CYTOMEGALOVIRUS & HERPES SIMPES VIRUSES

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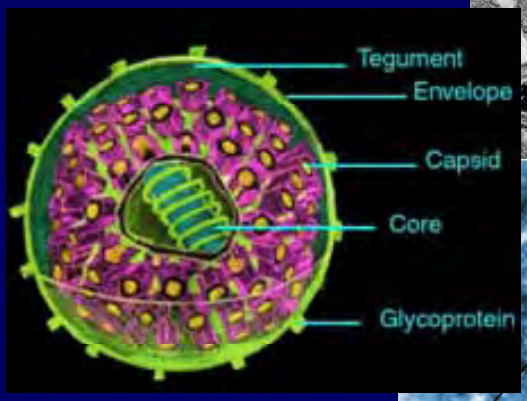
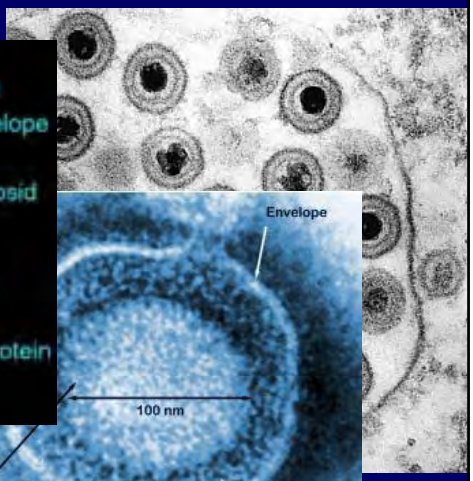
Clinically Relevant

HERPESVIRUS STRUCTURE





Enveloped viruses are labile in the environment

Shedding and survival of herpes simplex virus from 'fever blisters'

Ronald Turner, Ziad Shebad, Karen Osborne, J Owen Hendley

In nine adults with virus-positive herpes labialis, HSV was detected in the anterior oral pool of seven (78%) and on the hands of six (67%).

HSV isolated from patients with oral lesions were found to survive for as long as two hours on skin, three hours on cloth, and four hours on plastic.

Pediatrics. 1982 ; 70:547-9

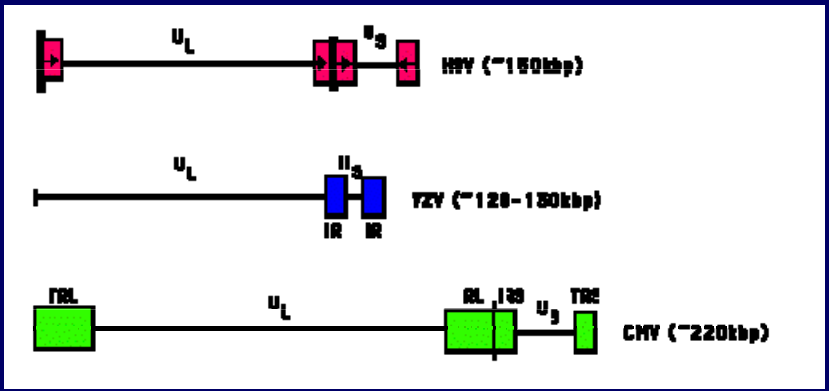
Reactivation and Shedding of Cytomegalovirus in Astronauts during Spaceflight

S Metha, R Stowe, A Feiveson, S Tyring, D Pierson

The reactivation of cytomegalovirus (CMV) in 71 astronauts was investigated, using polymerase chain reaction. A significantly greater shedding frequency was found in urine samples from astronauts before spaceflight (10.6%) than in urine from the healthy control subject group (1.2%). Two of 4 astronauts studied during spaceflight shed CMV in urine.

J Infectious Dis 2000; 182:1761

HERPESVIRUS GENOMIC ORGANIZATION



Double stranded DNA genome – high fidelity replication

CMV & HSV EPIDEMIOLOGY

- Agents are ubiquitous
- No seasonality
- US adult seroprevalence

  CMV = 58.9% (90.8% aged ≥ 80 years)

  HSV-1 = 57.7%

  HSV-2 = 17.0%
- Prevalence demonstrates racial and socioeconomic disparities
- Prevalence affected by behavioral factors

Longitudinal risk of HSV-1, HSV-2 and CMV infections among young adolescent girls

L R Stanberry, SL Rosenthal, L Mills, PA Succop, FM Biro, RA Morrow, DI Bernstein

A 3-yr longitudinal study of HSV-1, HSV-2, and CMV sero-prevalence was conducted in a cohort of 174 adolescent girls.

By study end, 81% were CMV seropositive, 49% were HSV-1 seropositive, and 14% were HSV-2 seropositive. Among girls with a history of sexual activity 18.9% were HSV-2 seropositive.

The attack rates, based on the number of cases per 100 person-years, were 13.8 for CMV infection and 3.2 for HSV-1 infection (among all girls) and 4.4 for HSV-2 infection (among girls with a history of sexual activity).

Clinical Infectious Diseases 2004;39:1433–1438

CMV TRANSMISSION

- Transmission – person-to-person or via infected fomites
- Viral shedding
  - urine
  - saliva
  - In a daycare center study an average of 11.2% children shed CMV – Arch Med Res 2005; 36:590-3.
  - cervicovaginal secretions
  - breast milk
  - semen (?)

CMV TRANSMISSION

- Intrauterine
  - most common congenital infection
- Perinatal
- Postnatal
  - infants, parents of young infants, daycare workers, hospital workers
  - most common route of mother-to-baby transmission is via breast feeding
- Blood transfusion
  - prevented by using blood from CMV seronegative donors or cotton wool filtered blood (removes WBCs & platelets)
- Organ transplantation
  - CMV seropositive donor to CNV seronegative recipient

Cytomegaloviruses are over 200 million years old ...no wonder they are so good at what they do

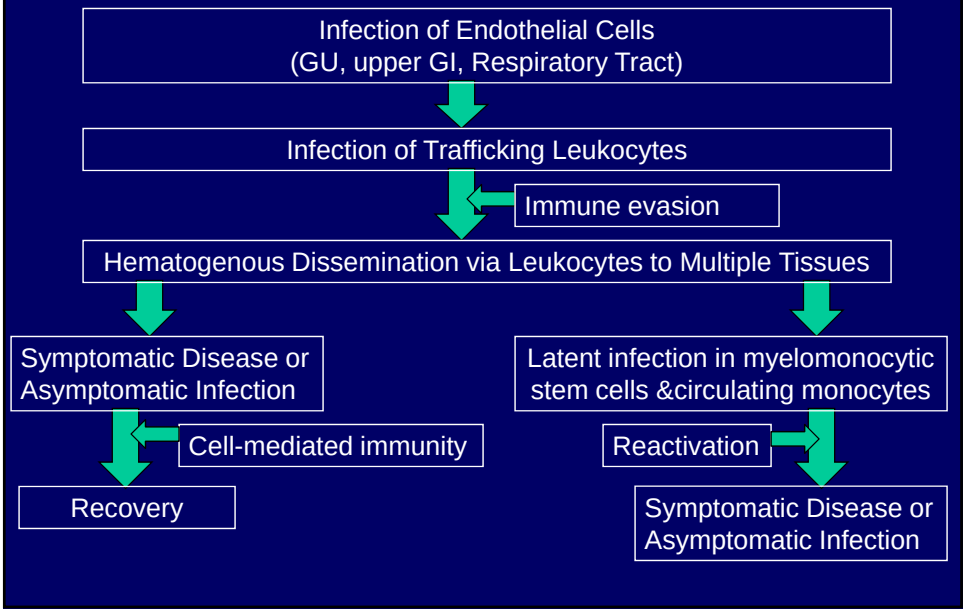
Human CMV (HCMV) has evolved with us since the beginning of our time (prior to invertebrate-vertebrate split).

For every defense mechanism we have, HCMV has at least one counter-mechanism…tit for tat

Unsuccessful viruses cannot overcome host defenses.

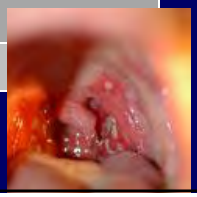
*eebweb.arizona.edu/Courses/Ecol409_509/ecol409.2008.lecture5.**ppt***

CMV PATHOGENESIS



COMMON CMV INFECTIONS

INFECTIOUS MONONUCLEOSIS	
Clinical Manifestations	Laboratory Findings
Fever	Atypical Lymphocytes
Hepatomegaly	Lymphocytosis
Lymphadenopathy	Mild Thrombocytopenia
Malaise and Fatigue	EBV or CMV antibodies
Splenomegaly	Heterophile antibodies
Pharyngitis/Sore Throat	
Rash	



CMV responsible for about 8% of IM cases

COMMON CMV INFECTIONS

CONGENITAL INFECTION	
Clinical Manifestations	Laboratory Findings
Hepatoslenomegaly	Elevated LFTs
Lymphadenopathy	Thrombocytopenia
Respiratory distress	Pneumonitis
Rash	CMV in body fluids
Microcephaly	

Infection can cause brain damage that may result in mental retardation, spasticity, seizures, deafness and/or blindness

http://congenitalcmv.blogspot.com/

COMMON CMV INFECTIONS

CMV is the most important post transplant viral pathogen

CMV DISEASES IN IMMUNOCOMPROMISED PATIENTS	
Manifestations	Manifestations
Fever	Myelosuppression
Hepatitis	Encephalopathy
Retinitis	Colitis
Pneumonitis	Rejection
Immunosuppression	Graft v Host Disease

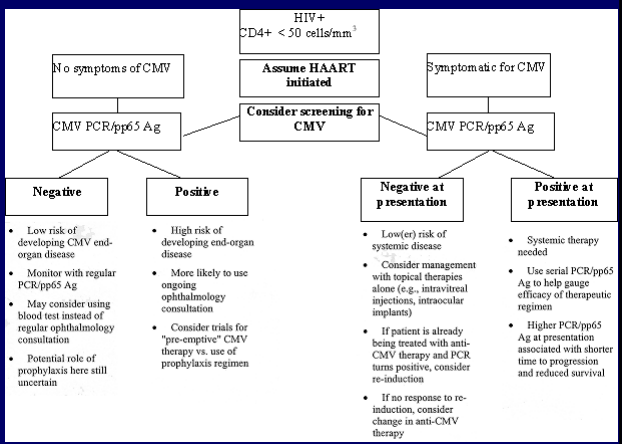
Disease likelihood determined by nature of the immunosuppression, solid organ transplantation, bone marrow transplantation or AIDS

PUTATIVE ASSOCIATIONS

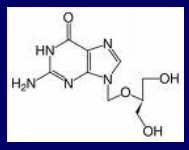
- ATHEROSCLEROSIS is an inflammatory disease
- Infection is a candidate inflammatory trigger
- Epidemiological studies link CMV infection with clinically manifest atherosclerotic disease
- CMV antigen and nucleic acid sequences in arterial smooth muscle cells of humans suggests that viral infection of the arterial wall may be common in the general population
- Some heart transplant recipients, who are immunosuppressed, and actively infected with CMV, are prone to develop accelerated atherosclerosis in the transplanted organ
- There may be a gene by environment interaction

CMV DIAGNOSIS

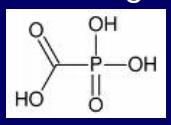
- Serology – IgG and IgM detection (anamnestic IgM responses can occur)
- Virus isolation
- Antigen (pp65) detection
- CMV DNA PCR



CMV TREATMENT



- Ganciclovir and Valganciclovir
- Foscarnet

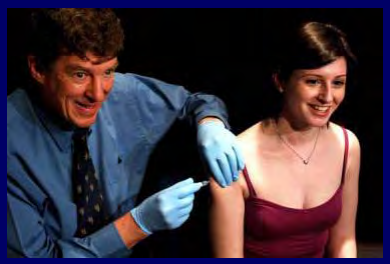


- Cidofovir

- All are viral DNA polymerase inhibitors
- Used exclusively in the treatment of CMV infection in immunocompromised patients
- Used for pre-emptive and prophylactic therapy
- Ganciclovir resistance reported in 5-10% of patients

CMV PREVENTION

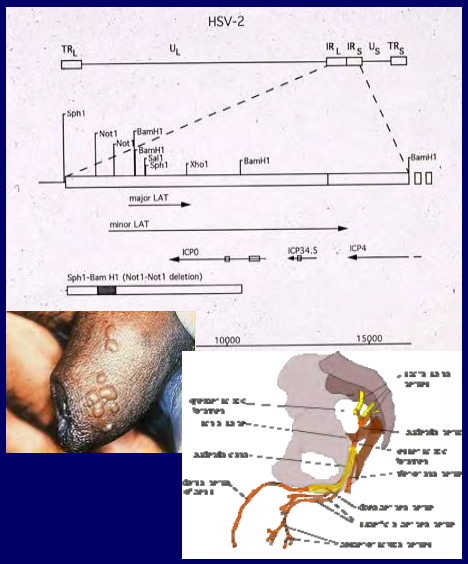
- Hand washing (1-30% of hospitalized patients and 100% of infected infants shed in urine and/or saliva)
- Use of CMV seronegative blood products
- Use of CMV seronegative organ donors (impractical)
- Antiviral prophylaxis
- CMV immune globulin
- Vaccines

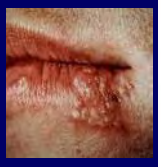


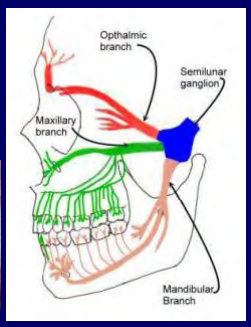
HSV TRANSMISSION

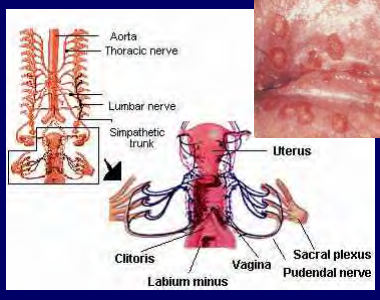
- Transmission – person-to-person (rarely by fomites)
  - Intrauterine (very rare)
  - Perinatal
  - Skin-Skin
  - Genital-Genital
  - Oral-Genital
  - Oral-Oral
- Viral shedding
  - saliva
  - oro-facial lesions
  - genital lesions and secretions
  - tears (?)
  - HSV-1 more commonly shed from oral cavity and HSV-2 more commonly from genital tract

HSV SITE-SPECIFIC RECURRENCES

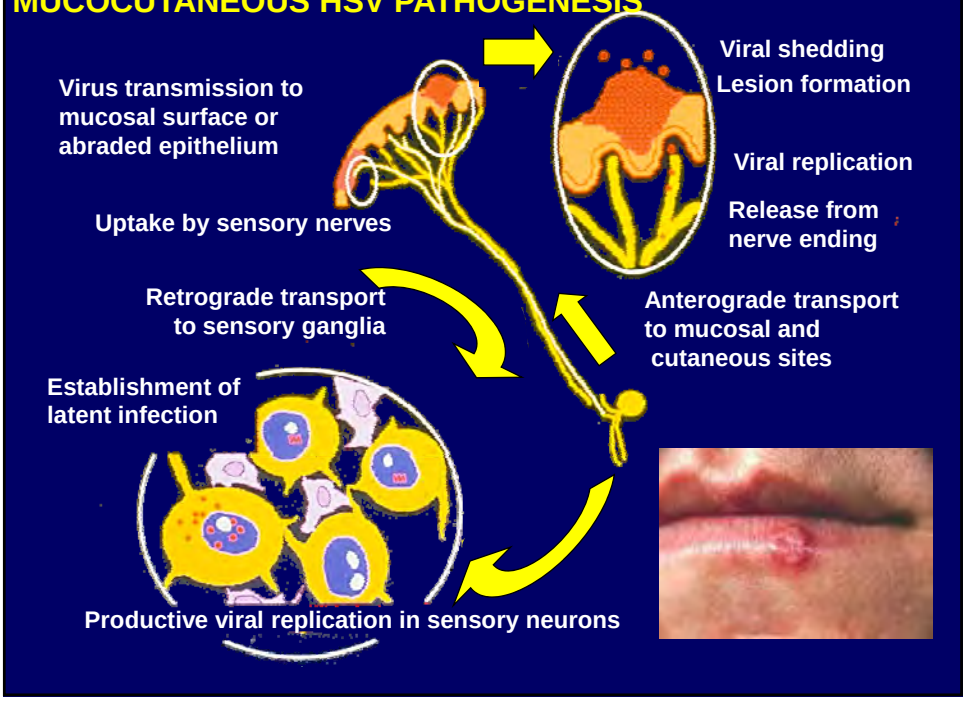






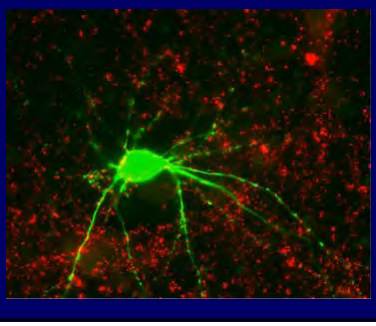


MUCOCUTANEOUS HSV PATHOGENESIS



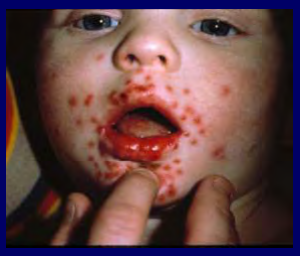
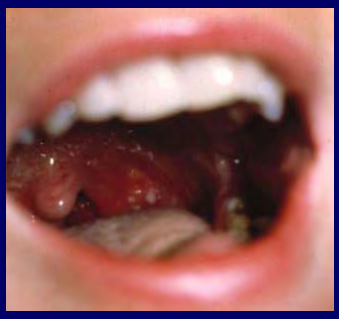
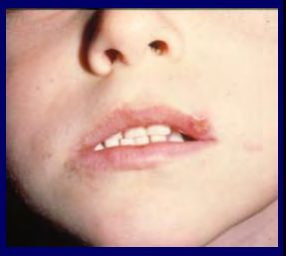
HSV INFECTIONS

- Clinical manifestations are determined by portal of entry, immune status of the host, and whether the infection is primary or recurrent
- HSV is a neurotropic virus that infects sensory ganglia hence pain is a common manifestation of mucocutaneous HSV infections



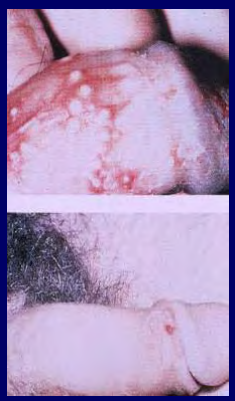
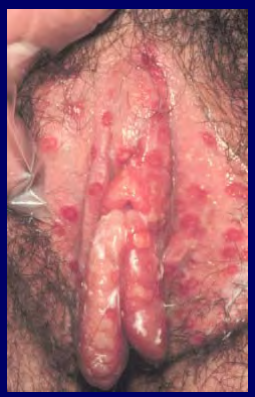
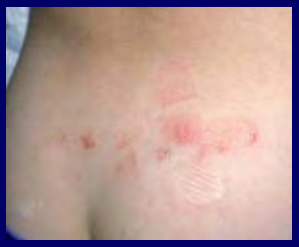
HSV INFECTIONS

- Primary v recurrent mucocutaneous infections
  - Primary oral-facial infection – herpes gingivostomatitis or pharyngitis
  - Recurrent oral-facial infection – herpes labialis

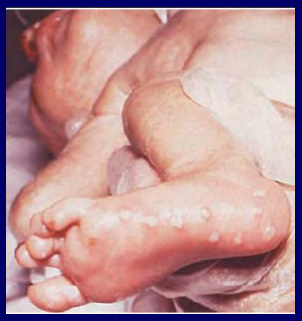
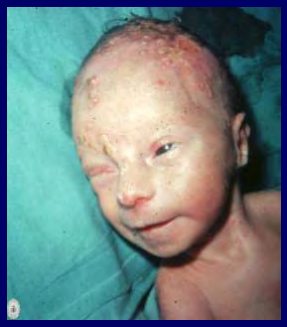
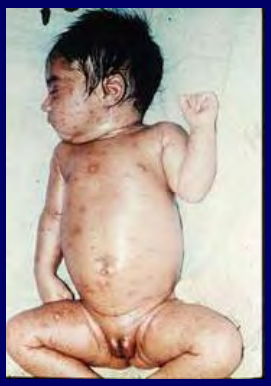
HSV INFECTIONS

- Primary v recurrent genital infections
  - Primary genital herpes
  - Recurrent genital herpes

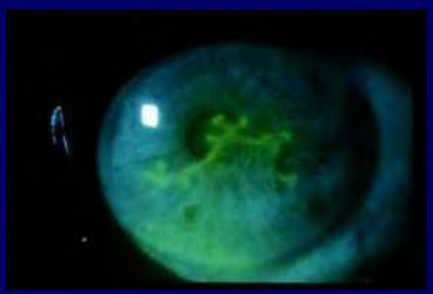
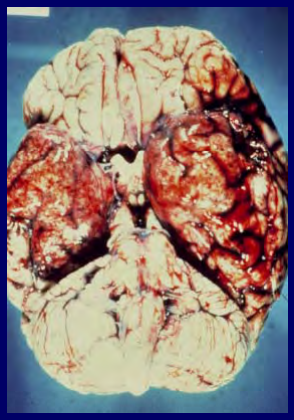
HSV INFECTIONS

- Neonatal herpes
  - Skin-eye-mouth
  - Central nervous system
  - Disseminated

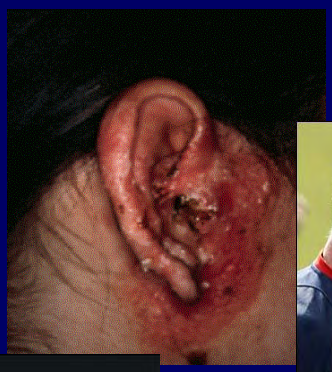
HSV INFECTIONS

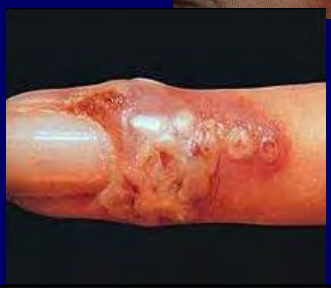
- Herpes encephalitis
- Herpes keratitis
- Herpes retinitis
- Herpes meningitis

HSV INFECTIONS

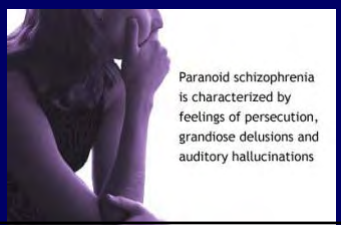
- Herpes gladiatorium
- Herpes whitlow
- Eczema herpeticum
- Disseminated herpes
- Erythema multifome
- Bells palsy





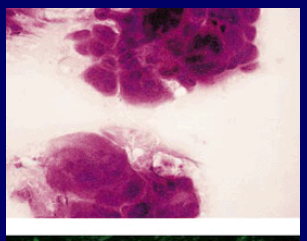
PUTATIVE ASSOCIATIONS

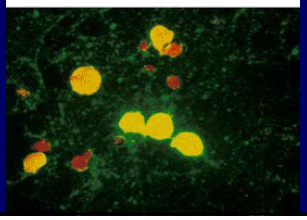
- Infectious agents have been implicated in the pathogenesis of SCHIZOPHRENIA
- Herpes simplex virus (HSV) has been suggested as a putative cause of schizophrenia based on its tropism for the nervous system and epidemiological studies linking herpes infection in pregnancy with schizophrenia.
  Yolken R, Viruses and schizophrenia: a focus on herpes simplex virus. Herpes 2004; 11:83A.



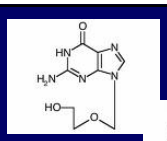
HSV DIAGNOSIS

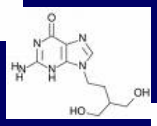
- Serology – IgG and IgM detection
  - Anamnestic IgM responses can occur; IgM tests unreliable; most tests cannot accurately distinguish HSV-1 and HSV-2
- Virus isolation
- Antigen detection
- HSV DNA PCR
- Tzacnk smear – unreliable
- Clinical diagnosis – unreliable
  - Langenberg, NEJM 1999, 341:1432

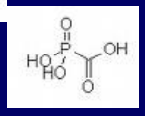




HSV TREATMENT





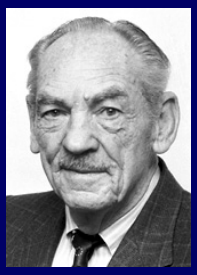


- Acyclovir and Valacyclovir
- Penciclovir and Famciclovir
- Foscarnet
- All are viral DNA polymerase inhibitors
- For life threatening HSV infections use on intravenous acyclovir
- Valacyclovir use has been shown to reduce risk of transmission of genital herpes from infected to susceptible partner
- Acyclovir resistance is rare but seen in profoundly immunocompromised patients
- Acyclovir, Valacyclovir and Famciclovir remarkably safe

HSV TREATMENT

- Nobel Prize in Physiology and Medicine 1988

Gertrude Elion



George Hitchings

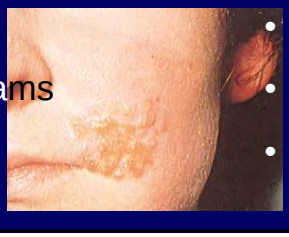
"Gertrude Elion and George Hitchings demonstrated differences in nucleic acid metabolism between normal human cells, cancer cells, protozoa, bacteria and virus. On the basis of such differences a series of drugs were developed that block nucleic acid synthesis in cancer cells and noxious organisms without damaging the normal human cells. A recent, successful application of their research ideas is exemplified by acyclovir (1977), the first effective drug in the treatment of herpes virus infections."

HERPES INFECTIONS MISCELLANEOUS THERAPIES

- Phototherapy
- Burn therapy (laser/N_2)
- Application of ice
- X-rays
- Benzoin
- Topical epinephrine
- Hydrogen peroxide
- Vitamins
- Diet therapy
- Ginseng
- Aloe vera extracts
- Various herbs
- Red algae
- Lactobacillus tablets

HERPES INFECTIONS MISCELLANEOUS THERAPIES

- Dimethyl sulfoxide (DMSO)
- Lysine
- Blistex
- Camphophenique
- Pyrethins
- Antibiotics
- Steroid creams



- Tannic acid
- Mercurochrome
- Potassium permangnate
- Gentian violet
- Silver nitrate
- Iodine
- Lithium
- Red wine

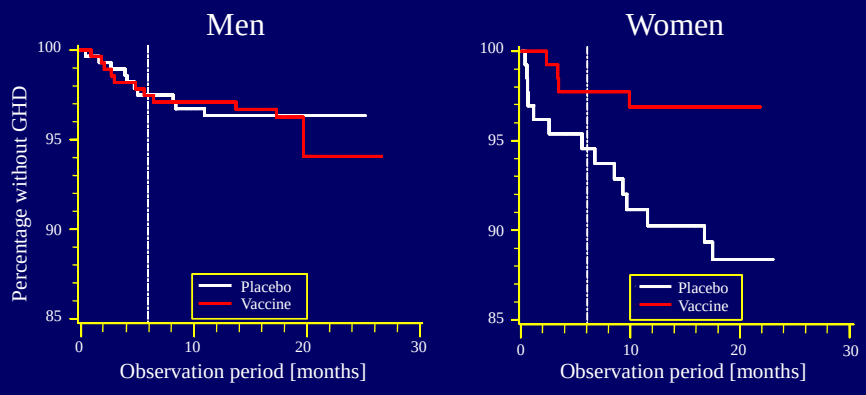
HSV PREVENTION

- Neonatal herpes
  - Cesarean delivery
  - Antivirals in final 4 weeks of gestation (unproven)
- Genital herpes
    - Abstinence
    - Valacyclovir use by infected partner
    - Condom use (limited benefit)
    - Vaccines (in development)

GSK HSV-2 VACCINE TRIALS

- Two double blind, randomized, placebo-controlled trials
- Study 1 (57 centers) enrolled 847 HSV-1 and HSV-2 seronegative partners of HSV-2 infected persons
- Study 2 (60 centers) enrolled 2491 (any serostatus) partners of HSV-2 infected persons
- Vaccinations: 0, 1, and 6 months – I.M. administration
- Follow-up period: 19 months
- Primary efficacy endpoint: Acquisition of HSV-2 disease

Study 1- GSK HSV-2 Vaccine
Genital Herpes Disease HSV 1-/2- Subjects

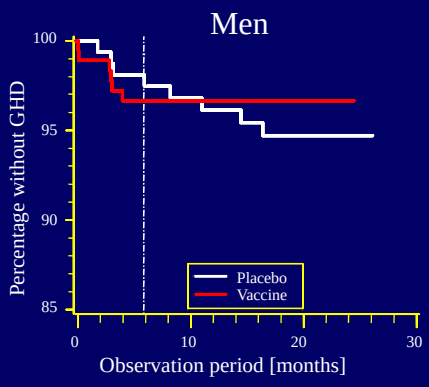


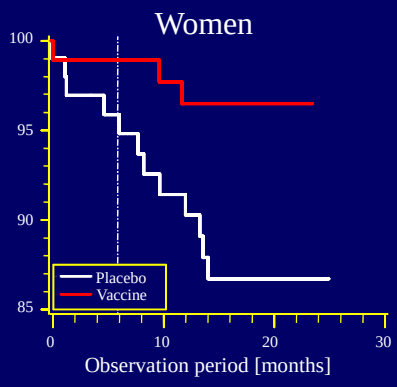
Vaccine Efficacy	p-value
-10.9%	0.81

Vaccine Efficacy	p-value
73.2%	0.01

Stanberry NEJM 2002;347:1652

Study 2- GSK HSV-2 Vaccine
Genital Herpes Disease HSV 1-/2- Subjects



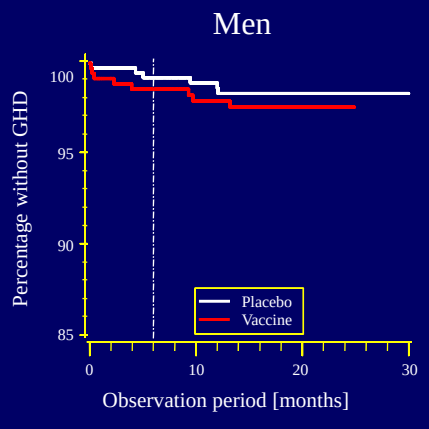


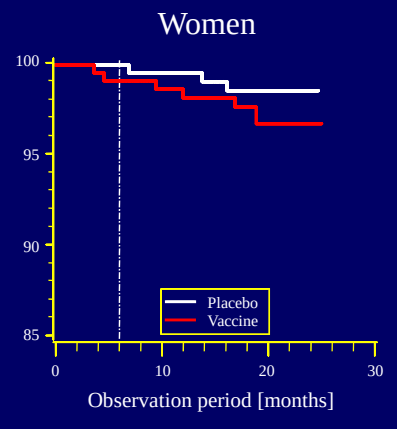
Vaccine Efficacy	p-value
32.2%	0.47

Vaccine Efficacy	p-value
74.4%	0.02

Stanberry NEJM 2002;347:1652

Study 2- GSK HSV-2 Vaccine
Genital Herpes Disease HSV 1+/2- Subjects





Stanberry NEJM 2002;347:1652

HSV-2 Vaccines: Key Questions

- What might explain the gender effect?
- Why did the vaccine not protect HSV-1 seropositive women?
- Would an HSV vaccine to protect against HSV-2 genital herpes also protect against genital herpes caused by HSV-1?
- Would a genital herpes vaccine protect against non-genital HSV infections including gingivostomatitis, encephalitis, retinitis and neonatal herpes?

CMV and HSV

Learning points

- Common, clinically relevant, ubiquitous viruses
- Transmission is by person-to-person spread
- Cause self-limited limited acute infection that results in establishment of a persistent life-long infection
- Persistent infection can reactivate to cause recurrent infection
- Myriad different clinical illnesses
- Safe antiviral drugs are effective at controlling the acute infection but ineffective in eliminating the persistent infection
- Current prevention strategies have limited effectiveness
- Promising vaccines are in development