproductive **life cycle is long (days),** with **infection progressing slowly** in cell culture systems.

-- They **form enlarged cells**, as exemplified by human cytomegalovirus infection.

-- These viruses can establish **latent infection** in **secretory glands, cells of the reticuloendothelial system,** and the **kidneys**.

Gamma herpesviruses

-- **Gamma herpesviruses** have the **most limited host range**.

-- They **replicate in lymphoblastoid cells *in vitro*** and **can cause lytic infections in certain targeted cells.**

-- **Epstein-Barr virus** is a member of this sub-family.

-- **Kaposi's sarcoma herpesvirus** is most closely related genetically to **Epstein-Barr virus.**

Replication and Latency

-- Following the onset of infection, **DNA is uncoated and transported to the nucleus of the host cell.**

-- This is followed by **transcription of immediate-early genes**, which encode for the **regulatory proteins**.

-- Expression of **immediate-early gene products** is followed by the expression of proteins encoded by **late genes**.

-- **Assembly of the viral core and capsid takes place within the nucleus.**

-- This is followed by **envelopment at the nuclear membrane** followed by transport through the **endoplasmic reticulum** and the **Golgi apparatus**.

-- Mature virions are transported to the outer membrane of the host cell **inside vesicles.**

-- Release of progeny virus is accompanied by **cell death**.

-- A unique characteristic of the **herpesviruses** is their ability to establish **latent infection** either **extra-chromosomal** or **integrated into host cell DNA**.

-- **Herpes simplex virus 1 and 2** and **varicella-zoster virus** all establish latency in the **dorsal root ganglia**.

-- **Epstein-Barr virus** can maintain latency within **B lymphocytes** and **salivary glands.**

-- **Cytomegalovirus**, and **Kaposi's sarcoma virus** have unknown sites of latency.

-- **Latent virus may be reactivated and enter a replicative cycle at any point in time.**

-- **Stimuli** that have been observed to be associated with the reactivation of latent **herpes simplex virus** have included **stress, menstruation,** and **exposure to ultraviolet light.**

Herpes Simplex Viruses

HSV type 1 and **type 2** are **closely related**, with nearly **70 % genomic homology.**

Clinical Manifestations and Pathogenesis

-- Critical factor for transmission of herpes simplex viruses is **intimate contact** between a person who is shedding virus and a susceptible host.

-- After incubation period of four to six days, **herpes simplex virus replicates in epithelial cells.**

-- As replication continues, **cell lysis** and **local inflammation** ensue, resulting in **characteristic vesicles** on an erythematous base.

-- **Regional lymphatics** and **lymph nodes** become involved: **viremia** and **visceral dissemination** may develop depending upon the **immunologic competence** of the host.

-- In all hosts, the virus generally **ascends the peripheral sensory nerves to reach the dorsal root ganglia.**

-- Replication of herpes simplex virus within neural tissue is **followed by retrograde axonal spread of the virus** back to other mucosal and skin surfaces via the peripheral sensory nerves.

-- Virus **replicates further in epithelial cells**, reproducing the lesions of the initial infection, until infection is contained through both systemic and mucosal immunity.

-- **Latency** is established when herpes simplex virus **reaches the dorsal root ganglia** after anterograde transmission via sensory nerve pathways.

Mucocutaneous Infections

Gingivostomatitis

-- This is usually caused by **HSV 1**, occurs most frequently in **children less than five years of age.**

-- It is characterized by **fever, sore throat, pharyngeal edema** and **erythema,** followed by the development of **vesicular or ulcerative lesions** on the **oral and pharyngeal mucosa.**

Genital Herpes

-- It is most frequently caused by **HSV 2**.

-- In individuals of either sex, primary disease is associated with **fever, malaise, anorexia,** and **bilateral inguinal adenopathy**.

Herpetic Keratitis

-- Herpes simplex keratitis is usually caused by **HSV1** and is accompanied by **conjunctivitis** in many cases.

-- The characteristic lesions are **dendritic ulcers** best detected by fluorescein staining.

-- **Deep stromal involvement** has also been reported and may result in **visual impairment.**

Other Skin Manifestations

Herpes simplex virus infections can manifest at any skin site.

Common lesions are on skin of the fingers, known as **herpetic whitlows**.

Wrestlers may develop disseminated cutaneous lesions known as **herpes gladiatorum.**

Neonatal Herpes Simplex Virus Infection

-- Mostly caused by **HSV 2**, it usually result from **contact of the fetus with infected maternal genital secretions** at the time of delivery.

-- Manifestations of neonatal **HSV** infection can be divided into **three** categories: 1) **skin, eye and mouth** disease; 2) **encephalitis**; and 3) **disseminated infection** involving multiple organs.

-- The mortality rate may be **15% for encephalitis** and **60 % with disseminated** infection.

-- Only **40 % of cases have normal development**, even with the administration of appropriate antiviral therapy.

Laboratory Diagnosis

-- **Typical CPE** in cell culture occurs in 1-3 days, after which virus is identified by **fluorescent antibody staining** or by detecting its proteins by **ELISA**.

-- A **rapid diagnosis** can be made by **Tzanck smear** of cells from the base of vesicle stained with Giemsa stain to look for **multinucleated giant cells**.

-- **Rapid diagnosis** of **encephalitis** and **neonatal herpes infection** can be made by using **PCR** to detect **HSV-1** DNA in the spinal fluid.

-- **Serology** can be useful for **primary but not recurrent infections**.

Epidemiology

-- Transmission of **HSV** is dependent upon intimate contact.

-- **Nosocomial spread** of **HSV 2** has been documented, particularly in newborn intensive care units.

Treatment

-- **Acyclovir** is the treatment of choice for **encaphilitis**, systemic disease caused by **HSV 1**, **neonatal infection** by **HSV 2**, **primary** and **recurrent genital herpes**.

-- It also **shortens duration of lesions** and **extent of shedding** of the virus.

-- **Treatment of primary infection does not prevent recurrence nor has any effect on latent state.**

Varicella-zoster Virus

Clinical Manifestations and Pathogenesis

-- **Varicella-zoster virus** is one of the **most common viruses** encountered by humans.

-- It is usually transmitted by **airborne routes (droplet spread)** with initial replication in the **oropharynx**.

-- In the susceptible or seronegative individual, replication of virus in the oropharynx leads to **primary viremia**, with subsequent development of a **vesicular rash**.

-- The **replication** of **VZV** in vitro is **similar** to that for **HSV**, although the period of replication is somewhat prolonged.

Varicella

Varicella, or **chickenpox**, is the manifestation of primary **VZV** infection.

It is **most common in young children** of preschool age and has a characteristic **disseminated vesicular rash** which appears after 14 to 17 days.

The rash **begins** on the **face** and **trunk** and spreads to the **extremities**.

-- The lesions of **chickenpox** are initially **vesicles** which become **pustular, crusted,** and then **scabbed** prior to healing.

-- The average duration of **lesion formation** is **three to five days** in the normal child; however, it is usually longer in adolescents and adults.

-- At the time of primary infection, it may establish **latency in dorsal root ganglia**.

Herpes Zoster

The recurrent form of **VZV** is **herpes zoster** or **shingles** which is a localized vesicular rash with a dermatomal distribution.

It initially appears within the **dermatome as erythema**, followed by the **development of vesicles** which may progress to **bullous lesions** in some cases.

The average time to healing for individuals with shingles ranges from **10 to 21 days**, depending upon the age and immune status of the individual.

Epidemiology

-- The spread of **VZV** depends upon **airborne droplet transmission** from a person who is shedding virus to a susceptible host.

-- Nearly **95% adults** have serologic evidence of infection with **VZV**.

-- It does not appear that **herpes zoster** can be transmitted from one individual to another.

-- **Spread of virus from the vesicles of herpes zoster may lead to the development of varicella in a susceptible host.**

Laboratory Diagnosis

-- **Clinical diagnosis is easy**.

-- In laboratory, **Tzanck smear** can help to find **multinucleated giant cells**.

-- **Definitive diagnosis** is by **isolation of virus in cell culture** and **identification with specific antiserum.**

Treatment

-- **No antiviral therapy** is needed for normal children.

-- Adults are treated with **acyclovir** to reduce duration and severity of symptoms.

-- Immunocompromised children should also be treated with **acyclovir.**

Cytomegalovirus

Pathogenesis

-- Replication of **CMV** **is most prominent in cells of glandular origin**, particularly in the **salivary glands** and the **kidneys**.

-- As a result, **large quantities of virus** can be shed in **saliva** and **urine**.

-- The **replicative cycle** of **CMV** in these organs is **more prolonged** and produces **characteristic multi-nucleated giant cells**.

-- It can cause **persistent infection** in various tissues, including those of the **salivary glands, kidneys,** and **peripheral blood leukocytes**.

-- This persistent infection leads to **chronic viral excretion** by the involved organ.

Transmission

-- Transmission of virus is through **contact with infected secretions.**

-- The average **incubation period is four to six weeks.**

-- Infections in **normal persons** are usually **asymptomatic.**

-- **CMV** enters a **latent stage primarily in monocytes** and can be reactivated when CMI is decreased.

-- **CMV** are able to **prolong latent stage by deceiving immune system.**

-- **Uniquely**, **the CMV infected cells do not display MHC class I-peptide complexes on their surface in a stable form.**

-- Its **suppression of cellular immunity** plays an important part in progression of systemic disease.

Epidemiology

-- Large quantities of virus can be excreted in **saliva** and **urine** for prolonged periods of time.

-- Transmission of virus from **mother to child** can occur by one of several routes, including infected **breast milk, cervical secretions,** and **saliva.**

-- **Reactivation** of **CMV** infection in **immunosuppressed** individuals can be particularly problematic.

-- Persons who receive **organs from seropositive persons** can develop a **life-threatening primary CMV infection.**

Laboratory Diagnosis

-- Special tubes called **shell vials** are used which contain **immunofluorescent antibody** which can make a diagnosis in 72 hours.

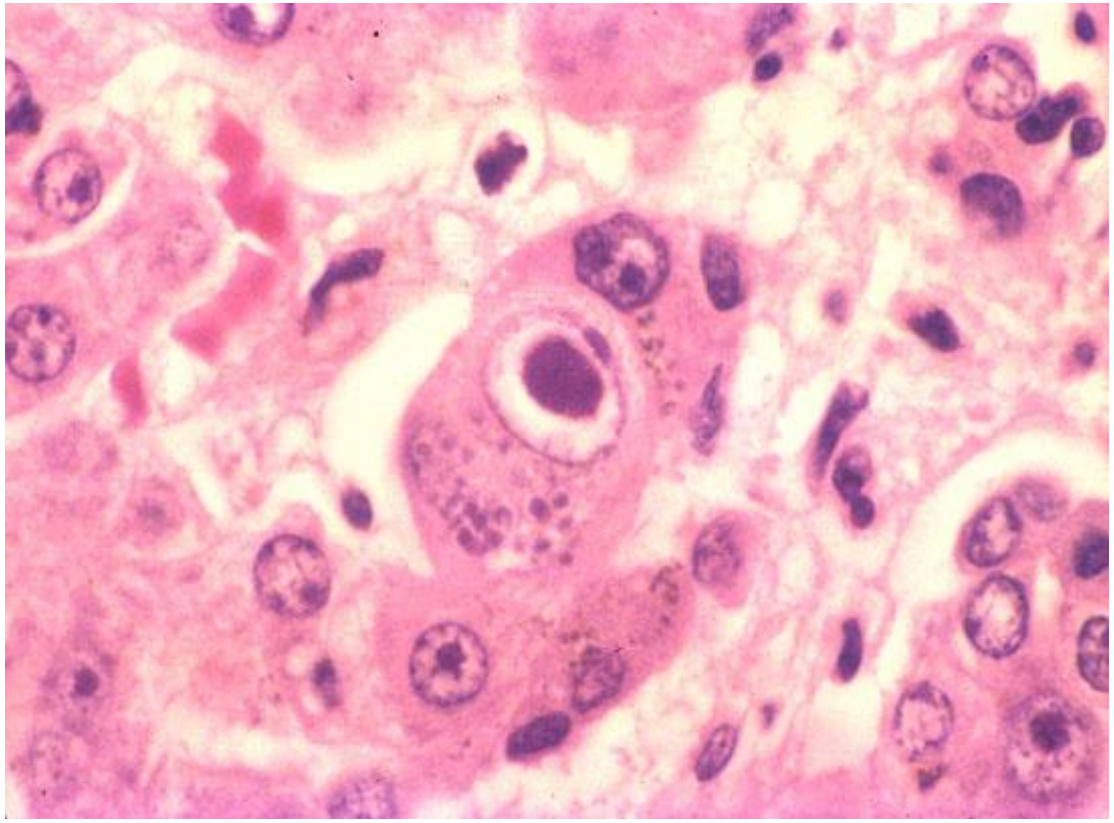
-- The viral culture can be tested for sensitivity towards **ganciclovir.**

-- A **four-fold or greater rise** in antibody titer is also **diagnostic.**

-- **PCR based tests** on body fluids are very useful.

Fluorescent antibody and **histologic staining for inclusion bodies in giant cells** surrounded by a **clear halo** can also be used.

They have an **owl's eye shape**.



Treatment

-- **Ganciclovir** is **moderatley effective** in treatment of **CMV** **retinitis** and **pneumonia** in patients with **AIDS**.

-- **Valganciclovir** can be taken orally and is effective against retinitis.

-- Unlike **HSV** and **VZV, CMV** is largely **resistant to acyclovir**.

Prevention

-- There is **no vaccine**.

-- Infants shed **CMV** in **urine**, so they should be isolated.

-- It should be assured that blood or transplanted organs are **CMV negative**.

Epstein-Barr Virus

Clinical Manifestations

-- Predominant findings of **EBV** **mononucleosis** are **malaise, myalgia, pharyngitis, cervical adenopathy, splenomegaly**, and **atypical lymphocytosis**.

-- **Anorexia** and **lethargy** are prominent.

-- **Hepatitis** is frequent; **encaphilitis** occurs in some patients. Spontaneous recovery occurs in 2-3 weeks.

-- Children with **X-linked lymphoproliferative syndrome** can have a much severe, **often fatal** form of disease.

EBV also causes **hairy leukoplakia** on the **lateral side of tongue**.

EBV infection **initiates cell division which in itself is non malignant.**

It is **associated with several cancers**, namely **Burkitt's lymphoma**, some forms of **Hodgkin's lymphoma** and **nasopharyngeal carcinoma**.

The progression to cancer is usually associated with reduced immunity.

Pathogenesis

-- **Epstein-Barr virus** is trophic for **B-lymphocytes** and remains in a **latent form**. Cytotoxic T lymphocytes react against infected B cells.

-- Replication occurs in **parotid gland**, as well as other **lymphatic tissues**.

-- Evidence of **lytic disease** (formation of multinucleated giant cells) is **not apparent.**

-- Immune response consists of **IgM production followed by IgG antibodies** which persist for life.

-- These antibodies are directed towards **viral membrane antigen**.

-- Nonspecific **heterophil antibodies** are also formed.

Epidemiology

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

-- **Exchange of saliva** provides a major route for **horizontal transmission** of infection.

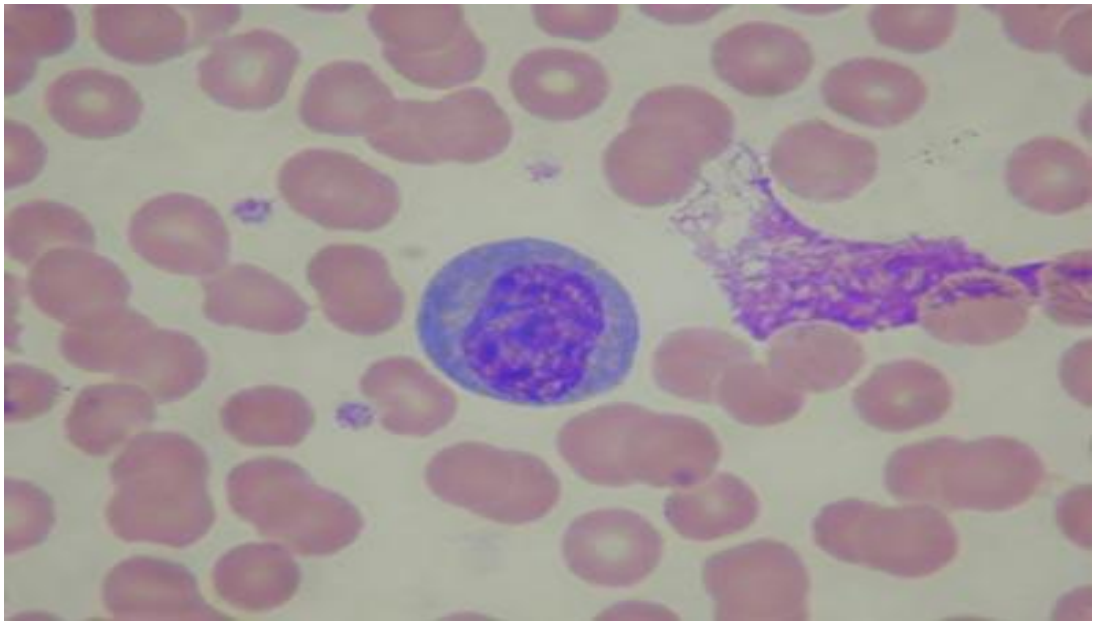
-- Excretion of virus from other sites does occur, but does not appear to be a major vector for transmission of infection.

Laboratory Diagnosis

There are two approaches:

Hematologic approach as **absolute lymphocytosis** occurs and **almost 30% lymphocytes are atypical** with large size, expanded nucleus and abundant, often vacuolated cytoplasm.

These are cytotoxic T cells reacting against infected B cells.



-- In **immunologic approach**, heterophil antibody detection is useful for early diagnosis as it is positive within 2 weeks.

-- **EBV specific antibody tests** are used for difficult cases.

-- **IgM VCA** (viral capsid antigen) antibody response can be used for **early illness** and **IgG** response for **prior infection**.

Treatment

-- No treatment is required for uncomplicated cases.

-- High doses of **acyclovir** may be useful in **life threatening cases**.


Thank You!