Herpesviridae

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Herpesviridae

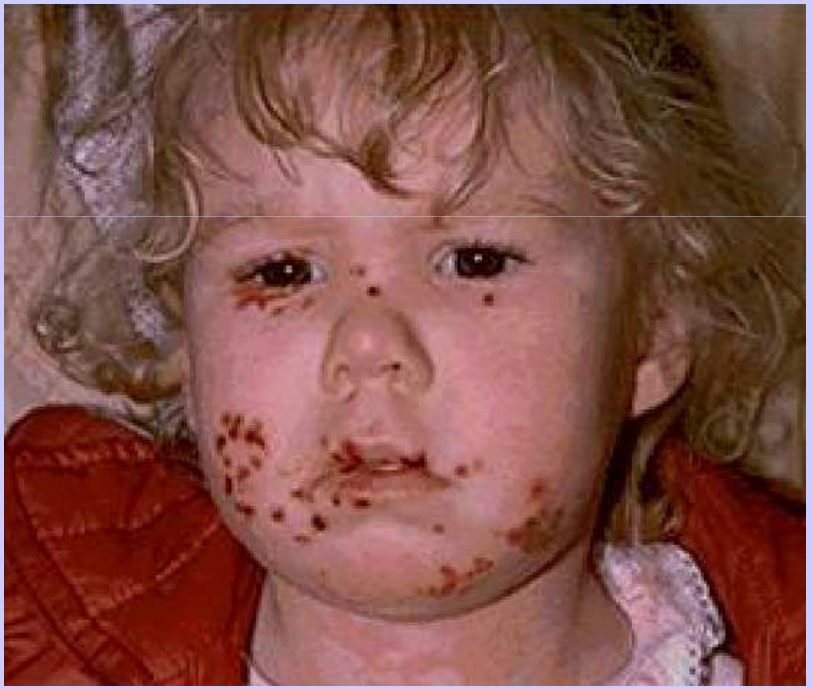
- The ***Herpesviridae*** are a large family of DNA viruses that cause diseases in humans and animals.
- *Herpesviridae* can cause latent or lytic infections.
- There are eight distinct viruses in this family known to cause disease in humans.

Human Herpes virus (HHV) classification

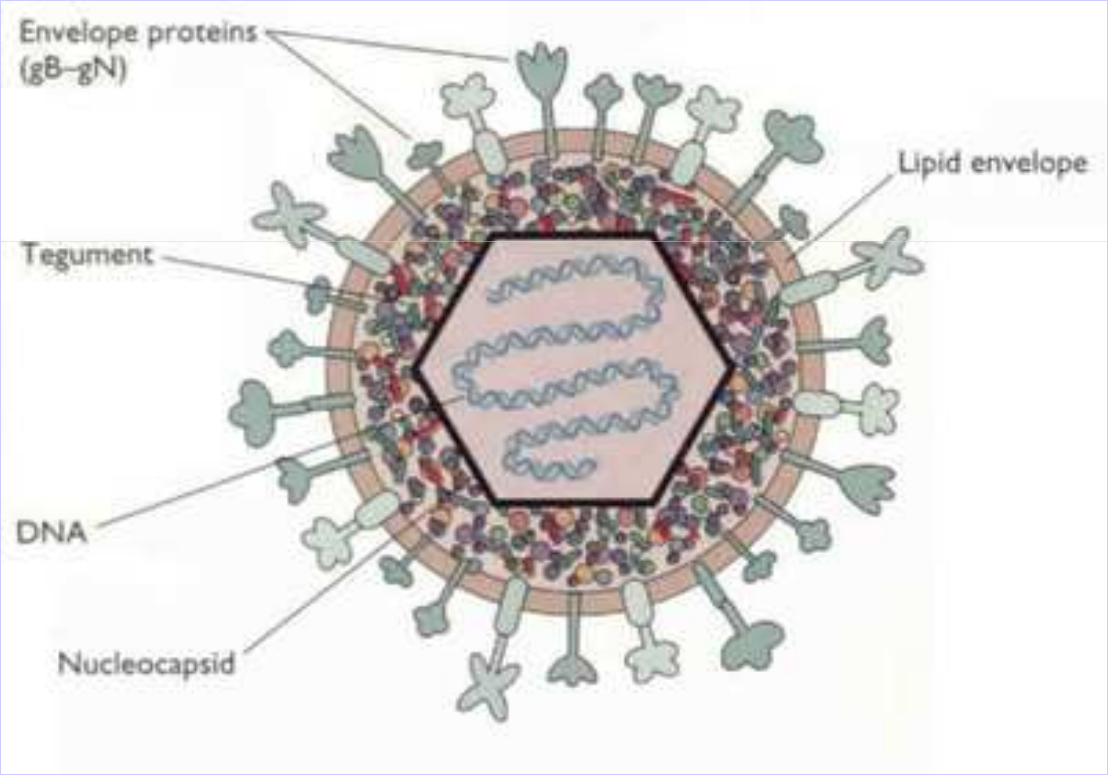
Herpes simplex virus-1	**Oral and/or genital herpes**
Herpes simplex virus-2	**Oral and/or genital herpes**
Varicella zoster virus	**Chickenpox and shingles**
Epstein-Barr virus	**Infectious mononucleosis ,Burkitt's lymphoma , CNS lymphoma in AIDS patients, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma, Hodgkin's disease etc**
Cytomegalovirus	**Infectious mononucleosis-like syndrome , retinitis etc.**
Roseolovirus	**roseola infantum or *exanthem subitum***
Herpes Virus 7	***exanthem subitum***
Kaposi's sarcoma-associated herpesvirus	**Kaposi's sarcoma, primary effusion lymphoma, some types of multicentric Castleman's disease**

Herpesviridae

- Large icosahedreal, double stranded DNA viruses
- Replicate in the nucleus of cells
- Enveloped with numerous glycoprotein spikes.
- Tendency to develop latent infections
- Most primary (initial) infections are asymptomatic (except for Varicella zoster)



Herpes Simplex Viruses (Genus *Simplexvirus)*



Herpes Simplex Virus

- Ist Human herpes virus discovered in 1922
- Two serotypes HSV 1 & HSV 2 in 1962
- The virus grow in a variety of primary and continuous cell cultures.
- Two types can be differentiated by the following features;

1) antigenic differences using type specific monoclonal antibodies.

2) on chick embryo CAM type 2 form larger pocks resembling variola.

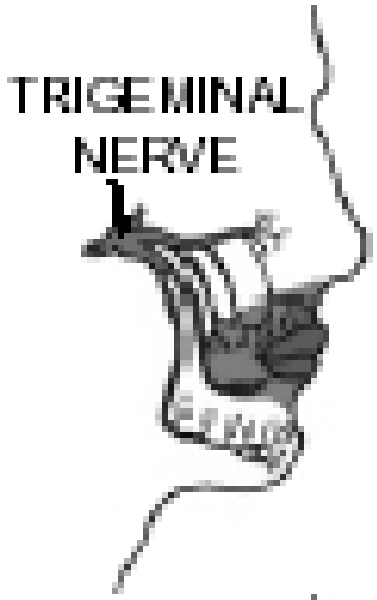
3)Type 2 strain replicate well in chick embryo fibroblast cell, while type 1 strain do so poorly.

4) the infectivity of type 2 is more temperature sensitive than type 1

5) type 2 are more neurovirulent, more resistant to antiviral agents.

Pathogenesis

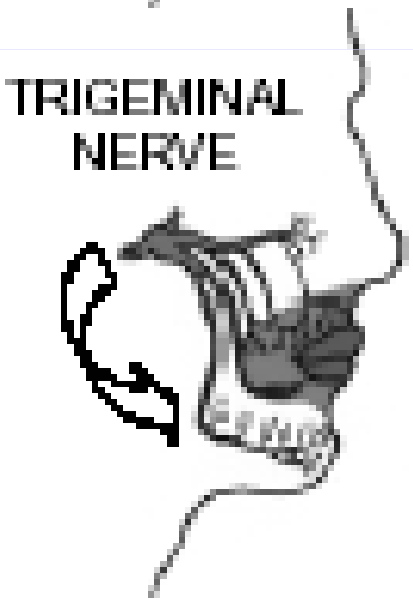
- HSV 1 infection generally limited to oropharynx transmission through respiratory droplets.
- HSV 2 infection usually acquire by sexual contact.
- Virus must come in contact with mucus membrane or abraded skin for initiation of infection.
- After primary infection virus is transported to dorsal root ganglia and remains latent.(trigeminal & Sacral ganglia)



Latent Infection

1. Viral DNA resides in sensory cells of trigeminal nerve ganglion

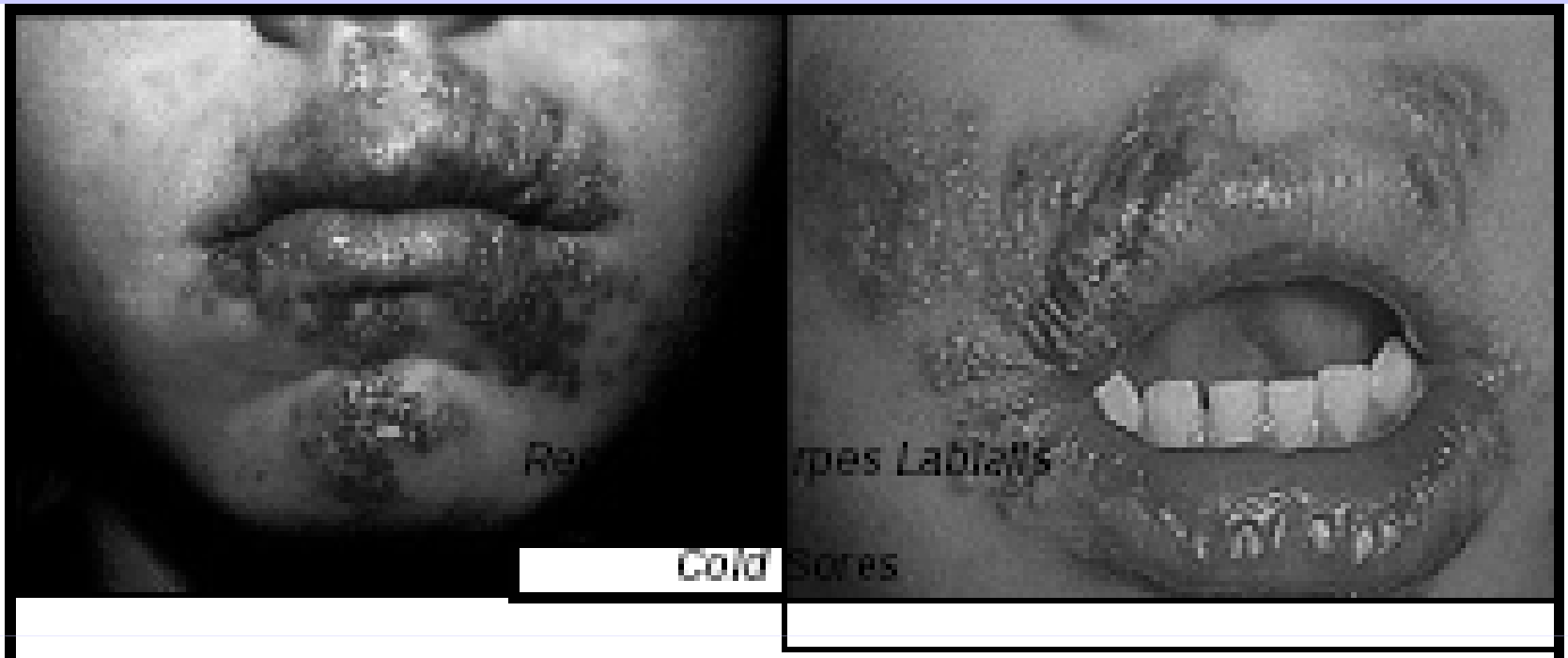
2. Asymptomatic - No virus or virion proteins produced



Recurrent Infection

1. Virus replicates and travels down sensory nerve fiber to infect epithelial cells around the nose and mouth

2. Symptoms are usually a milder form of primary infection



- Recurrent orpharyngeal infections occur in about 38% of the population
- Prodrome of pain, burning, tingling, followed by vesicles 24-48 hrs later (sometimes fever)
- Recurrence may be asymptomatic. About 1-5% of healthy adults excrete HSV-1, 30% of immunocompromised.
- Factors leading to recurrence are highly variable and poorly defined

Herpes simplex Type 1
Viral acquisition

- **Usually infection is a result of contact with saliva or other infected secretions.**
- **Half of kids are infected by at least 2 to 5 years of age. Two thirds of adults have detectable antibodies.**
- **Only one quarter of primary infections are symptomatic so many are infected and don’t know**
- **People often walk around with HSV-1 in their saliva and don’t know. They serve as a reservoir for others to get infected.**

Clinical Manifestation

- Manifestation of infection may include fever, sore throat, ulcerative& vesicular lesion, gingivostomatitis, edema & lymphadenopathy.
- Incubation period- 2 – 12 days
- symptom last for 2 – 3weeks.
- Primary infection in adults often results in phrayngitis in association with mononucleosis syndrome.

Clinical manifestations of infection HSV Type 1

- Primary
  - Oral - symptomatic, asymptomatic
  - Genital - symptomatic, asymptomatic
  - Ocular - keratoconjunctivitis
  - Peripheral - eg. whitlow
  - Encephalitis

Recurrent

Oral, ocular, peripheral

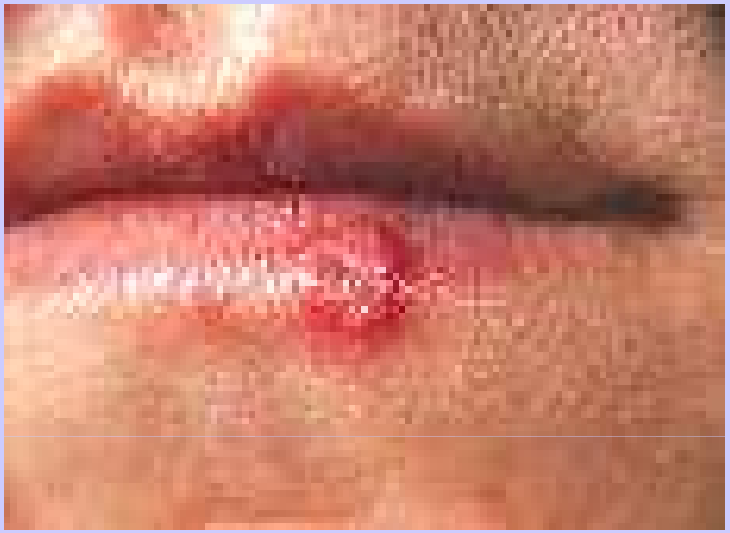
Symptomatic

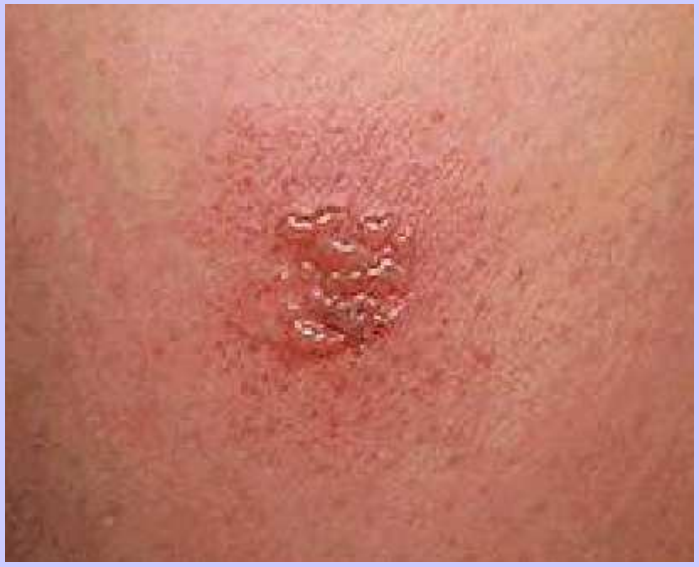
Asymptomatic shedding

Primary gingivostomatitis

- This usually occurs in children less than six years of age.
- The incubation period is 2-12 days, but is usually around 6 days.
- Intra-oral lesions usually are covered with a greyish, white plaque.
- Lesions involve the lips, palate, tongue and gums
- Infection is self limited but may cause considerable discomfort.

Herpes labialis





- Usually cold sores occur along the mucocutaneous junction of the lips.
- They may be single or clustered.
- They may develop following stress or another trigger or without an apparent stimulus.
- The duration is usually 10-14 days.
- Treatment is usually necessary only in immune-compromised patients.

HSV-2 infections

- Not synonymous with genital herpes however:
  - These are primarily infections of the genital tract
  - Neonates can be infected at the time of delivery
  - Extra genital lesions do occur
- Sexual transmission
- The prevalence of HSV-2 antibodies in the population depends on the experience of the patient population.

Genital Herpes infections

- The first episode tends to be more severe and of longer duration.
- Lesions in females are usually vulvar, cervical or perianal.
- Lesions in men are usually on the glans or shaft of the penis.
- Primary and recurrent infection are often associated with fever, malaise, inguinal lymph node inflamation, headache, and occasionally, neck stiffness.

Natural history

Neonatal infections

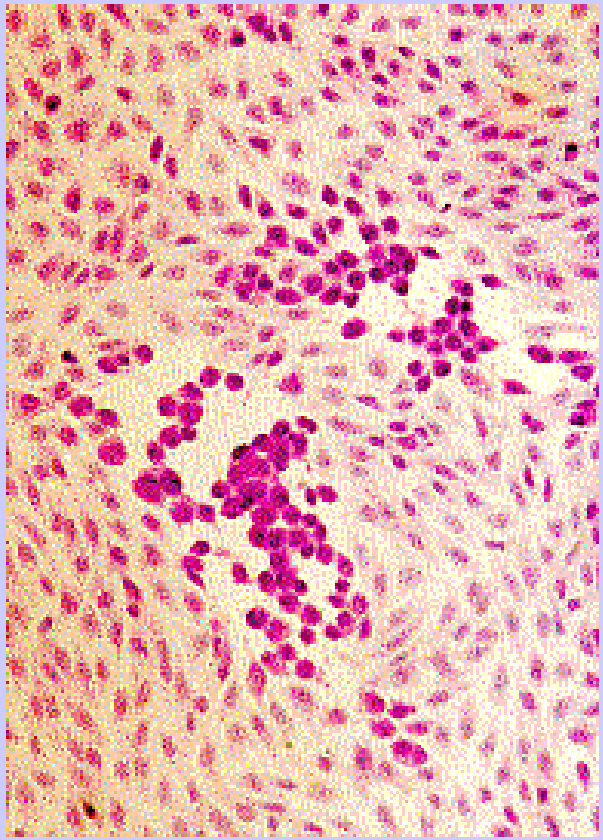
- Usually these are due to HSV-2.
- Approximately half of the children born to mothers with active lesions will be infected.
- Clinical syndromes include:
  - Encephalitis
  - Disseminated multi-organ infection (liver, spleen, lungs)

HSV infections in immuno-compromised patients

- Infections occur usually in patients with decreased cell mediated immunity.
- Usually causes include drugs, malignancy, and AIDS.
- Infections usually represent recurrence rather than primary infection.
- Other organ systems may be involved, i.e., esophagus, bowel, and lungs.

Laboratory Diagnosis of HSV infection

- Direct Detection
  - Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV
  - Immunofluorescence of skin scrappings - can distinguish between HSV and VZV
  - PCR - now used routinely for the diagnosis of herpes simple encephalitis
- Virus Isolation
  - HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days for a result to be available.
- Serology
  - Not that useful in the acute phase because it takes 1-2 weeks for before antibodies appear after infection. Used to document to recent infection.



Cytopathic Effect of HSV in cell culture: Note the ballooning of cells.

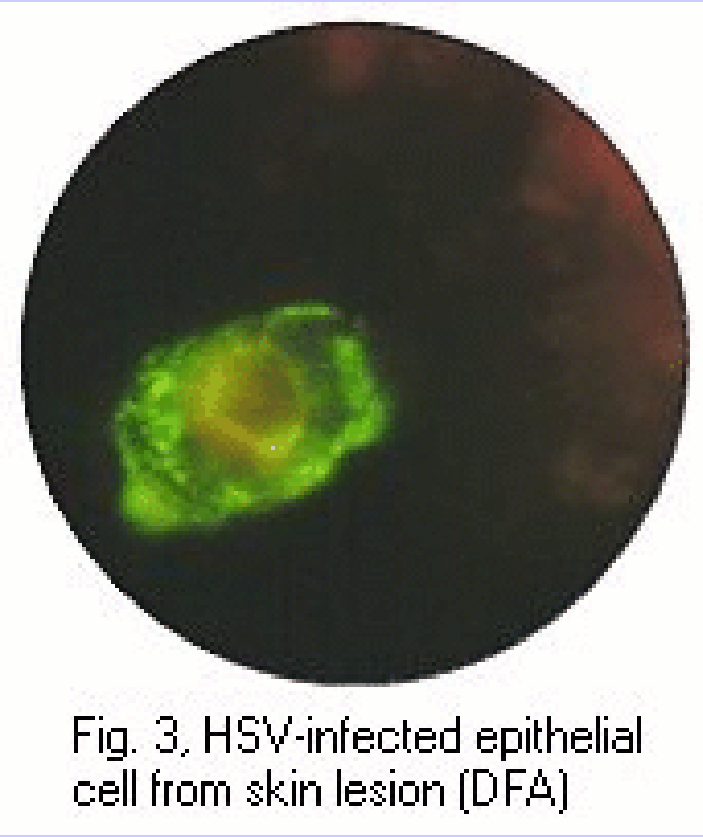


Fig. 3, HSV-infected epithelial cell from skin lesion (DFA)

Positive immunofluorescence test for HSV antigen in epithelial cell.)

Treatment of HSV infections

- In normal hosts treatment provides only a 1-2 day benefit esp for cold sores
- Acute primary genital infections may be treated with acyclovir
- Recurrent genital infection can be prevented with the use of long term prophylactic acyclovir.
- Acyclovir can also be used to treat serious infections in severely immuno-compromised patients and in brain or systemic infections.

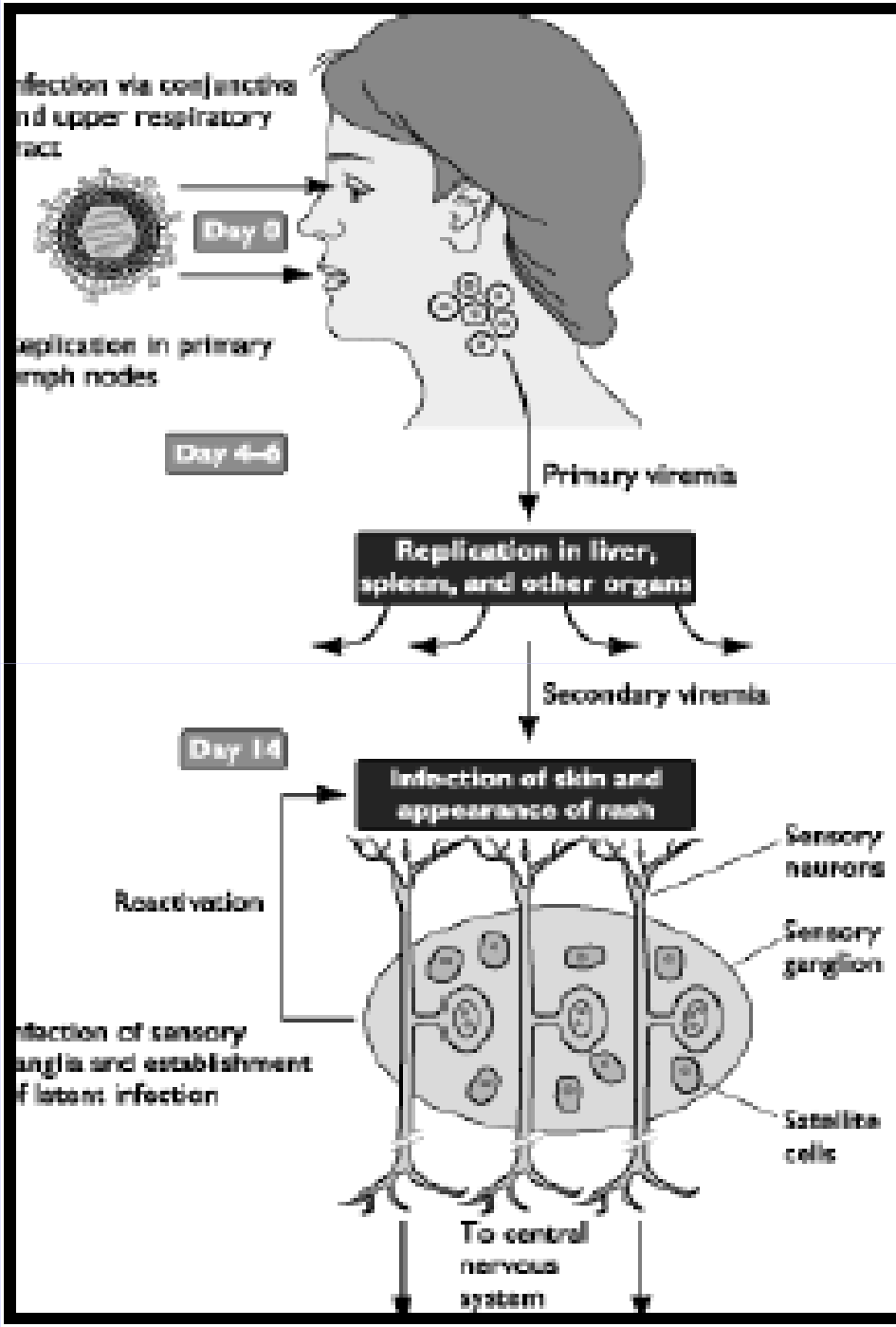
VARICELLA ZOSTER VIRUS

- **Clinical disease recognised in two forms**
- **Primary infection - Varicella (Chicken Pox)**
- **Reactivation - Zoster**

PRIMARY VARICELLA PATHOLOGY

- **disease is usually benign. Manifests as a viral exanthem (rash)**
- **Virus enters via mucosa of URT and oropharynx or via the Conjunctiva**
- **Viral replication occurs in primary site and virus disseminates via the blood stream.**
- **Clinical**

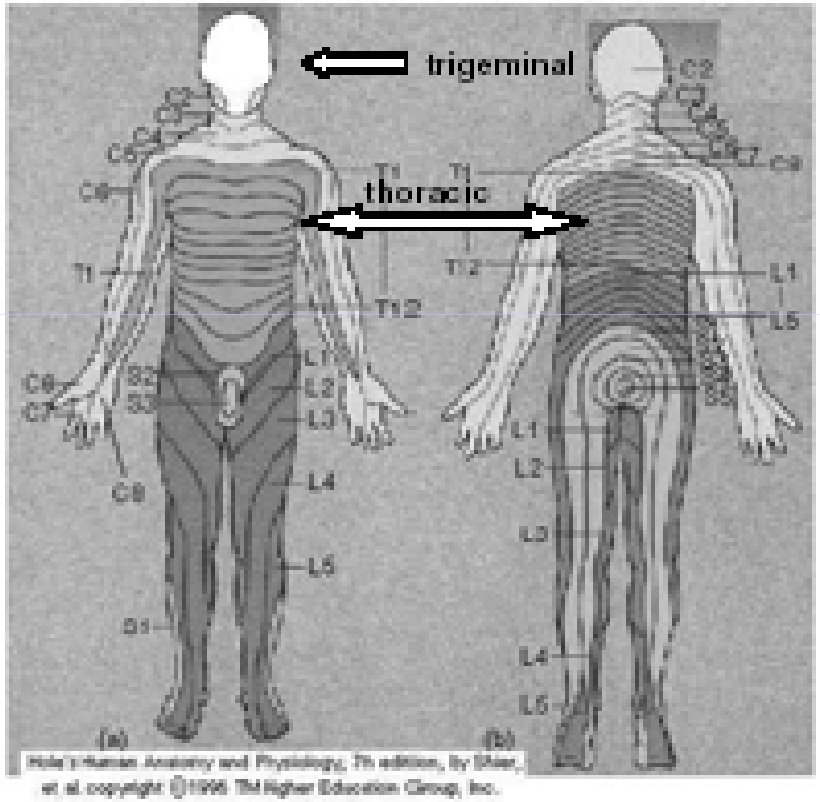
- **Virus replication then occurs in cells of the reticuloendothelial system (blood mononuclear cells)**
- **Virus replication is initially limited by specific and nonspecific immunological responses but in most individuals these are overwhelmed and extensive secondary viremia occurs**



- Secondary viremia is associated with prodromal symptoms (fever) which first appear 14-15 days after initial infection
- Secondary viremia is usually terminated after 3 days by humoral and cell-mediated factors
- Fever is followed by a maculopapular rash forming lesions over 2-4 days. These may appear on scalp, trunk, extremities and mucosal surfaces.
- Vesicles contain fluid with infectious virus, and dry over 1-3 weeks.

SECONDARY ZOSTER PATHOLOGY

- Virus spreads to the ganglia by systemic virus
- Sets up latent infection in ganglion without replication or cell damage.
- Reactivation as herpes zoster involves the ganglia and spinal nerves corresponding to the dermatome involved in the primary infection
- The areas supplied by the trigeminal nerve (opthalmic) and thoracic ganglia are most often involved



CYTOMEGALOVIRUS

- CMV is considered to be the "oldest" type of herpesvirus in evolutionary terms.
- CMV is the prototype of beta-herpesviruses
- CMV found in many species, and is species specific
- CMV infection is of primary concern in immunocompromised (AIDS) and transplant patients

CYTOMEGALOVIRUS EPIDEMIOLOGY

- Humans are the only reservoir for human CMV and transmission occurs by person to person contact
- CMV is very labile and close or intimate contact is necessary for spread of infection
- Often the salivary gland becomes infected and is probably site of chronic infection.
- Intermittent shedding of CMV from many sites is common in seropositive hosts
- Sources of infection include oropharyngeal secretions, urine, cervical and vaginal secretions, breast milk, tears, faeces and blood

CYTOMEGALOVIRUS CLINICAL

Normal Host

- Primary infection in the normal host usually results in mononucleosis (about 8% of IM cases; majority by EBV)
- Rare complications include pneumonia, hepatitis and CNS disease
- Infection induces both a humoral (IgM, IgG and IgA) and CMI response.
- In children < 7 yrs CMV infection may result in severe liver, or respiratory disease
- Recurrent disease is rare in the normal host but common in the immunocompromised

CYTOMEGALOVIRUS CLINICAL

Immunocompromised Hosts

- Recurrent infections may be severe and/or fatal in transplant (BMT) and AIDS patients.

  Pneumonia and CNS disease as the most serious manifestations in these subjects

- CMV is also commonly associated with allograft rejection in transplant (BMT) patients

- CMV infection predisposes to fatal bacterial, fungal and parasitic infections in AIDS and transplant patients

- CMV is leading cause of morbidity and mortality in these patient groups

CYTOMEGALOVIRUS CLINICAL

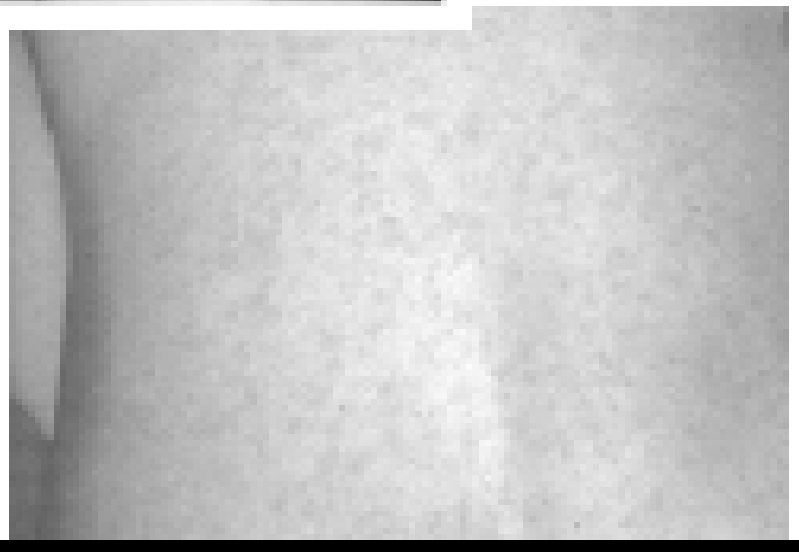
Congenital Infections

- CMV is the leading viral cause of congenital abnormalities
- 0.2 – 2% of all infants are infected *in utero*. 10% of these will develop significant or permanent brain damage.
- CMV is the most common cause of viral mental retardation in Western world
- A common feature of congenital infection is infection of the liver resulting in hepatitis.
- In addition, sensorineural hearing loss, microcephaly and periventricular calcification may occur.

HUMAN HERPESVIRUS - 6

- First isolated from PBMC of patients in 1986 during attempts to isolate HIV
- Later isolated from patients in Africa and the UK and subsequently was found to be ubiquitous.
- Grows predominantly in activated lymphocytes – similar to gamma herpesvirus like EBV
- Genetic similarity and growth cycle to CMV led to classification as a beta-herpesvirus
- Two variants of HHV-6 have been identified on basis of genetic and biological properties (variants A and B)

HUMAN HERPESVIRUS - 6



Primary Infection

- HHV-6 causes exanthem subitum (Roseola) in children
  - Benign disease
  - Fever, rash
  - Complications include febrile convulsions
  - 60-70% of infections are unapparent
  - Variant B is predominant cause

EPSTEIN-BARR VIRUS

- EBV was first isolated in 1964 from tumour samples taken from patients in Africa with Burkitt's lymphoma.
- First herpesvirus whose genome was completely cloned and sequenced.
- Envelope and tegument proteins differ in size from other herpesviruses.
- Two EBV types (A & B) circulate in most human populations
- 1968 shown to be a common cause of infectious mononucleosis in adolescents

Epstein-Barr virus

- The usual source of infection is the saliva of persons shedding the virus.
- The virus has an affinity for receptors on the surface of B cells.
- Viral infection results in local replication and a secondary viremia. There is proliferation of both B cells and the T8 (suppressor) subset of T cells.

Epidemiology of EBV infection

- 50% of 5 year olds have been infected
- Children are very usually asymptomatic.
- There is a second wave of infection during the teens who are more frequently symptomatic
- By age 40, 90-95% of adults have antibodies

- EB virus infection may lead to the following clinical conditions.
- Infectious mononucleosis
- EBV associated malignancies
- Burkitt's lymphoma.
- Lymphoma in immunodeficient persons ,nasopharyngeal carcinoma in person of Chinese origin.

EPSTEIN-BARR VIRUS CLINICAL

Normal Host

- Sub-clinical infections in infants >2 years old
- Infectious Mononucleosis (glandular fever) in adolescents
  - 4-7 week incubation
  - insidious onset and vague clinical presentation
  - fluctuating fever, pharyngitis, lymphadenopathy, spleen enlarged and liver affected
- Illness usually persists for several weeks, and rarely beyond several months. An association with CFS has been proposed but not proven.

EPSTEIN-BARR VIRUS CLINICAL

Immunocompromised Host

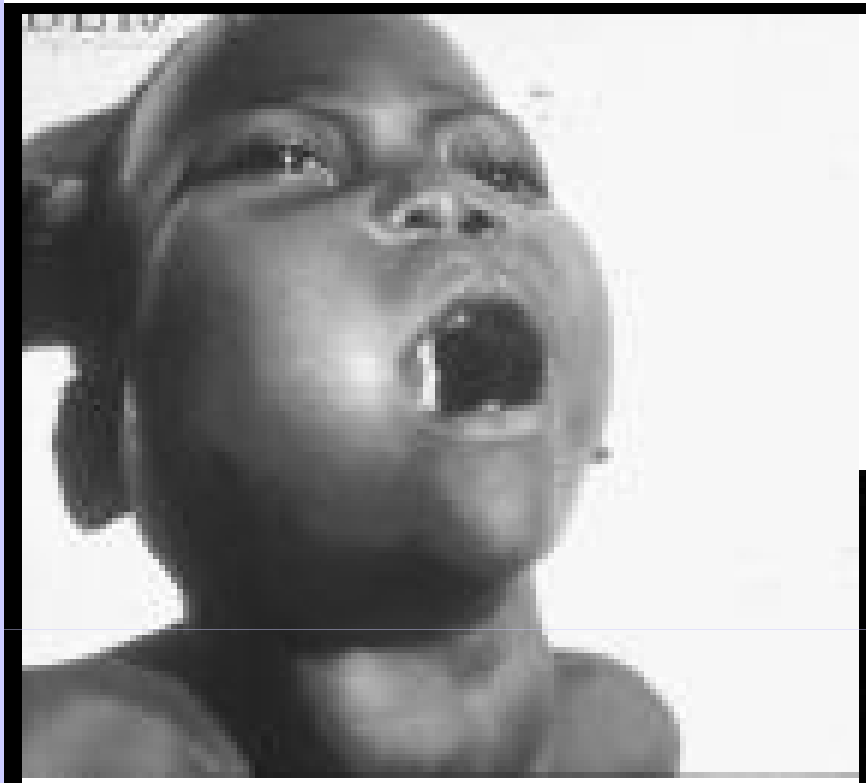
- **May result in unrestrained EBV replication**
  - any organ system can be affected; lungs & liver
  - produces B-cell lymphomas in some T-cell deficient genetic disorders
- **Pneumonitis and CNS disease are rare.**

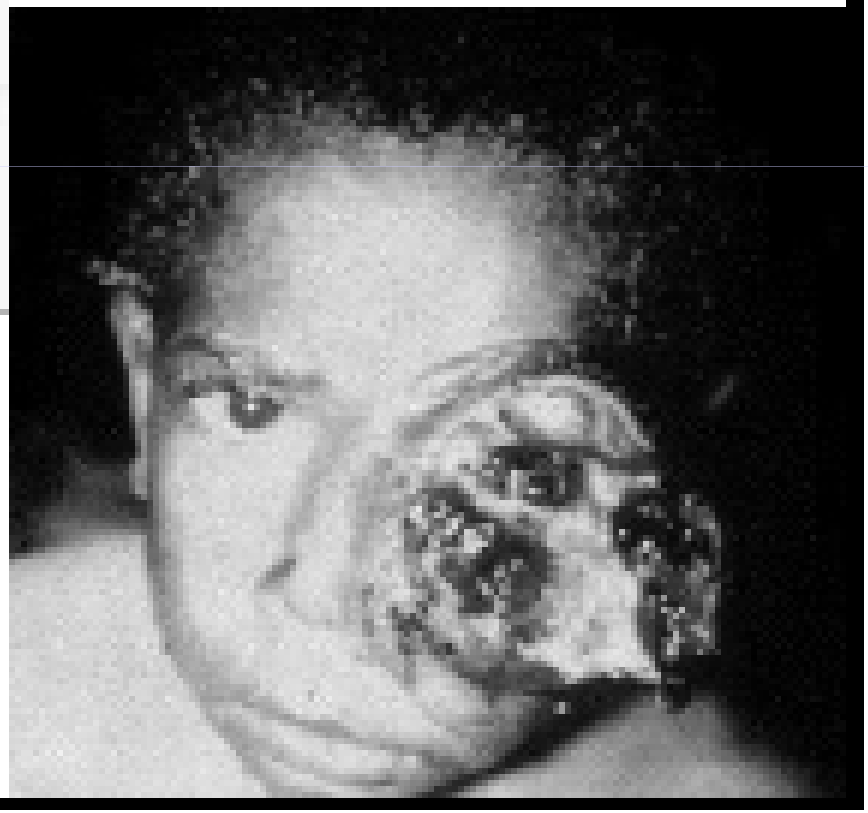
EPSTEIN-BARR VIRUS CLINICAL

Neoplasms - Burkitt's lymphoma

- Burkitt's lymphoma is the most common childhood malignancy in equatorial Africa & PNG (80% of childhood cancers)
- First isolation of EBV was from tumour tissues from patients with BL
- These areas are also endemic for malaria. Continuous infection with malarial parasite causes polyclonal B cell stimulation and together with rampant malnutrition, suppresses T cell responses. This results in a greater number of EBV-infected proliferating B cells which increases the probability of development of cytogenetic abnormalities (ie cancer)

Burkitts Lymphoma





EPSTEIN-BARR VIRUS CLINICAL

Neoplasms **-** Nasopharyngeal carcinoma

- Nasopharyngeal carcinoma due to EBV is rare in Europeans but common in southern China. Etiological factors include EBV, genetic susceptibility and environmental factors.
- Most common cancer in China & eskimos
- up to 40 years between infection & cancer
- EBNA-1 expression is up-regulated
- Ethnic restriction - genetic predilection or dietary cofactor

Diagnosis of EBV infection

- Increased lymphocytes and monocytes
- Atypical lymphocytes (usually >30%)
- Neutropenia (low neutophils) and thrombocytopenia (low platelets)
- Most have elevated liver enzymes
- Heterophile antibodies
  - Antibodies which cross react with sheep or horse red blood cells
  - Usually determined using a Monospot or similar test.
  - A positive test is very specific (97%)
- Other specific serologic tests directed against viral antigens

HUMAN HERPESVIRUS - 8

- First detected in 1995 in Kaposi sarcoma biopsies from AIDS patients.
- DNA sequences detected by differential PCR. Virus was not isolated or visualised.
- Genome sequence analysis identified a new herpesvirus classified as a gamma-herpesvirus
- Contains a "pirated oncogenic cluster" of cellular genes

Clinical manifestations of EBV infections

- **Infectious mononucleosis**
  - **The incubation period is 4-6 weeks.**
  - **The illness may last from 2-8 weeks.**
  - **Fatigue may persist for months**
- **Symptoms and signs**
  - **tonsilar enlargement**
  - **pharyngeal redness with or without pus**
  - **cervical adenopathy (80-90%)**
  - **large liver and spleen**
  - **skin rash, esp. after ampicillin**