VIROLOGY

Herpes

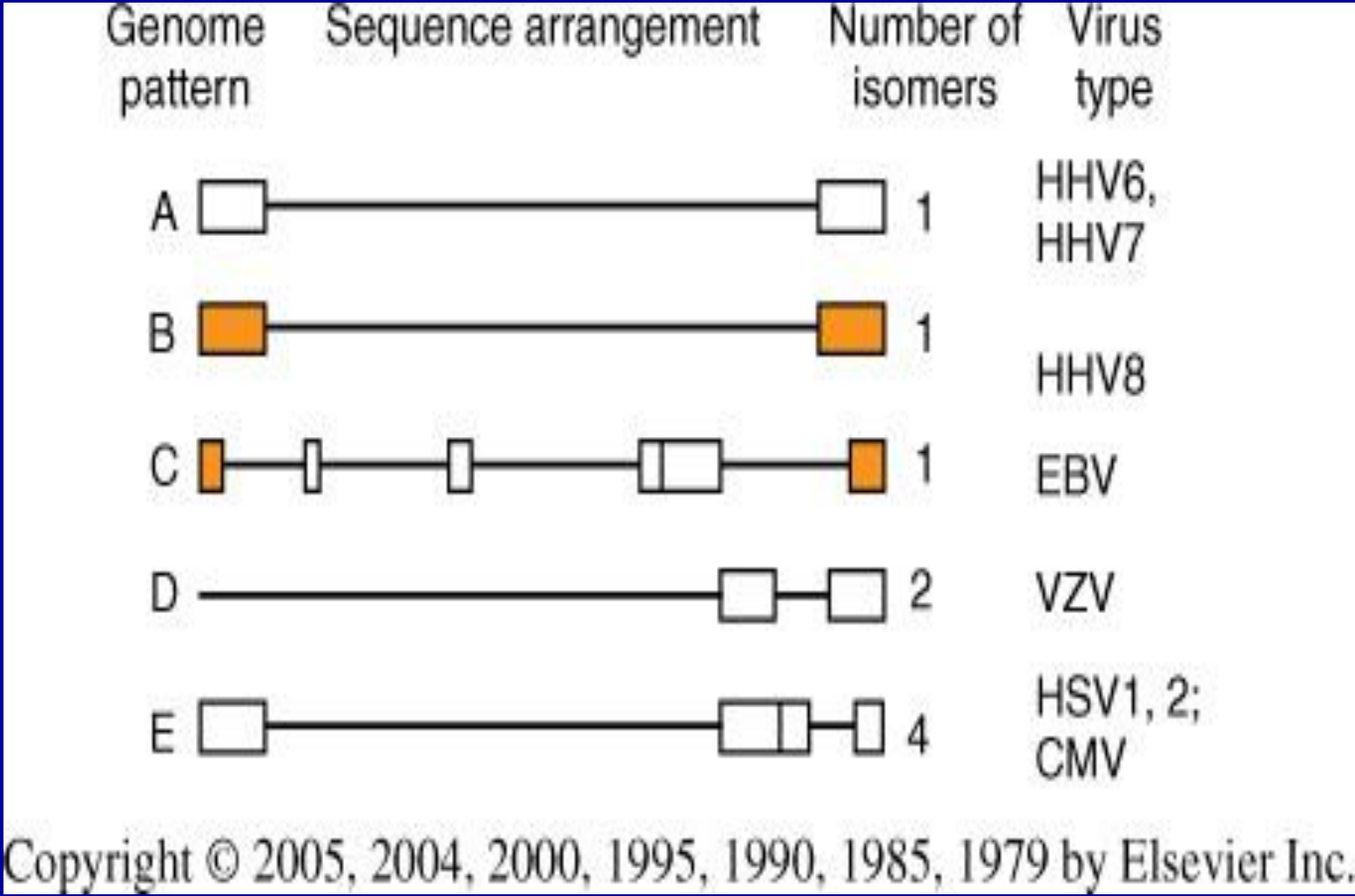
The gift that keeps giving

OVERVIEW OF HERPESVIRUSES

Family: *HERPESVIRIDAE*

- **SUBFAMILY:**
  - **Alphaherpesvirinae**
    - **Herpes simplex virus 1 (HSV-1)**
    - **Herpes simplex virus 2 (HSV-2)**
    - **Varicella zoster virus (HSV-3)**
  - **Betaherpesvirinae**
    - **Cytomegalovirus (CMV or HSV-5)**
    - **Human herpesvirus 6 (HSV-6)**
    - **Human herpesvirus 7 (HSV-7)**
  - **Gammaherpesvirinae**
    - **Epstein-Barr virus (HSV-4)**
    - **Kaposi's sarcoma herpesvirus (KSHV or HSV-8)**

GENOME ORGANIZATION



Organization of five genome types of human herpesviruses. The *large boxes* denote major repeat elements, between or adjacent to which are unique sequences. Some major repeats contain multiple copies of the same sequences, as indicated by *vertically divided boxes*.

Different strains infect different cells

- **Herpes simplex virus grows readily in epithelial cells and fibroblasts of humans, monkeys, rabbits, mice**
- **Varizella zoster virus (VZV) grows well in human epithelial cells and fibroblasts**
- **Viruses replicating in epithelial cells are associated with mucocutaneous infection**

- **Epstein-Barr virus (EBV) can be cultivated only in human B lymphocytes**
- **Human herpesvirus 7 grows only in CD4+ T lymphocytes**
- **Human herpes virus 8 (KSHV) remains to be replicated in laboratory – unknown**
- **Cytomegalovirus (CMV) grows well only in human fibroblasts**

LATENCY

- All herpesviruses induce lifelong latent infection in their host
- Mechanism of latency is incompletely understood and different viruses have different strategies
- Latency occurs only in small numbers of specific cell types

- **Latent herpes simplex, varicella zoster and EBV genomes don’t integrate into the cell’s genome; possibly all herpesviruses are like that**

- **Latency is not absolute silence - is characterized by expression of small set of viral genes**

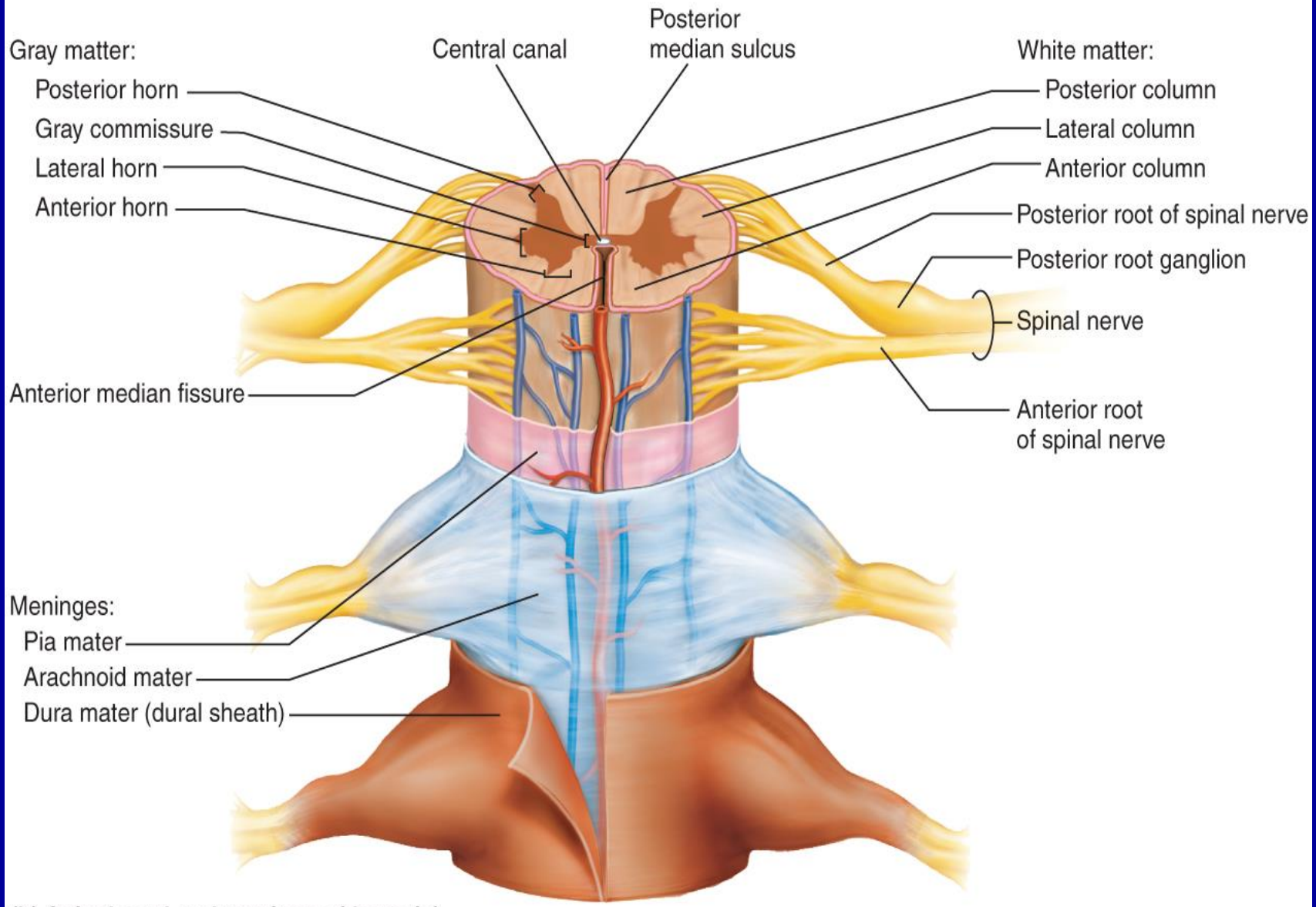
- **Some of them code functional proteins found in latently infected cells**

- **Some, like HSV, encodes transcripts (mRNA), which accumulate in latently infected neurons, possibly causing reactivation**

TABLE 131-2 Features of the Usual Productive, Latent, and Transforming Infections Caused by Herpesviruses in Humans

	Infection in Healthy Humans				
Virus	*Primary Infections*	*Recurrent Infections*	*Infection in the Compromised Host*	*Site of Latency*	*Association with Human*
Herpes simplex virus 1	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Genital herpes	Herpes labialis Keratoconjunctivitis Cutaneous herpes	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Visceral infections	Sensory neurons	None
Herpes simplex virus 2	Genital herpes Cutaneous herpes Gingivostomatitis Aseptic meningitis Neonatal herpes	Genital herpes Cutaneous herpes Aseptic meningitis	Genital herpes Cutaneous herpes Disseminated infection	Sensory neurons	None
Varicella-zoster virus	Varicella	Dermatomal zoster	Disseminated infection	Sensory neurons	None
Cytomegalovirus	Mononucleosis Hepatitis Congenital cytomegalic inclusion disease	?	Hepatitis Retinitis Other visceral infections	Monocytes? Neutrophils?	None
Epstein-Barr virus	Mononucleosis Hepatitis Encephalitis	?	Polyclonal and monoclonal lymphoproliferative syndromes Oral hairy leukoplakia	B lymphocytes	African-type Burkitt's lymphoma, CNS lymphoma, Hodgkin's disease, and other lymphomas Nasopharyngeal carcinoma Leiomyosarcoma
Human herpesvirus 6	Roseola infantum Fever and otitis media Encephalitis	?	Fever Pneumonitis Encephalitis Bone marrow suppression	CD4 lymphocytes?	Rare B cell lymphomas?
Human herpesvirus 7	Roseola infantum	?	?	CD4 lymphocytes?	None
Human herpesvirus 8	Mononucleosis? Febrile exanthem?	?	Fever Bone marrow aplasia?	?	Kaposi's sarcoma Multicentric Castleman's disease Primary effusion lymphoma
Simian herpes B virus	Mucocutaneous lesions Encephalitis	?	?	Sensory neurons in monkeys	None

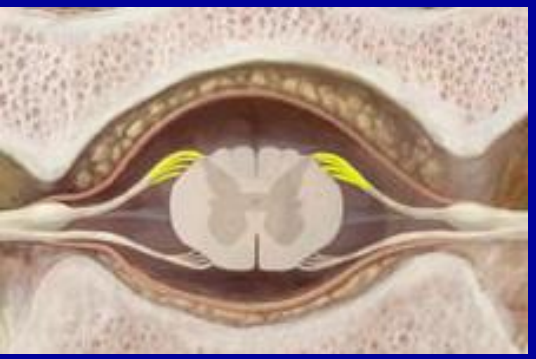
?, Inadequate data.



(b) Spinal cord and meninges (thoracic)

Spinal Nerve

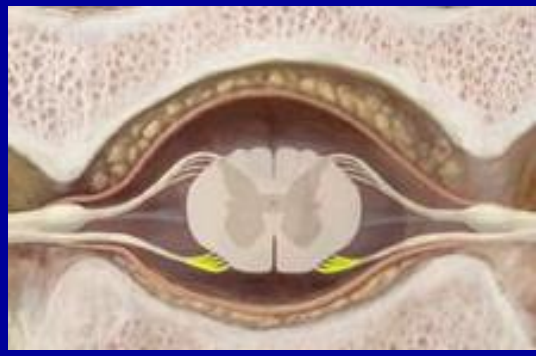
dorsal rootlets



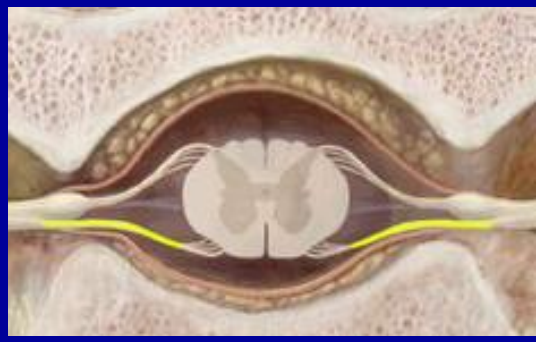
dorsal root

dorsal root gangion

ventral rootlets



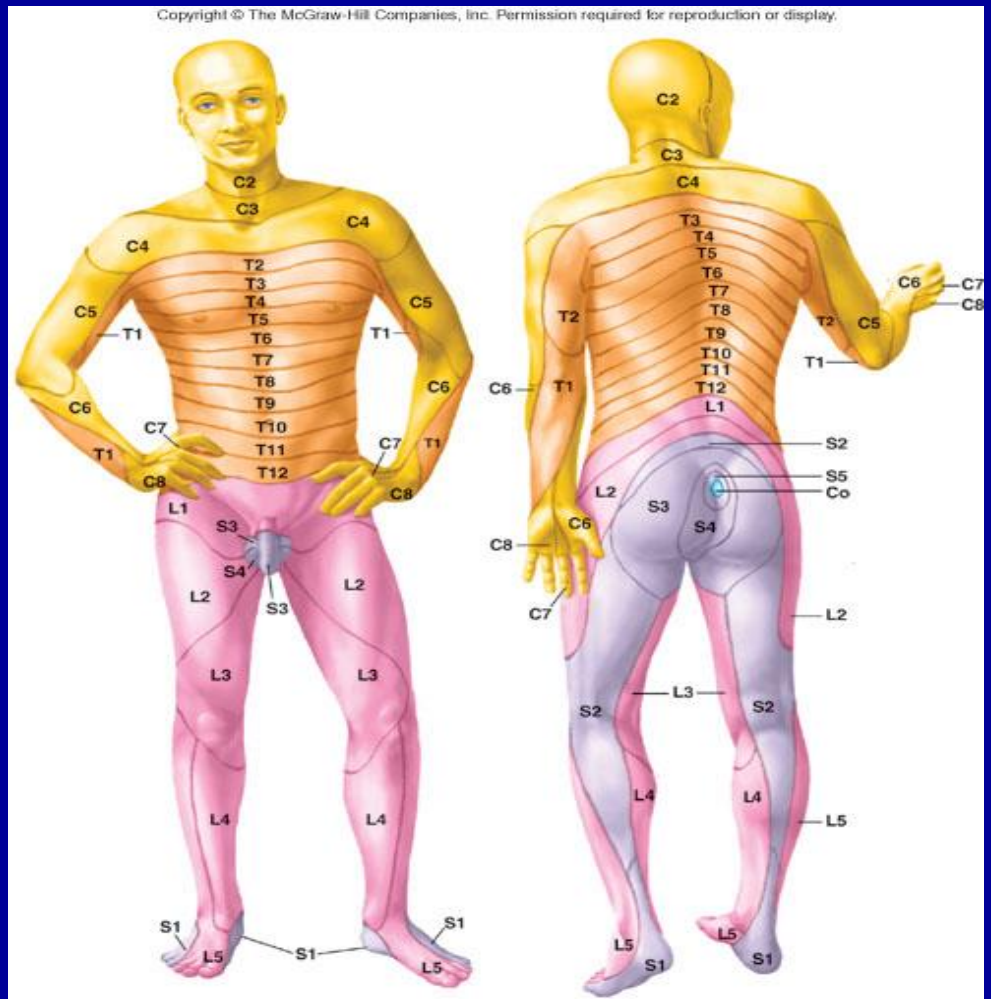
ventral root



spinal nerve

Dermatomal Map

- Spinal nerves indicated by capital letter and number
- **Dermatomal map**: skin area supplied with sensory innervation by spinal nerves



HERPES SIMPLEX VIRUS -1 (HSV-1)

HERPES SIMPLEX VIRUS-2 (HSV-2)

HERPES SIMPLEX VIRUS

- INTRODUCTION
- STRUCTURE
- VIRAL REPLICATION
- PATHOGENESIS
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS & TREATMENT

INTRODUCTION

- Have been documented since the ancient Greeks
- Hippocrates used the word “herpes” meaning to creep or crawl to describe the spreading nature of skin lesions
- Shakespeare wrote of recurrent HSV labial (associated with lips) lesions
- 18th century HSV was first time associated with genital infections by physician to King Louis XIV
- 19th century it was recognized that HSV transmits through person-to-person

- **20th century:**
  - **Human immune responses**
    - **Presence of neutralizing antibodies of newly and previously infected individuals**
    - **recurrent labial lesions**
    - **Reactivation of latent infection (ability to recur in the presence of humoral immunity)**
  - **Antigenic differences of HSV1 vs 2 discovered**
  - **Epidemiology**
    - **Humans are only reservoir for transmission to other humans**

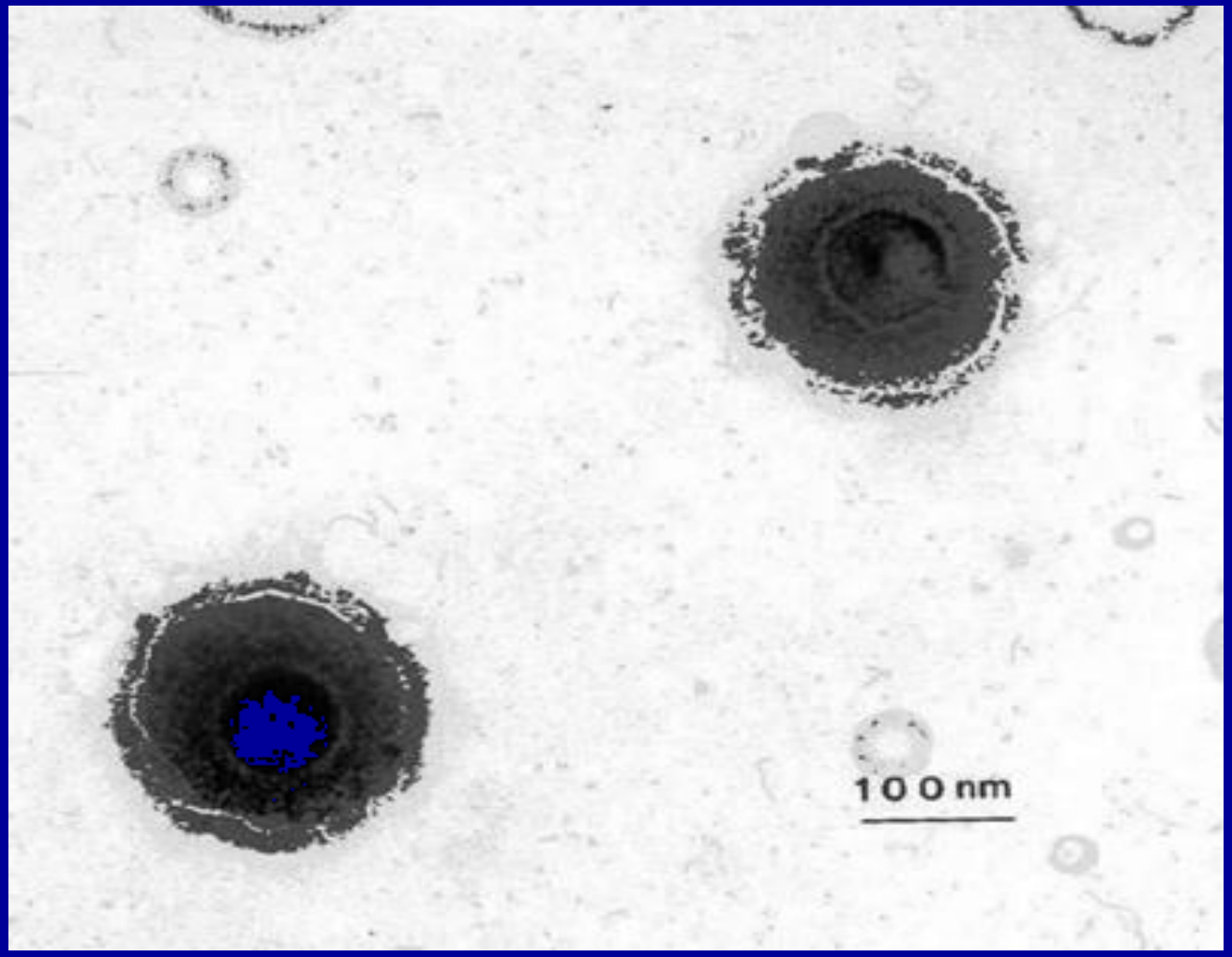
HERPES SIMPLEX VIRUS

- INTRODUCTION

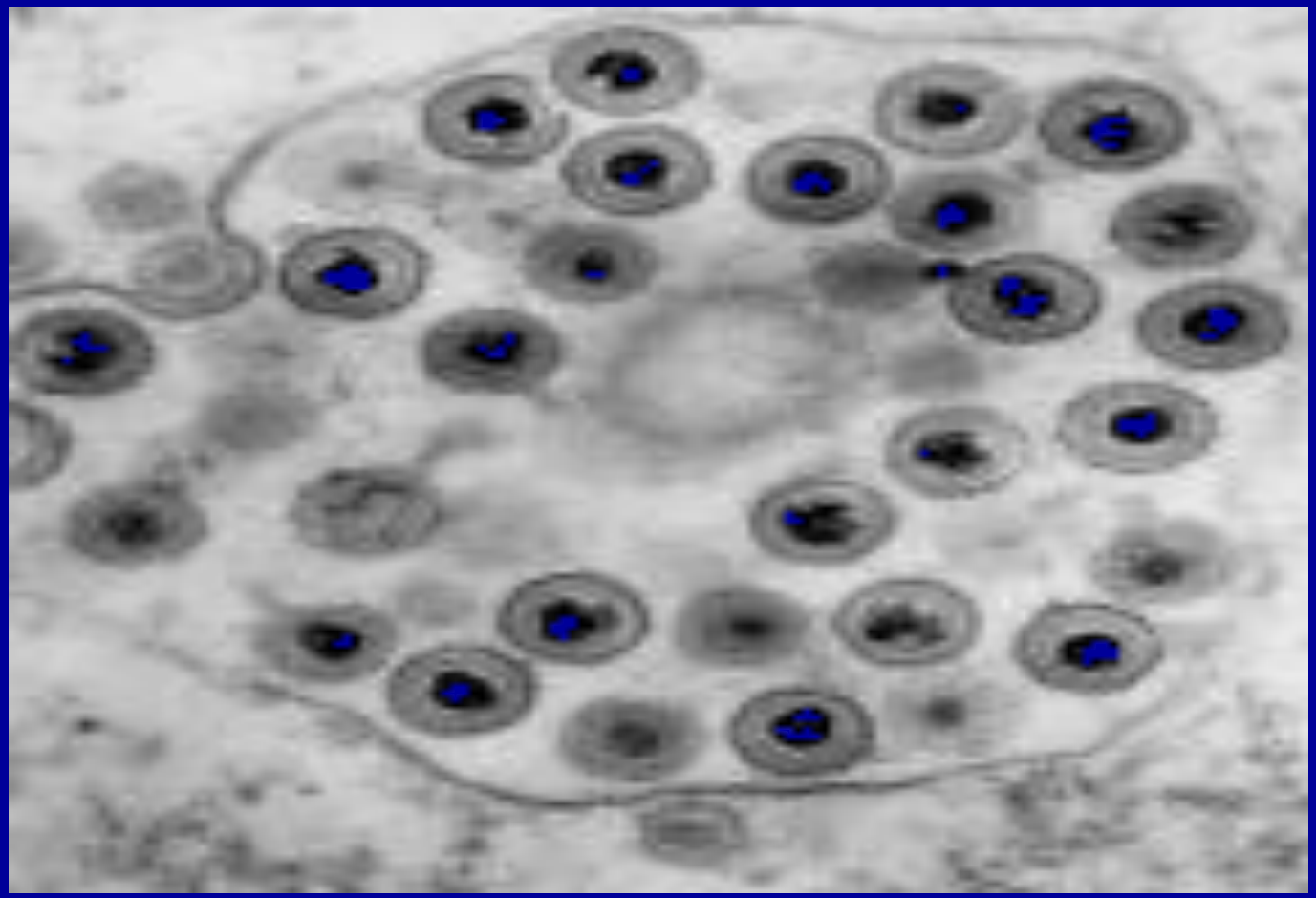
- STRUCTURE
  - VIRION
  - GENOME

- VIRAL REPLICATION
- PATHOGENESIS
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS & TREATMENT

Negative stain EM

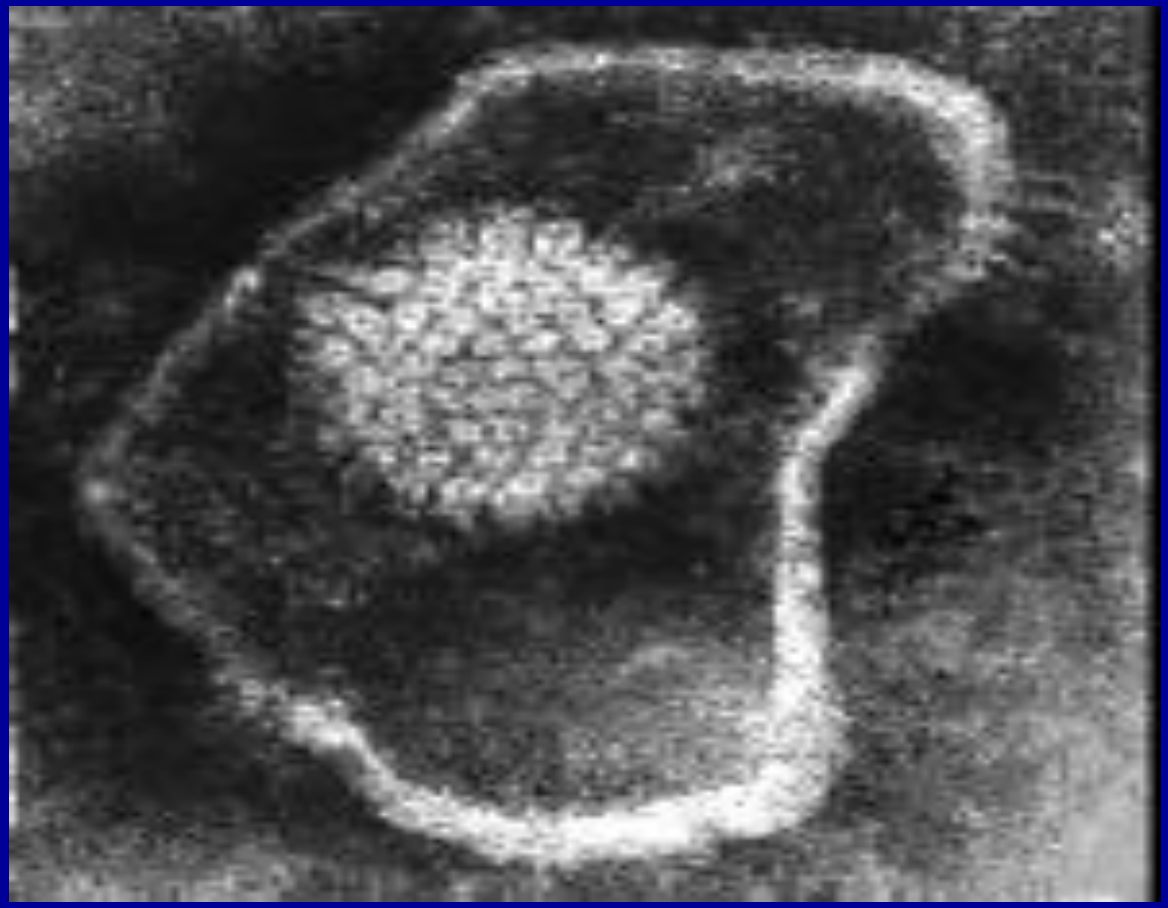


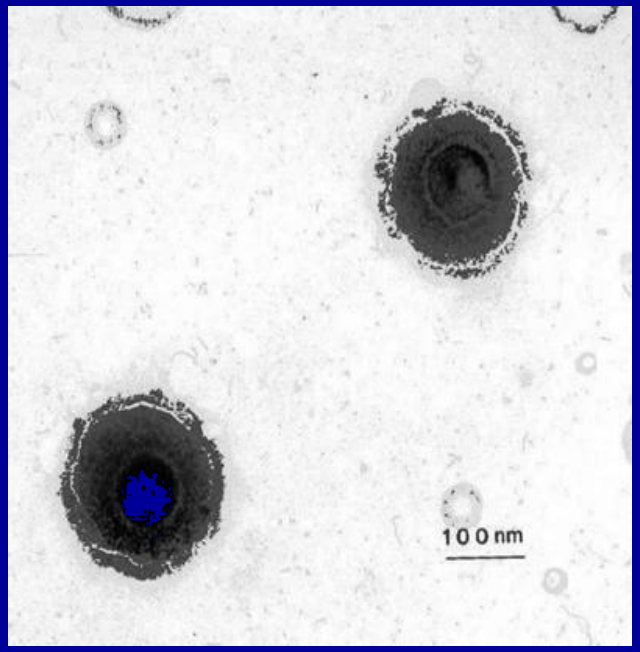
Thin section of virus particles as they leave the nucleus of an infected cell



Micrograph from F. A. Murphy, School of Veterinary Medicine, University of California, Davis.

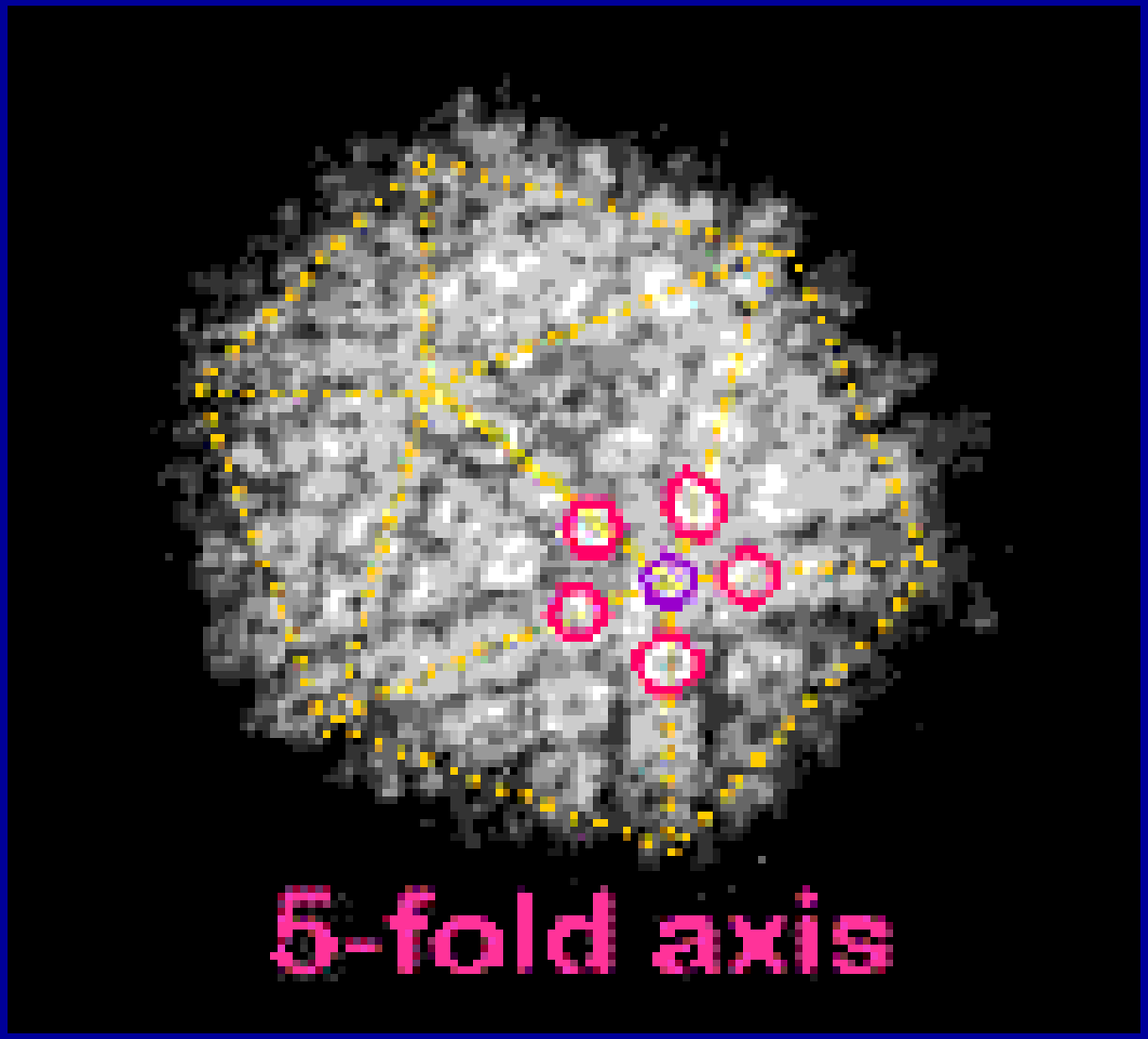
Negative stained EM

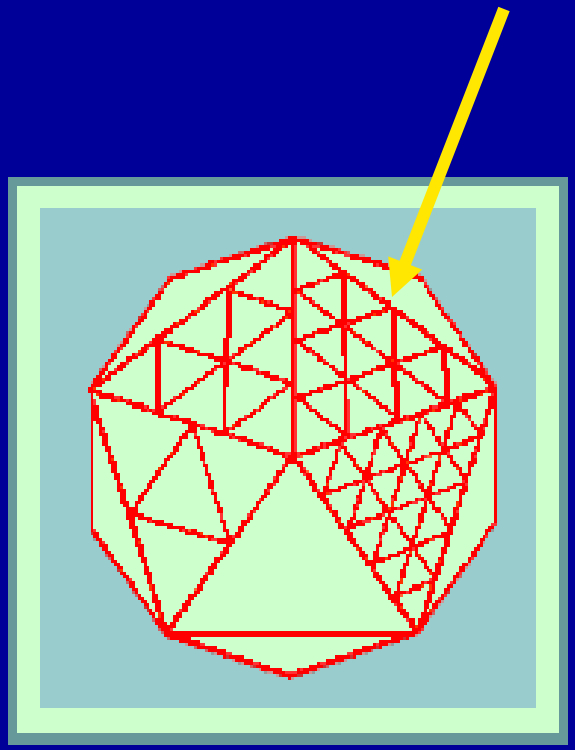




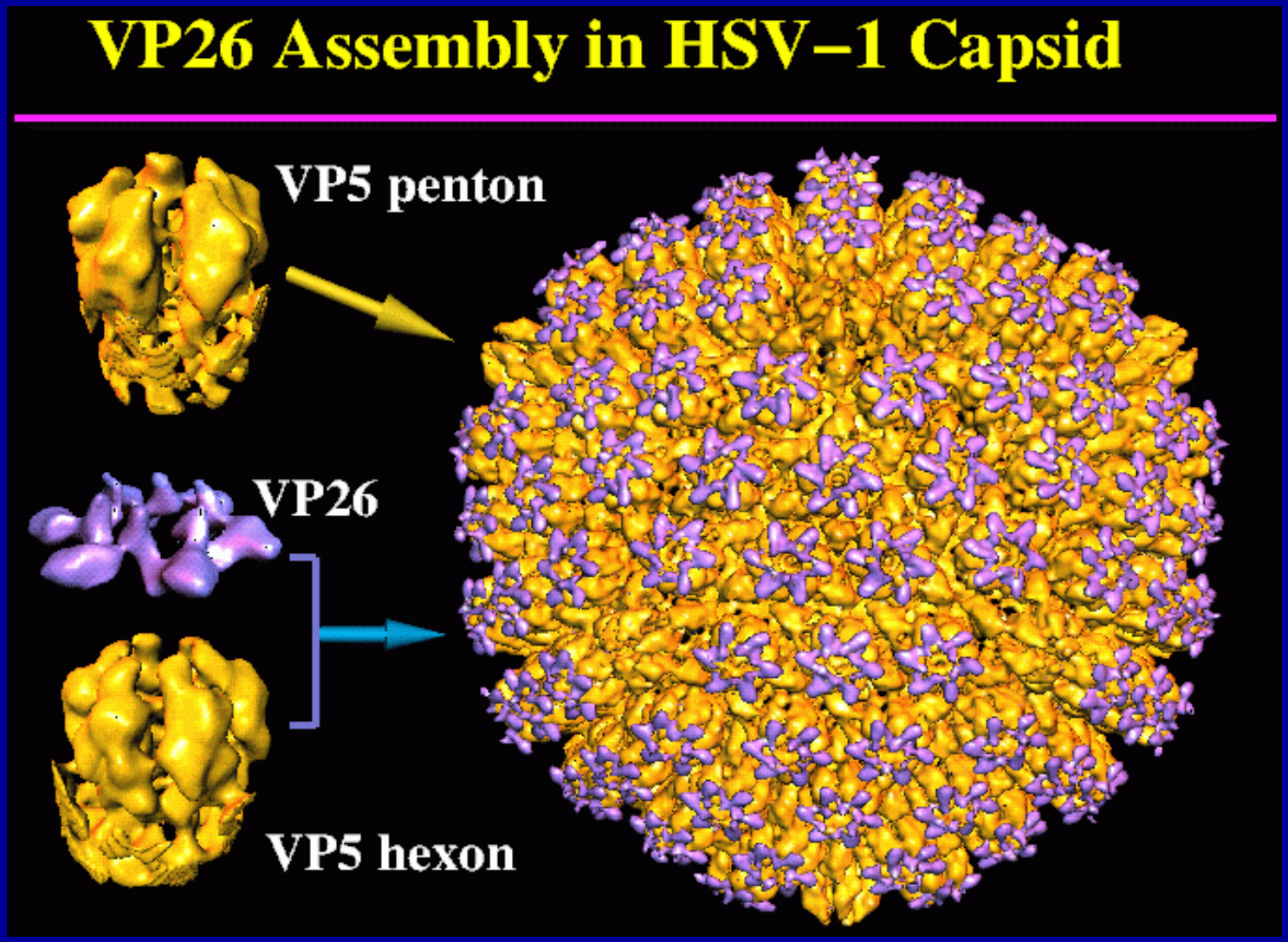
Linda Stannard, of the Department of Medical Microbiology, University of Cape Town

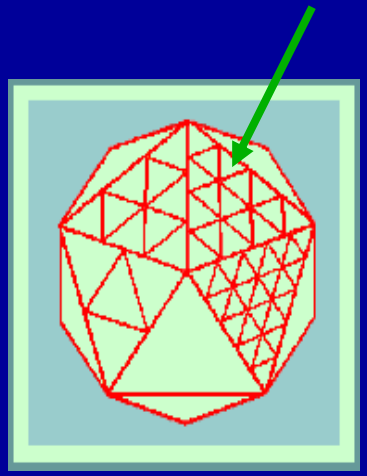
- The herpes virus CAPSID is an icosahedron of triangulation number T = 16
- There are 12 pentavalent capsomers (one at each apex)
- 150 hexavalent capsomers. Each capsomer has a deep central indentation

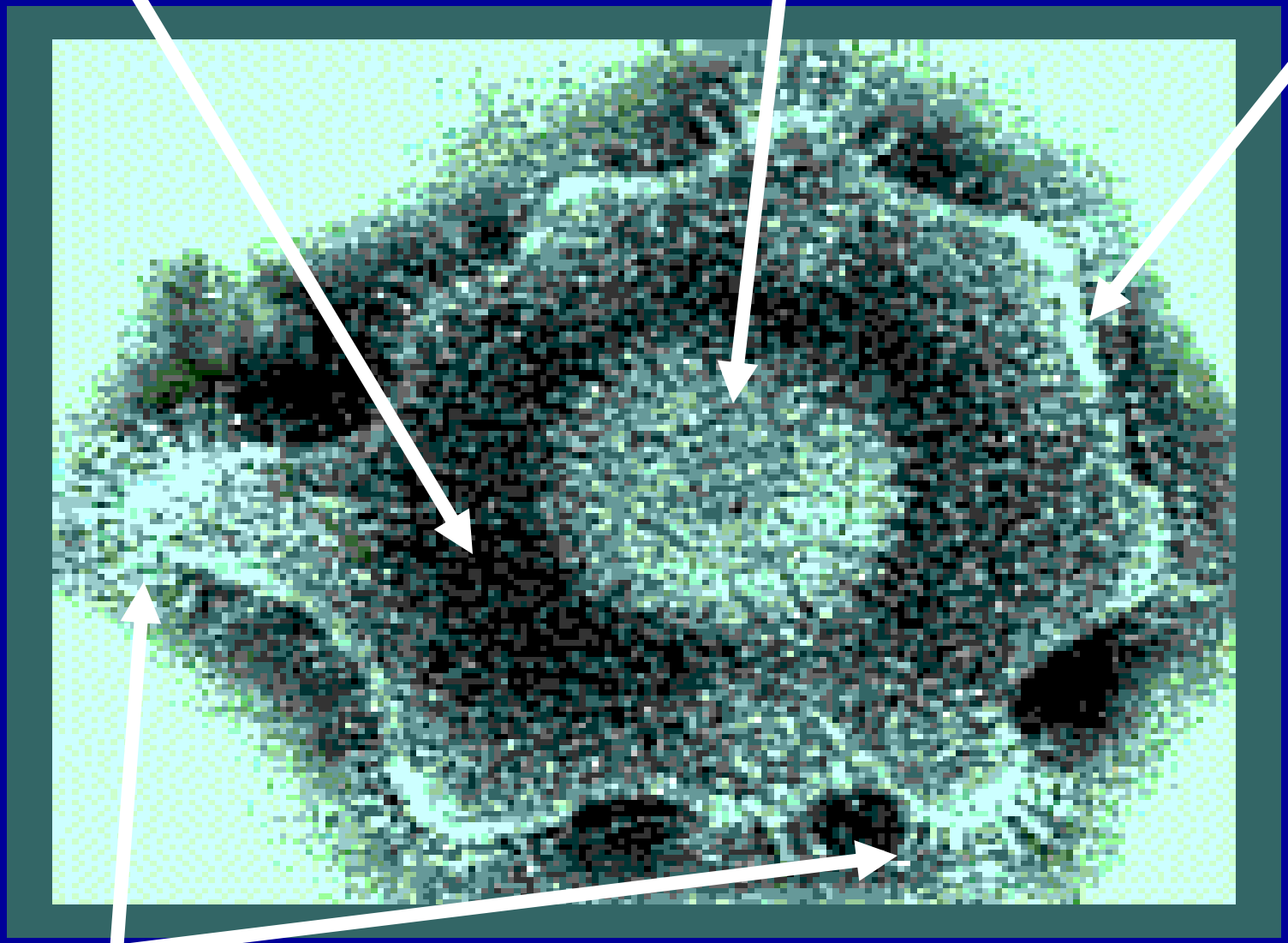




VP26 Assembly in HSV–1 Capsid







Linda Stannard, of the Department of Medical Microbiology, University of Cape Town

STRUCTURE

- HSV-1 virions contains at least 30 distinct proteins (another 10 are suspected)

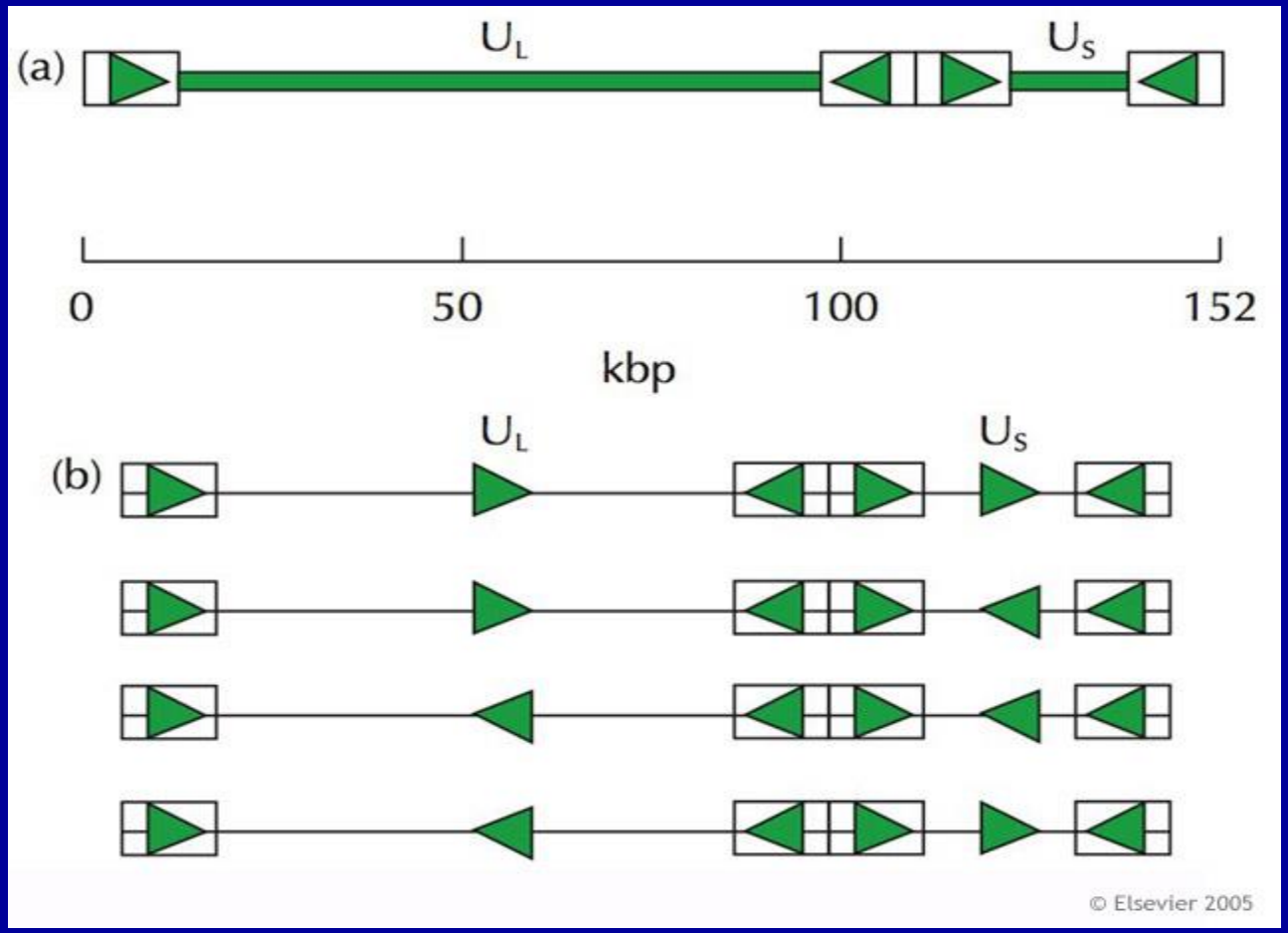
- ENVELOPE:
  - At least 11 are on the surface of the virion = envelope
  - At least 10 are glycosylated - gB, gC, gD, gE, gG, gH, gI, gK, gL and gM

- TEGUMENT:
  - Amorphous layer (no strict structure)
  - Contain several virus encoded proteins
  - Set the stage for effective viral replication
  - E.g. VP16 enhances the transcription of α-genes
  - E.g. vhs causes non-specific degradation of mRNA (take-over of the cell)

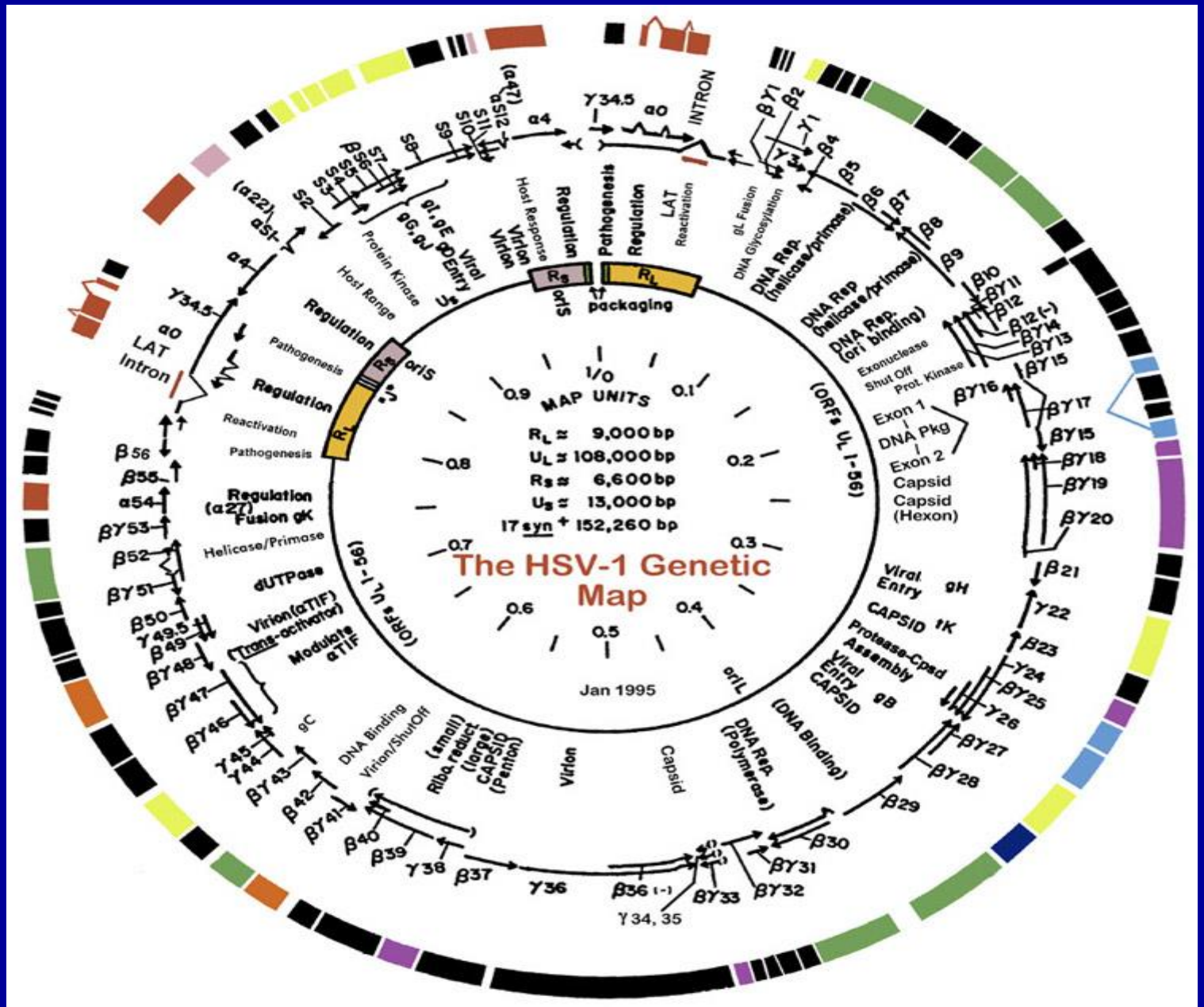
Genomic structure

- DNA is linear and double stranded
- Encodes at least 90 unique transcriptional units
  - of this at least 84 encode protein
- Since viral proteins studied to date have been shown to perform several functions, it is likely that HSV encodes several hundred functions

Genome organization



- Inverted repeats allow formation of four different isomeric forms of the genome
- Infected cells consist of equimolar amounts of each forms
- All are functionally equivalent
- involves recombination between terminal repeats and internal inverted repeats


The HSV-1 Genetic Map
Jan 1995
MAP UNITS
1/0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
R_L ≈ 9,000 bp
U_L ≈ 108,000 bp
R_S ≈ 6,600 bp
U_S ≈ 13,000 bp
17 syn + 152,260 bp
(ORFs U_L 1-56)
(ORFs U_L 1-56)
R_S
R_L
ori$S$
ori$L$
packaging
INTRON
α0
α4
γ34.5
LAT
Intron
LAT
Reactivation
Pathogenesis
Regulation
Host Response
Virion
Viral Entry
Protein Kinase
Host Range
DNA Rep.
(helicase/primase)
DNA Rep.
(ori binding)
Exonuclease
Shut Off
Prot. Kinase
Exon 1
DNA Pkg
Exon 2
Capsid
Capsid
(Hexon)
Viral Entry
CAPSID
Protease-Cpsd
Assembly
Viral Entry
CAPSID
DNA Rep.
(Polymerase)
(DNA Binding)
Capsid
Virion
(small)
Ribo. reduct.
(large)
CAPSID
(Penton)
DNA Binding
Virion/ShutOff
Helicase/Primase
dUTPase
Virion(αTIF)
(trans-activator)
Modulate
αTIF
Fusion gK
Regulation
(αZ?)
Reactivation
Pathogenesis
Regulation
Pathogenesis
Regulation
Host Response
Virion
Viral Entry
gL Fusion
DNA Glycosylation
gC
gH
gK
gB
γ34, 35

HERPES SIMPLEX VIRUS

- INTRODUCTION
- STRUCTURE

- VIRAL REPLICATION
  - Virus attachment and entry
  - Replication
  - Assembly and maturation

- PATHOGENESIS
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS & TREATMENT

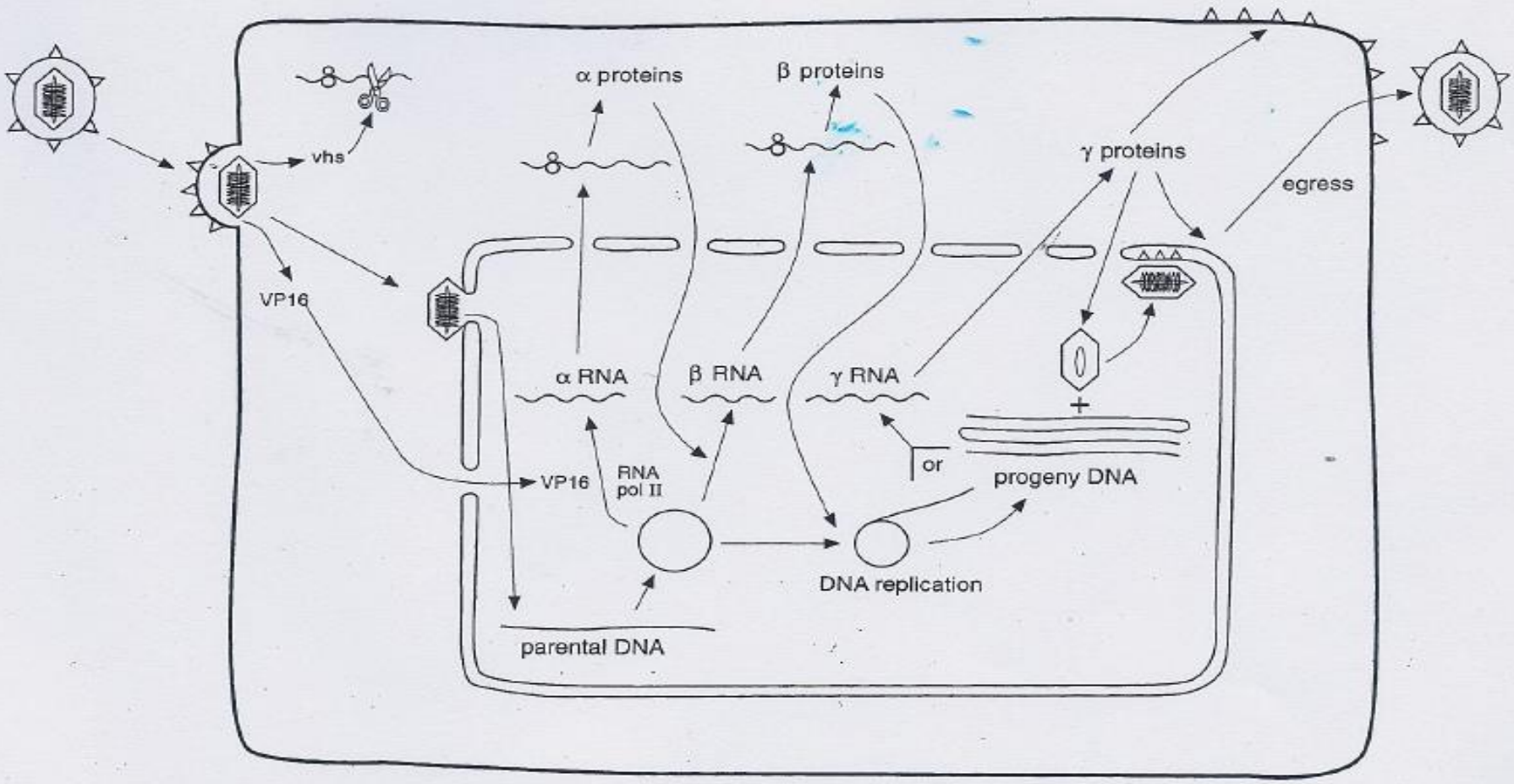
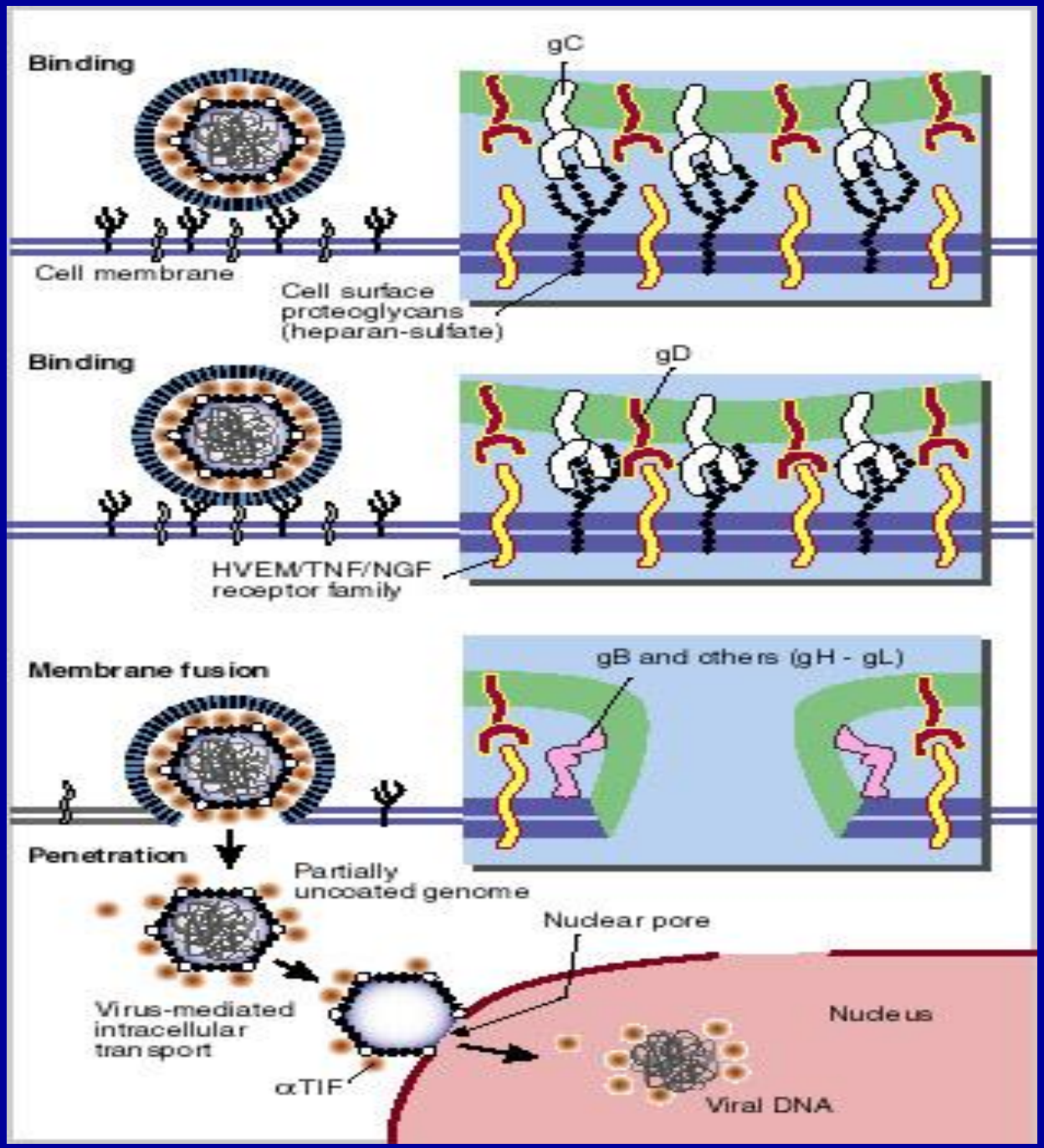


FIG. 3. Diagram of the replication cycle of HSV. At the *upper left,* the virion binds to the cell plasma membrane, and the virion envelope fuses with the plasma membrane, releasing the capsid and tegument proteins into the cytoplasm. The vhs protein acts to cause degradation of mRNAs. The capsid is transported to the nuclear pore, where the viral DNA is released into the nucleus. The viral DNA circularizes and is transcribed by host RNA polymerase II to give first the IE or α mRNAs. IE gene transcription is stimulated by the VP16 tegument protein. Five of the six IE proteins act to regulate viral gene expression in the nucleus. They transactivate E or β gene transcription. The E proteins are involved in replicating the viral DNA molecule. Viral DNA synthesis stimulates L or γ gene expression. The L proteins are involved in assembling the capsid in the nucleus and modifying the membranes for virion formation. The filled capsid buds through the inner membrane to form an enveloped virion, and the virion exits from the cell by mechanisms described in the section on Virion Assembly and Egress.

HSV proteins in entry

- To initiate the infection, HSV must attach to the cell surface receptors, fuse its envelope to the plasma membrane and allow the de-enveloped capsid to be transported to the nuclear pores
- Viral glygoproteins gB and gC are required for the initial interaction of the virion with heparin-sulfated proteoglycans
- gB, gD, gH and gL mediate the fusion of the envelope with the plasma membrane



gB &gC

gD

gB, gD, gH, gL

VP16 (= αTIF)

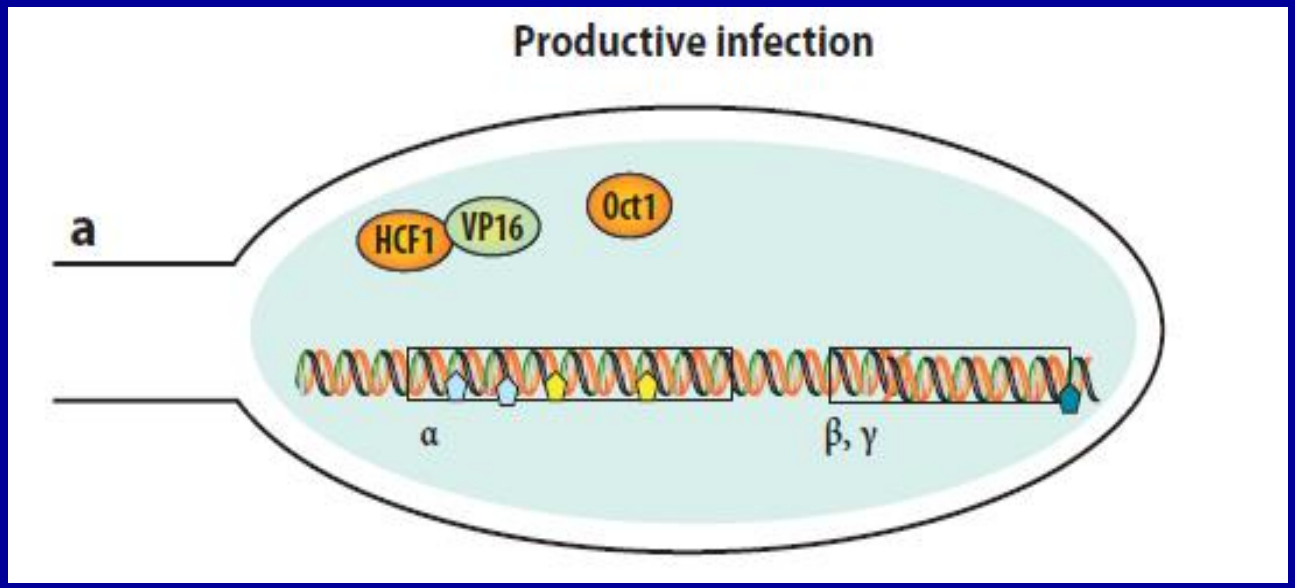
Cellular receptors

- Three cellular receptors for HSV
- Nectin-1 cell adhesion molecule (widespread)
  - Mediate entry in all HSV-1 strains
  - Fibroblasts, epithelial, neural and hematopoietic cells
  - Human tissues such as skin, brain and spinal ganglia
- Nectin-2α and 2δ
  - Primary receptor for HSV-2 (only genital)
  - Do not mediate entry of the wild-type HSV-1
- Heparin-sulfated proteoglygan
  - Are broadly distributed in human cells

Activation of β gene expression

- Most β proteins assist viral nucleic acid metabolism e.g.
  - Synthesis of viral DNA
    - Viral DNA polymerase
  - Increase the pool of deoxyribonucleotides
  - Repair viral DNA
  - Viral protein kinases
    - Modify function of viral proteins after translation

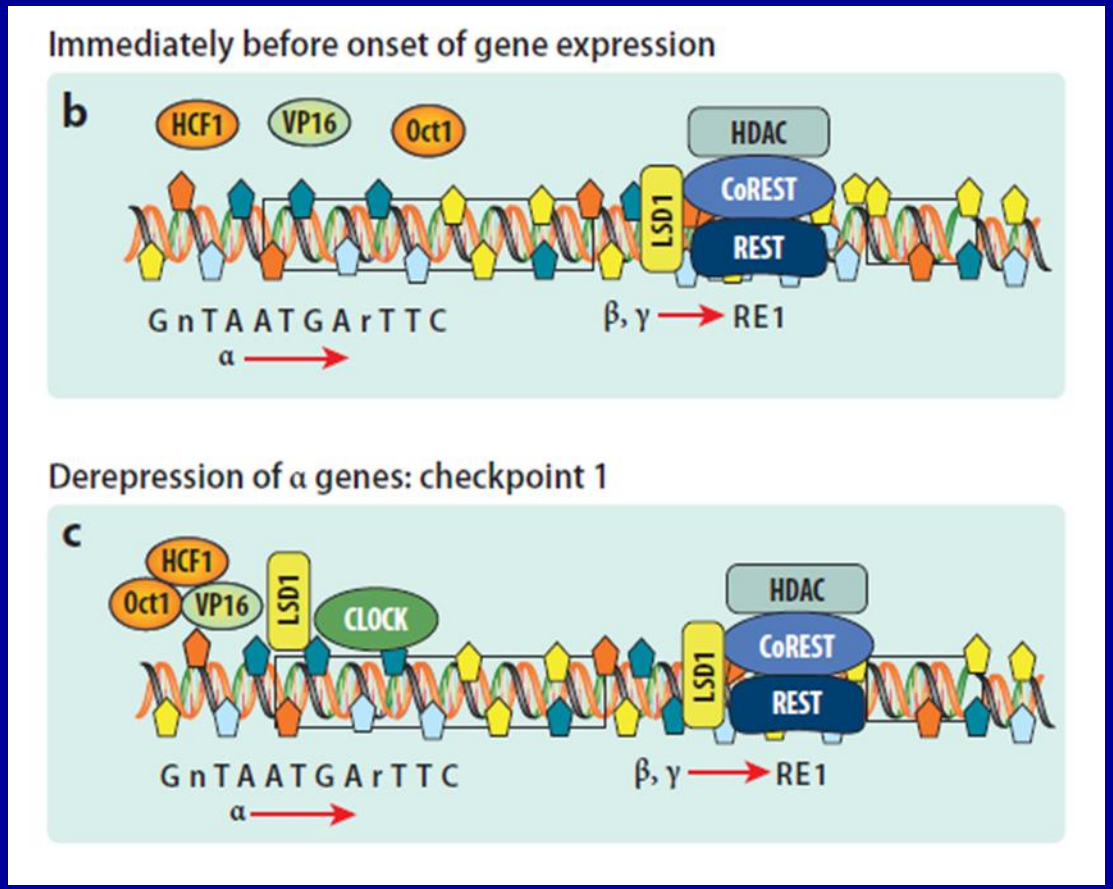
- β proteins are the main target for antiviral chemotherapy like acyclovir



Moment of entry of viral DNA into the nucleus:

- **Viral DNA is coated by repressive histones and other repressors into a structure called a facultative heterochromatin.**

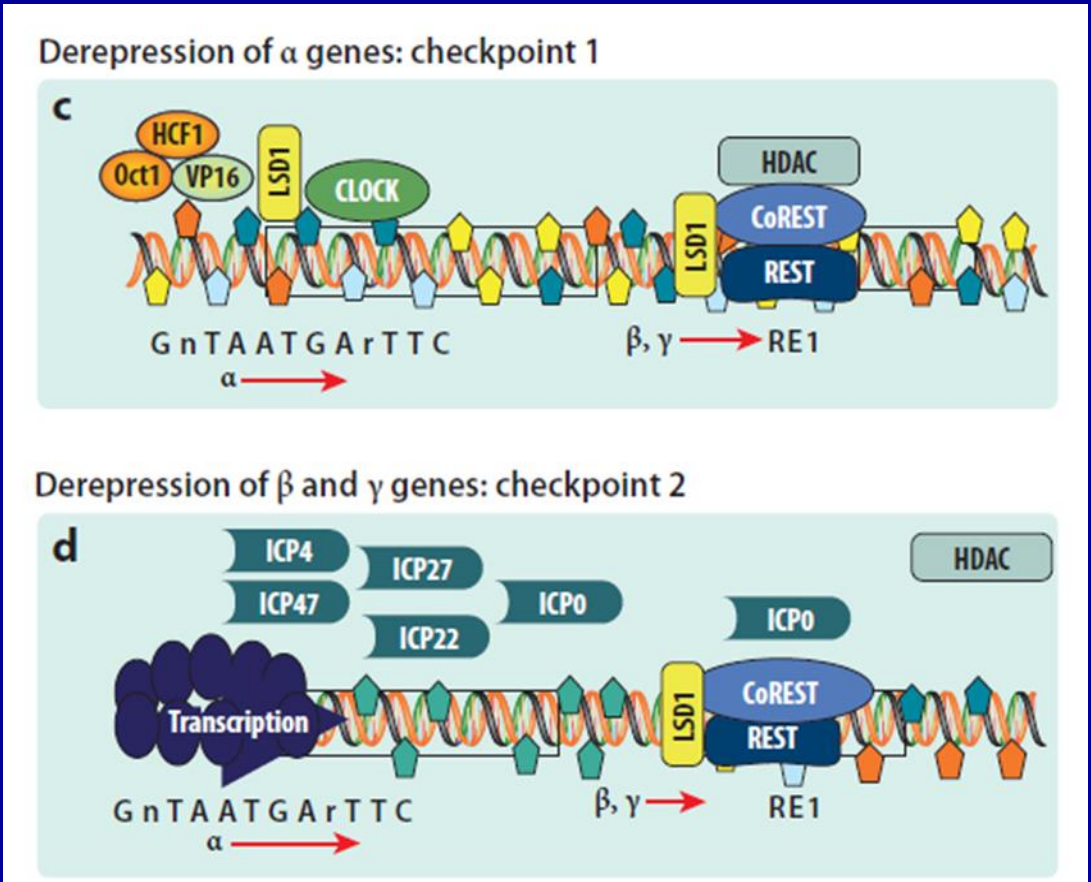
- **The objective is to silence the DNA. Herpes is frozen.**



-HCF1: host cell factor 1
-LSD1: lysine specific demethylase 1
-ICP0: infected cell protein 0
-HDAC1: histone deacetylase 1
-HDAC2: histone deacetylase 2
-CoREST: Co-RE1 silencing transcription factor
-REST: RE1 silencing transcription factor
-HCLR: repressor complex containing HDAC 1 or 2, CoREST, LSD1, and REST
-VHS: virion host Shutoff
-CLOCK histone acetyl transferase

To get around this, virion protein 16 (VP16), a tegument protein introduced into cells during infection, recruits several host proteins to the promoters of α genes, enabling transcription.

It breaks the ice for alpha transcription.



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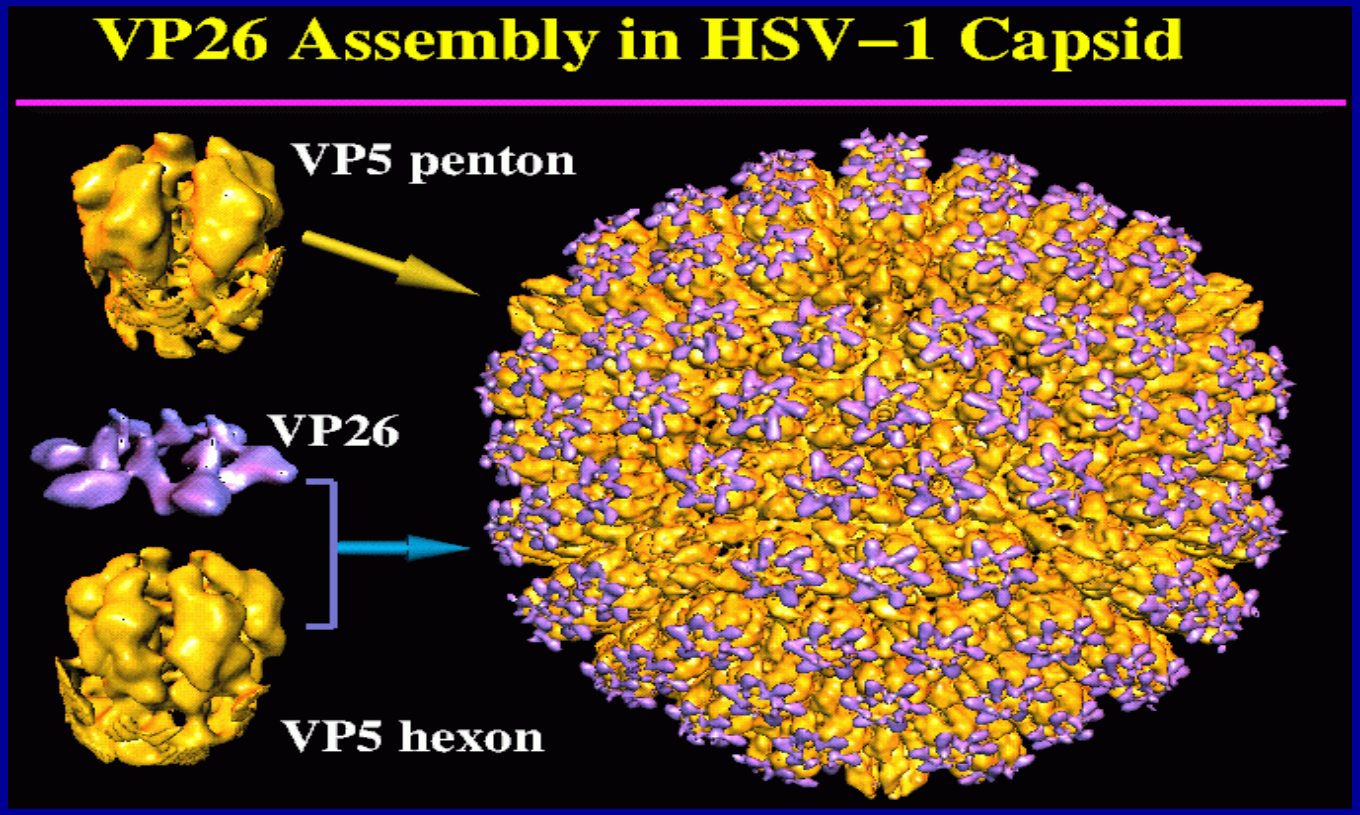
-REST: RE1 silencing transcription factor
-HCLR: repressor complex containing HDAC 1 or 2, CoREST, LSD1, and REST
-VHS: virion host Shutoff
-CLOCK histone acetyl transferase

The second checkpoint is repressed the HDAC2, CoREST, repressor complex.

Alpha 0 binds to CoREST (Co-RE1 silencing transcription factor) and dislodges the (HDACs), and in the course of this process β and γ1 genes are derepressed.

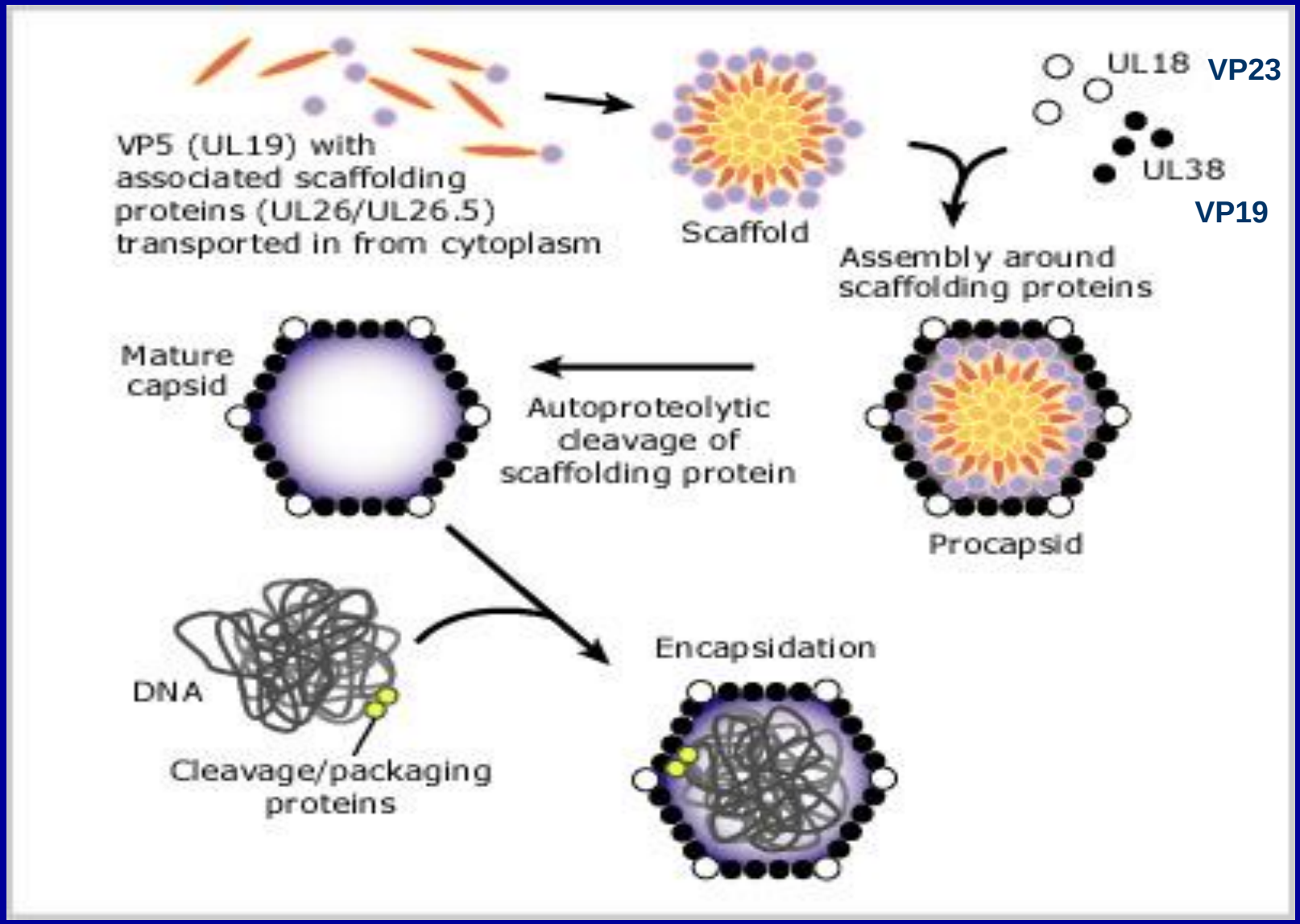
(The proteins made by alpha transcription break the ice for beta and gamma transcription.)



-CAPSID:

- Four major proteins + several others
- VP5, VP19, VP23 and VP26
- VP19 anchors viral DNA into the capsid
- VP23 links hexon capsomers

CAPSID PRODUCTION BY LATE PROTEINS



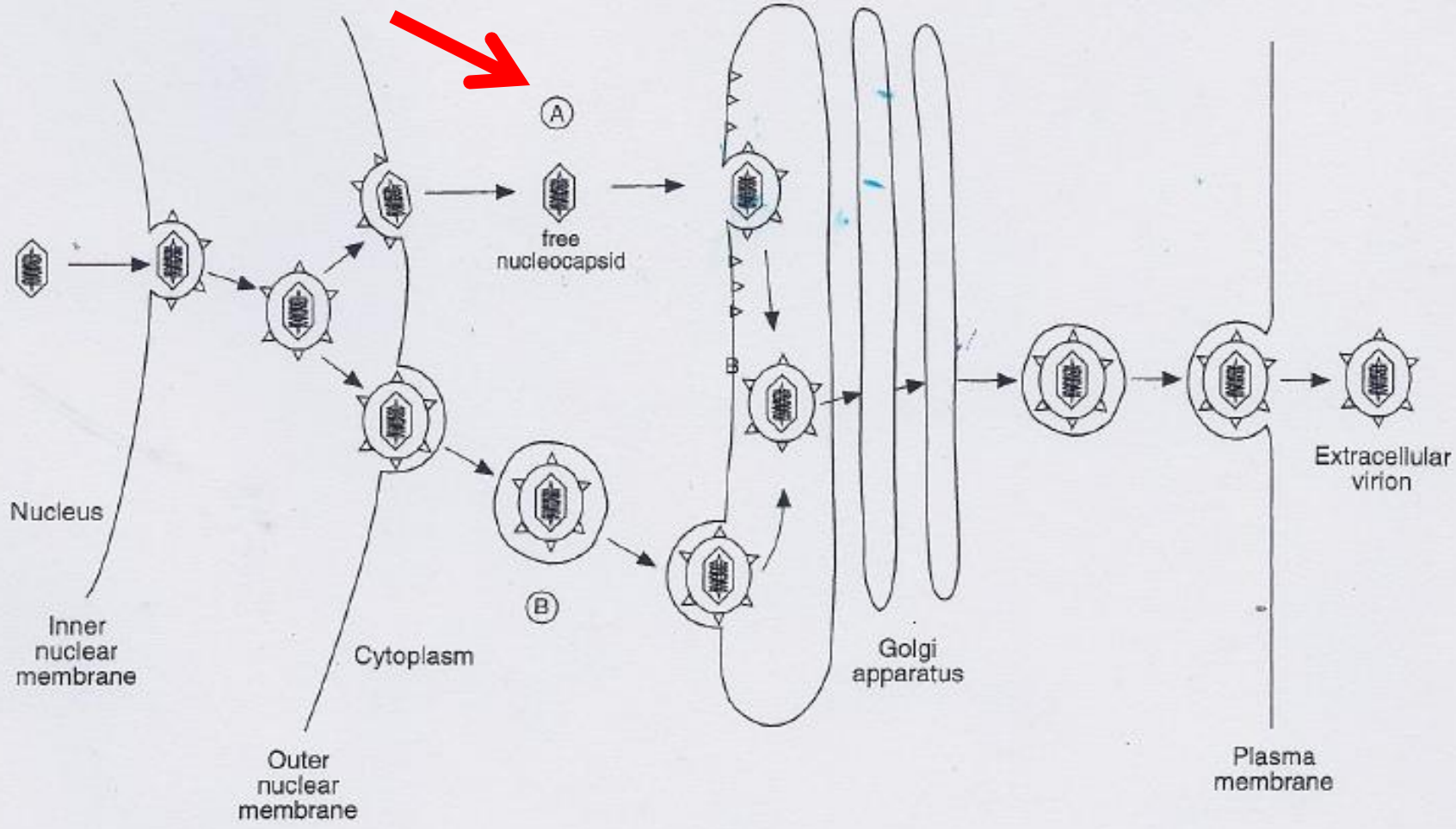


FIG. 10. Diagram of pathways of egress. HSV capsids bud through the inner nuclear membrane, forming an enveloped virion particle. Egress of the virions from the host cell may occur by either of two general pathways. **A:** The envelope fuses with the outer nuclear membrane, de-enveloping the capsid and releasing it into the cytoplasm. The capsid then buds into the Golgi apparatus, forming an enveloped virion, which is transported to the surface by vesicular transport. **B:** The virion particle buds through the outer nuclear membrane and is transported by vesicular movement through the Golgi apparatus to the exterior of the cell.

Cellular effects of replication

- Viral replication takes approximately 18 hours
- In the process, cell become irreversibly damaged
  - cellular chromosomes are degraded
  - Nucleolus falls apart
  - Golgi is fragmented and dispersed
  - Microtubules (cytoskeleton) are rearranged
  - Cells die. It is a mystery why the area does not become numb (redundancy? New cell generation?)
- All of these events are
  - To prevent host response to infection
  - To enhance the capacity of the infected cell to export virions

HSV encodes range of proteins to block host responses to infection

- Tegument protein vhs causes degradation of mRNA and shut-off of molecular synthesis at the early stages of infection – cell stops making its own proteins

- At the same time VP16 enhances the transcription of α genes. Within few hours only viral proteins are synthesized in the infected cell

- RNA splicing is blocked by α27 protein
  - Only few viral genes are spliced
  - Mostly affects cellular RNA processing

- α47 Blocks MHC class I presentation by binding to TAP molecules which jams the mechanism

- HSV blocks early apoptosis of infected cells

- The presence of dsRNA in the nucleus triggers a cellular defense to shut down ALL protein synthesis.
  - Double stranded RNA formation leads to activation of cellular kinase which shuts down eIF-2α (translation initiation factor) causing the total shut-off of protein synthesis
  - ICP34.5 binds to protein phosphatase 1α and redirects it to de-phosphorylate eIF-2α, (turning it back on) thus, disarming this host response to infection

HERPES SIMPLEX VIRUS

- INTRODUCTION
- STRUCTURE
- VIRAL REPLICATION

- PATHOGENESIS
  - Neurovirulence and latency

- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS & TREATMENT

Pathology and pathogenesis

- Infection causes virus-mediated cellular death and associated inflammatory responses (many inflammatory cells)

- Infection induces
  - Ballooning of the cells with nuclear degeneration
  - Cell lose intact plasma membranes and form multinucleated giant cells

- With cell lysis, clear vesicular fluid appears between the epidermis and dermal layer containing large quantities of infectious virus

- scarring is uncommon

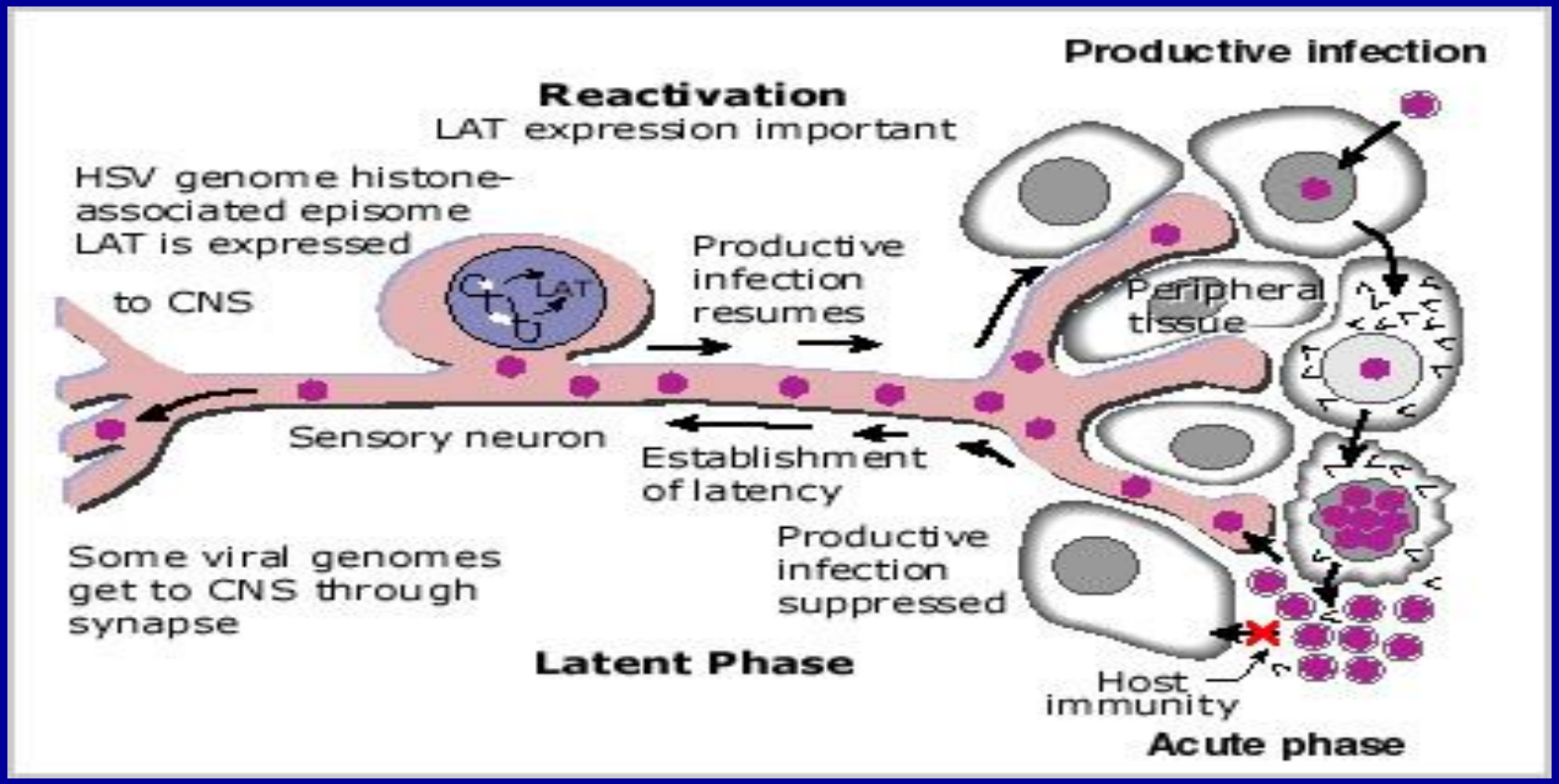
- **Transmission is by intimate contact**
- **Incubation period between 4-7 days**
- **The virus must come in contact with mucosal surfaces or abraded skin for infection to be initiated**
- **The more severe primary infection (size, number of lesions) the more likely recurrences will appear**
- **Most infections result in latency although replication sometimes leads to disease, even life-threatening infection e.g. encephalitis**
- **After latency is established, a stimulus (e.g. stress, fever, a date) causes reactivation**

Neurovirulence and latency

- Has capacity to invade and replicate in CNS and establish latent (not lytic) infection in dorsal root ganglia = neuroinvasiveness

- Neurovirulence appear to be the function of numerous genes
  - E.g. neuronal cells do not produce proteins for DNA replication (because they don’t divide)
  - HSV produces its own DNA polymerase, Thymidine kinase (primary target of acyclovir)

NEUROINVASIVENESS



-Virus enters nerve endings and is transported to the nucleus of sensory nerves innervating mucosal epithelium.

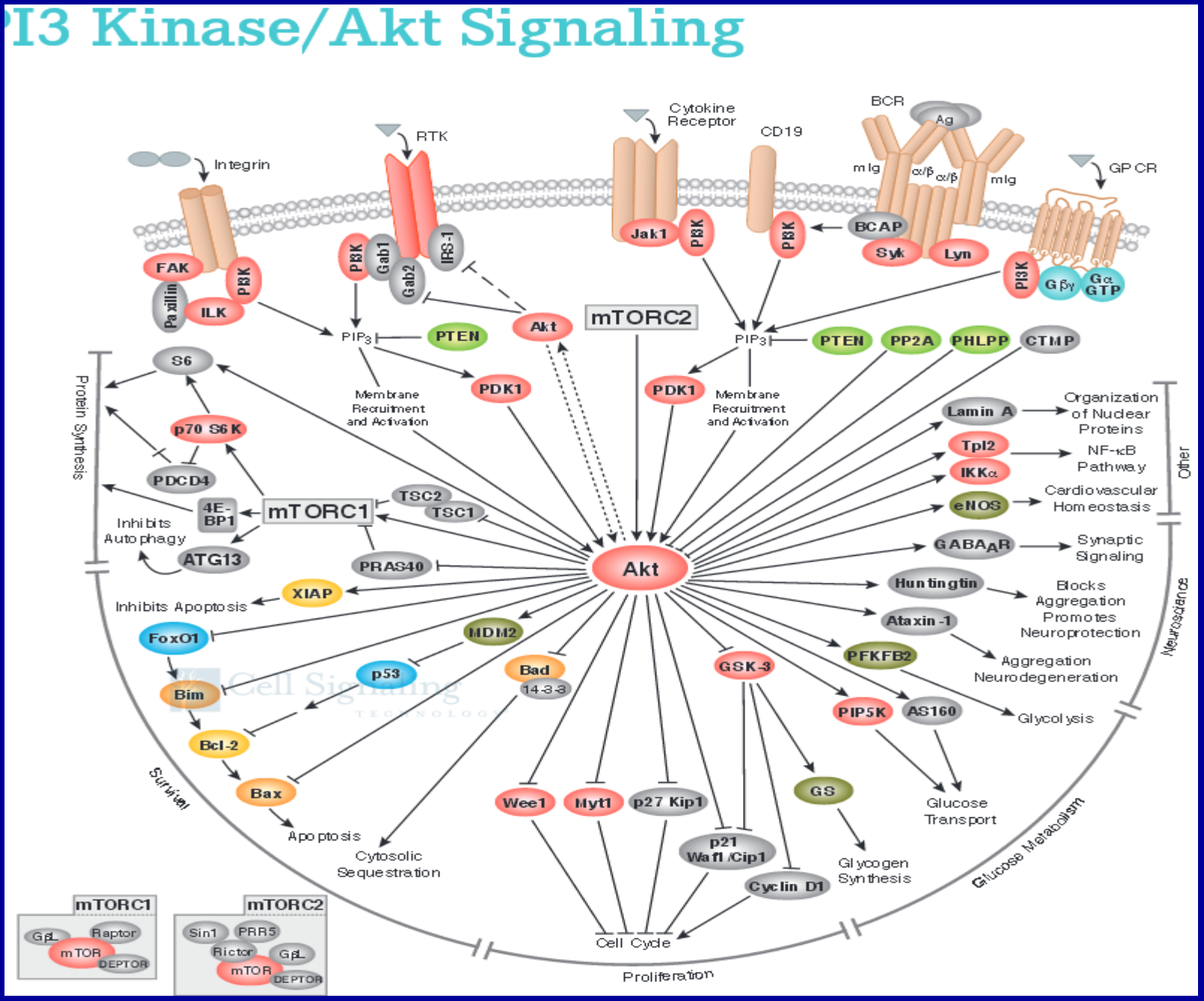
-In latently infected neurons genome persists as circular DNA and is periodically reactivated

- Infectious virus is carried to peripheral tissue by axonal transport, usually to cells at or near the site of initial infection

Latency Associated Transcripts

- LATs are viral mRNA's which regulate herpes during latent infection.
- They keep the viral genome suppressed so it doesn't reproduce a lot and cause lysis (kill the cell).
- They also prevent apoptosis so infected cell stays around.
- Accumulation of LAT's partially reactivates parts of the genome so viral shedding occurs in 10 to 20% of asymptomatic days.
- Stressors reactivate the whole genome, causing an active lesion with a lot of viral shedding.

PI3 Kinase/Akt Signaling



Courtesy of Cell Signaling Technologies

- **Although neurons are destroyed during virus reactivation, why aren't innervated sites anesthetized following virus reactivation?**

- **This frequently asked question has no compelling response.**

- **As noted elsewhere, it is conceivable that nerve fibers from adjacent neurons extend into the area vacated when the neuron innervating that site is destroyed.**

- **We also cannot exclude the possibility that destroyed neurons are replaced by neuronal stem cells.**

HERPES SIMPLEX VIRUS

- INTRODUCTION
- STRUCTURE
- VIRAL REPLICATION
- PATHOGENESIS
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS & TREATMENT

EPIDEMIOLOGY

- These viruses are distributed worldwide
- Humans remain sole reservoir for transmission to other humans
- No seasonal variation in incidence of infection
- Over 1/3 of world population have recurrent HSV infections and thus can transmit virus
- Overall seroprevalence increases with age and is affected by socioeconomic status
  - Middle-class by the age of 30 yrs ~40-60%
  - Lower sosioeconomic by early adolescence 70-80%
- Seroconversion of university students occurs at an annual frequency of ~5-10%

HSV 1

- **In the period from 2005 through 2010 in the United States, the seroprevalence of HSV-1 was 53.9% among persons 14 to 49 years of age**

- **High prevalence of antibodies to HSV-1 exist worldwide and there is a high rate of geographic variation**
  - **worldwide 67% infected**
  - **Some population have ~95%**

Genital HSV infections (HSV-2)

- **Usually acquired by sexual contact, thus antibodies to this virus is rarely detected before the age of onset of sexual activity**
- **Most genital HSV infections are caused by HSV-2 but increasing amonts of infections are caused by HSV-1**
- **Distinction is significant:**
  - **HSV-1 infections usually less severe and less prone to recur**
- **Number of new cases annually ~ 500 000 in USA**
- **<u>40 to 60 MILLION Americans are infected with HSV-2.</u>**

- **In the period from 2005 through 2010 in the United States the seroprevalence of HSV-2 was 15.7% among persons 14 to 49 years of age.**

- **The seroprevalence of HSV-2 had decreased from a rate of 21.2% recorded in the period from 1988 through 1994. However, genital infection by HSV-1 is on the rise.**

- **Preexisting HSV-1 antibodies provide only partial protection against acquisition of HSV-2.**

- **An oral HSV1 infection generates antibodies making a genital HSV1 infection unlikely.**

- **Decreasing oral HSV 1 infections (good news) make genital HSV 1 infections more likely (bad news for oral sex).**

- **Factors which influence HSV 2 infections:**
  - **Gender: women grater than men**
  - **Race: African-Americans more than Caucasians**
  - **Marital status: divorced more than single or married**
  - **Place of residence: city more than suburb**
  - **Genital Herpes is an important risk factor in HIV contagion.**

- **Studies also indicate that the highest seroprevalence of HSV-2 in USA is among female prostitutes = 75% and is virtually identical to that in prostitutes in Tokyo. Highest detected in Dakar, Senegal were 95.7% of prostitutes were HSV-2 positive**

- **The number of different sexual partners correlates directly with the acquisition of HSV-2**
  - **11 to 50 sexual partners during lifetime**
    - **Women: Probability becoming infected is 62%**
    - **Heterosexual men: 35%**
    - **Homosexual men: ~60%**

- **Estimated risk of susceptible females for contracting HSV from infected males is 80% following single contact**

- **As with HSV-1 in mouth, HSV-2 can be excreted in the absence of symptoms providing reservoir for transmission of infection - HSV is a chronic infection rather than intermittent one.**

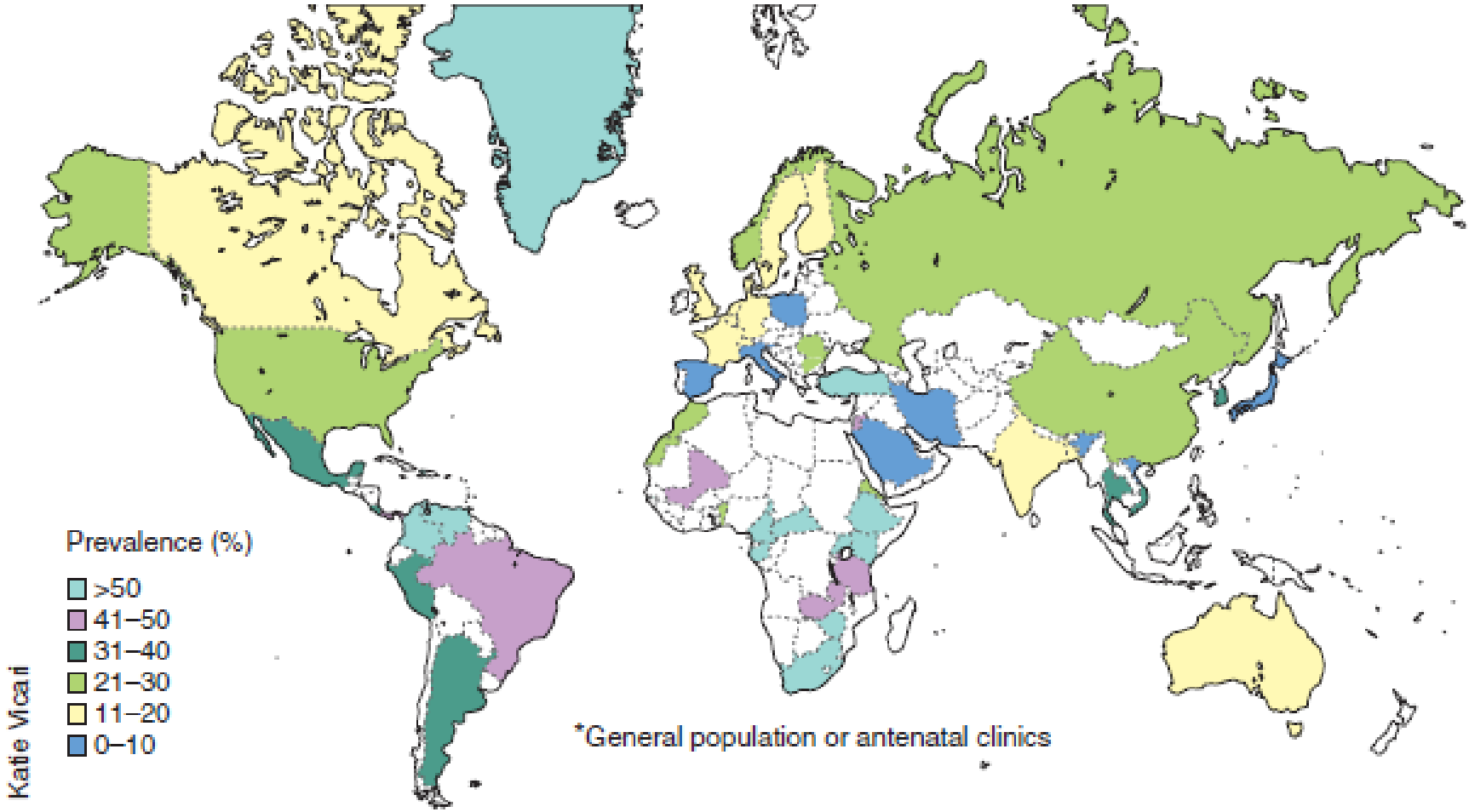


Figure 1 Prevalence of HSV-2 infection in women. Map is based on published studies within the last 15 years using serological assays that can accurately differentiate HSV-2 from HSV-1 infection. White indicates no available data.

HERPES SIMPLEX VIRUS

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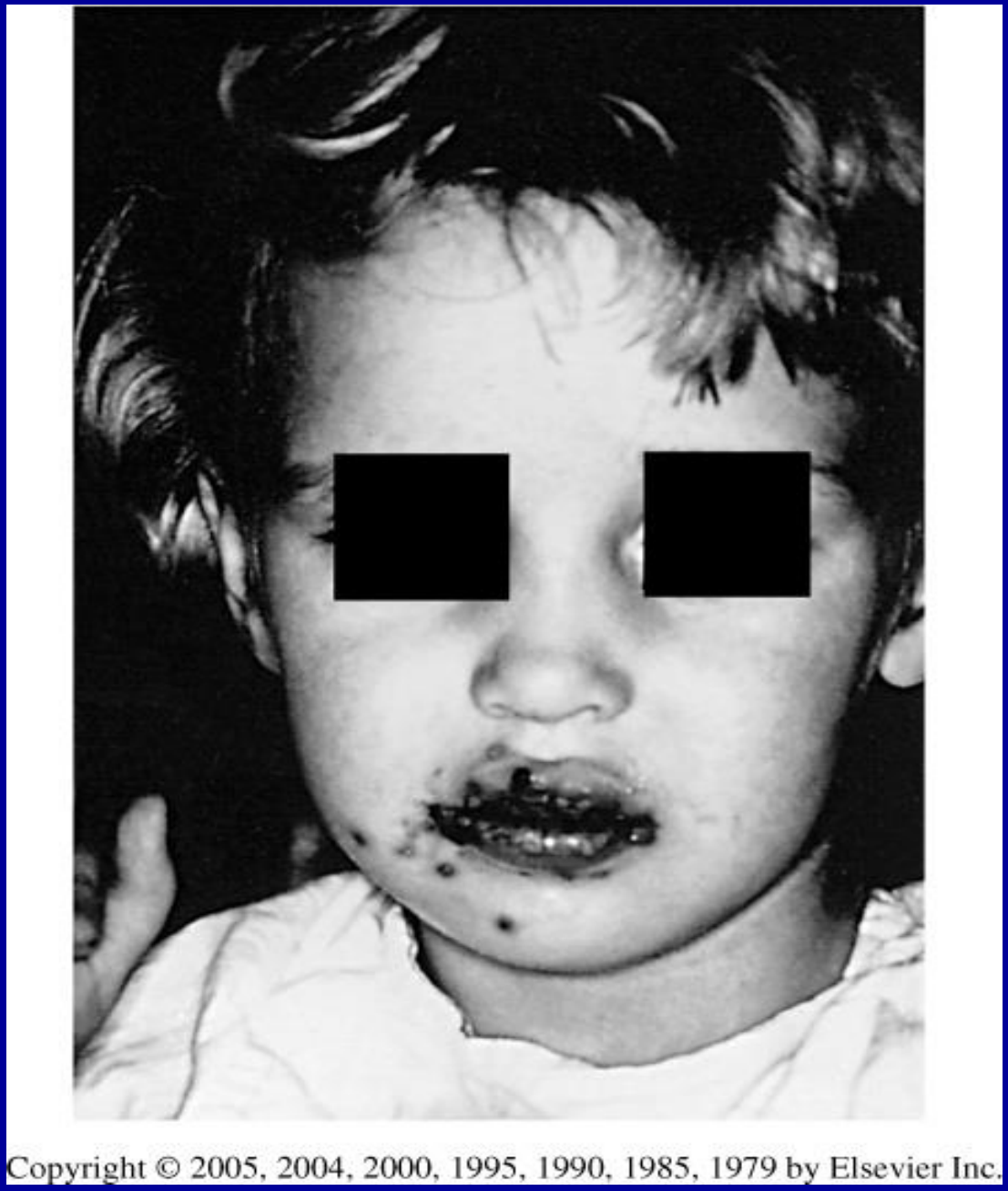
Clinical manifestations

- Primary Oropharyngeal disease
  - Great variety in clinical symptoms of primary infections
  - Asymptomatic infection is the rule rather than the exception; as high as 2/3.
  - When symptomatic: fever, sore throat, ulcerative and vesicular lesions, anorexia, malaise
  - Duration of illness typically 2-3 weeks

- Recurrent orolabial lesions
  - Pain, burning, tingling and itching which is followed by the formation of vesicles
  - Lesion is generally localized with three to five vesicles
  - Duration of illness typically 7-10 days

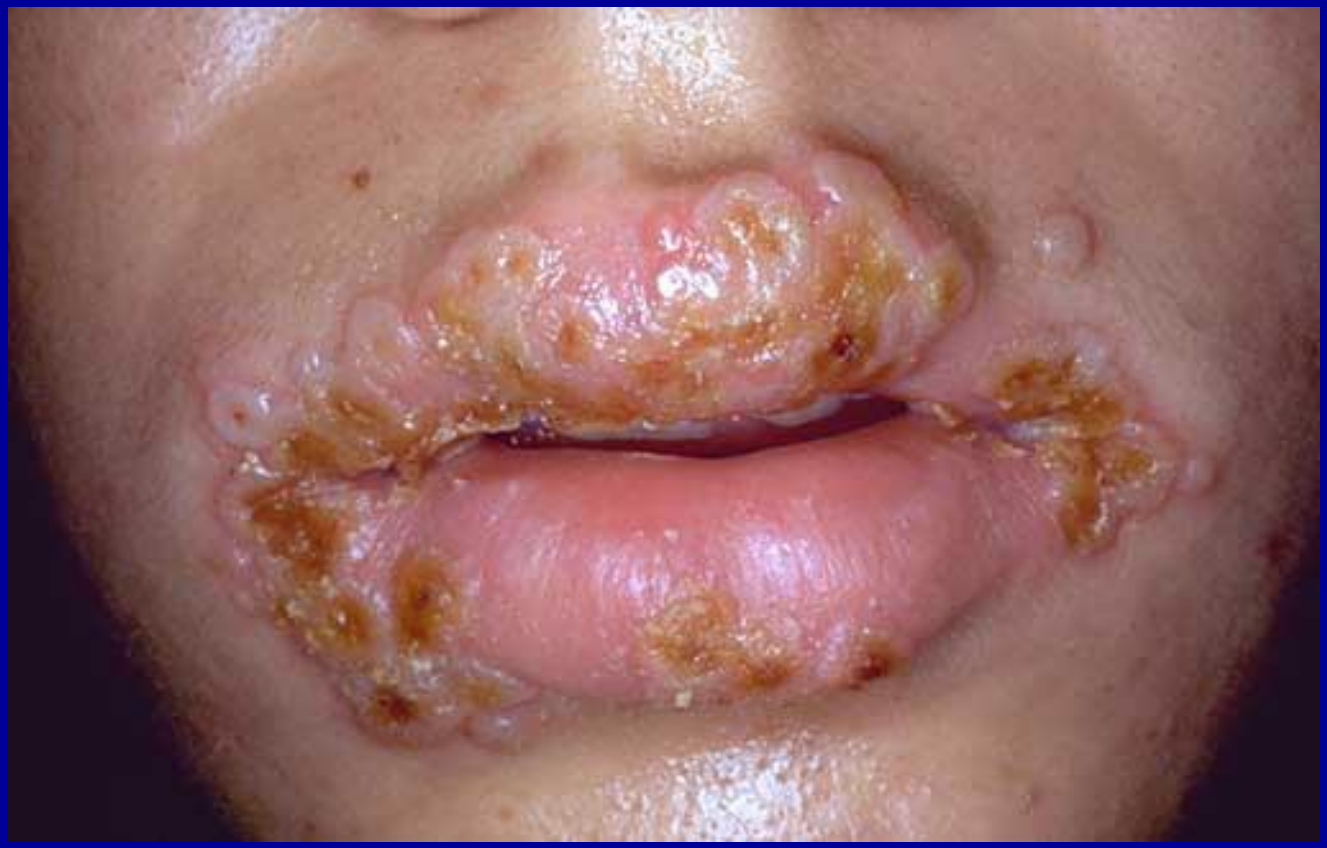
Brace Yourself

Here come the pics.



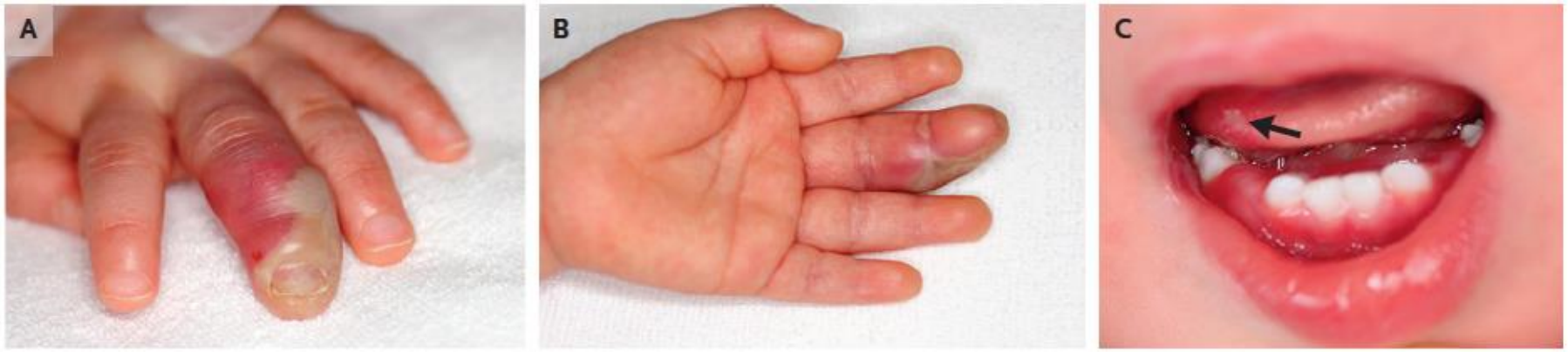
Primary Herpes simplex virus 1 infection in a child

PRIMARY ORAL HSV INFECTION



Courtesy of Dermnet.com, Interactive Medical Media LLC

Herpetic Whitlow



A previously healthy 1-year-old girl was admitted to the hospital with a 4-day history of fever, along with erythema and swelling of the left third finger. Bacterial cellulitis was suspected, and intravenous cefazolin was initiated. However, over the next 36 hours, the fever persisted (with a maximum temperature of 39°C), the finger was noted to have visible vesicles, and the fingertip became pale (Panels A and B). Further history revealed that the child often sucked her fingers, and examination of the oral cavity was notable for gingival inflammation and tongue lesions (Panel C, arrow). Polymerase-chain-reaction assay of a specimen from an oral lesion was positive for herpes simplex virus type 1 (HSV-1). Primary HSV-1 infection in young children commonly causes gingivostomatitis and fever. Thumb and finger sucking can lead to digital HSV infection, known as herpetic whitlow. In this patient, cefazolin was discontinued and intravenous acyclovir was initiated. Within 2 days, the symptoms began to resolve, and treatment was switched to oral valacyclovir. The patient was discharged home and completed a 10-day course of antiviral therapy. Resolution of the skin lesion was confirmed at the outpatient clinic 9 days after discharge.

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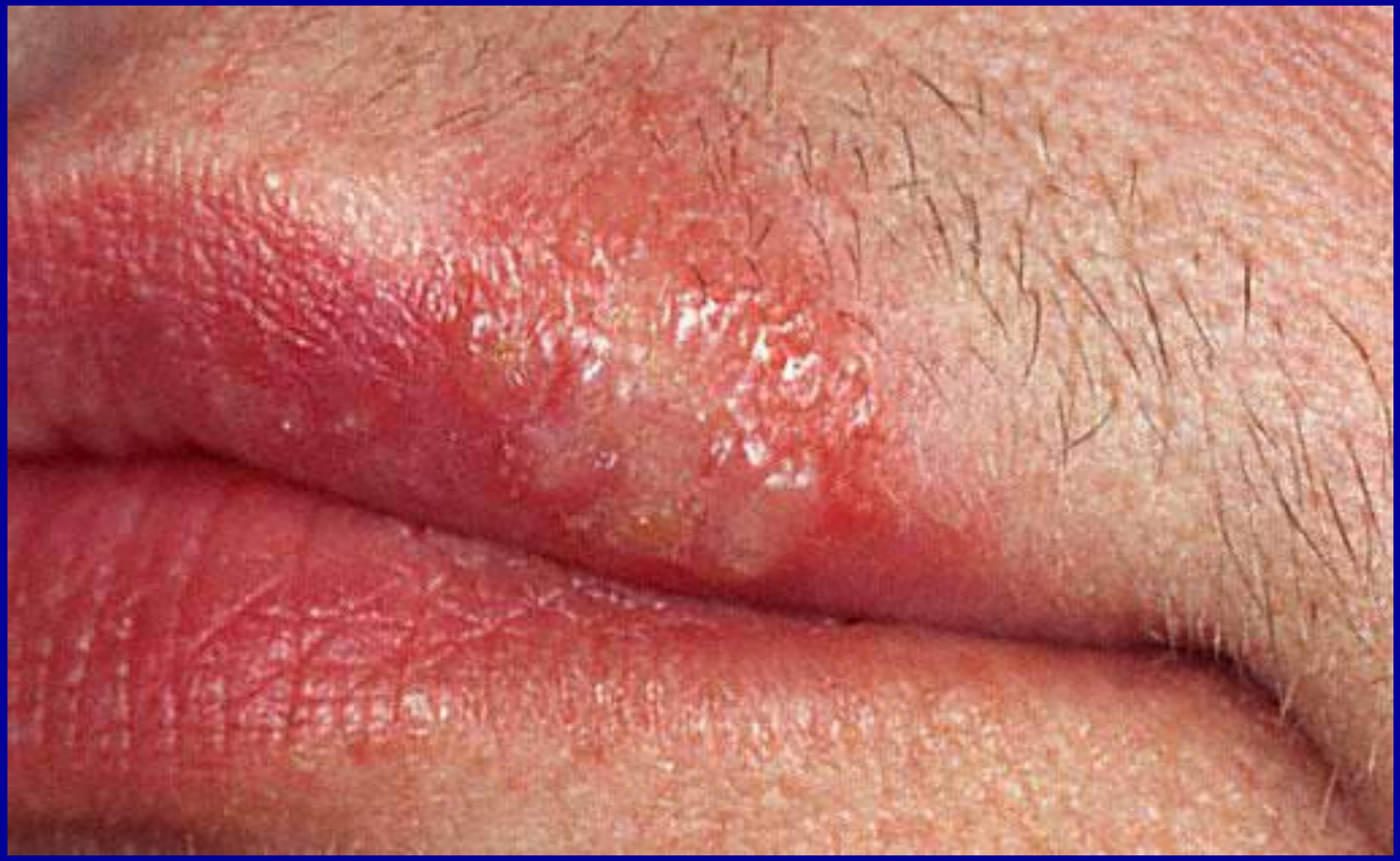
RECURRENT ORAL HERPES



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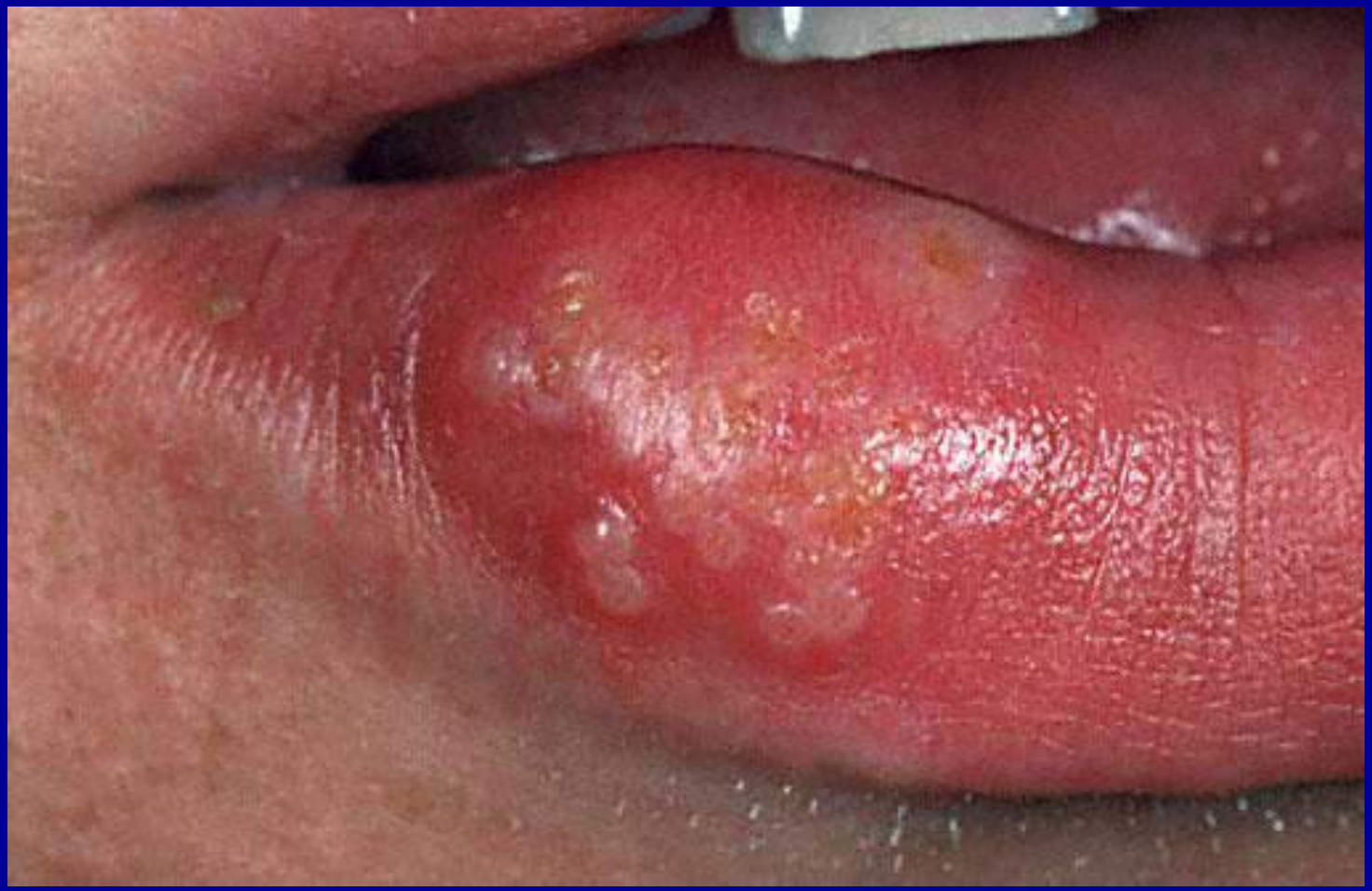
RECURRENT ORAL HERPES



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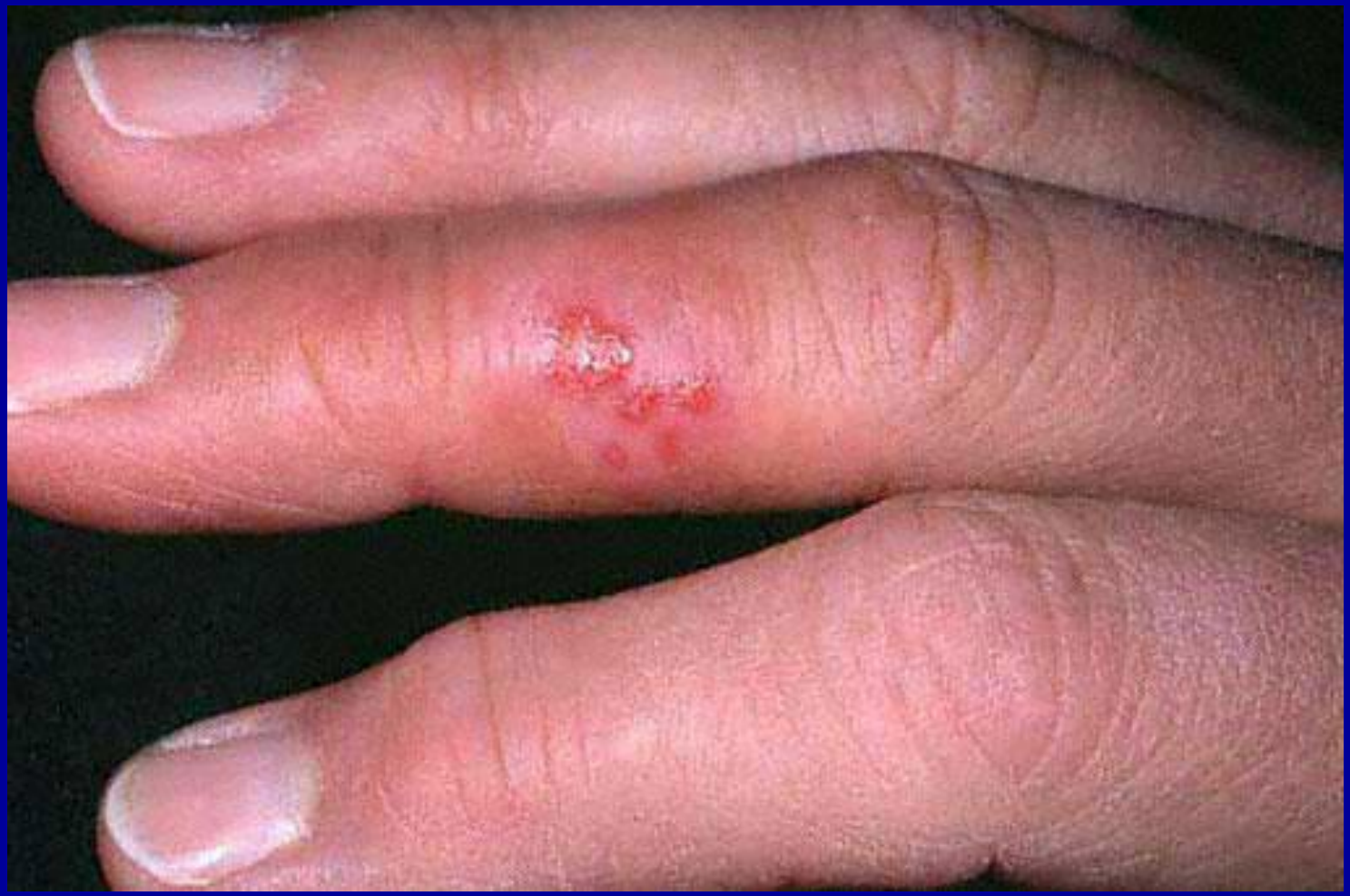
CUTANEUOS HSV INFECTION



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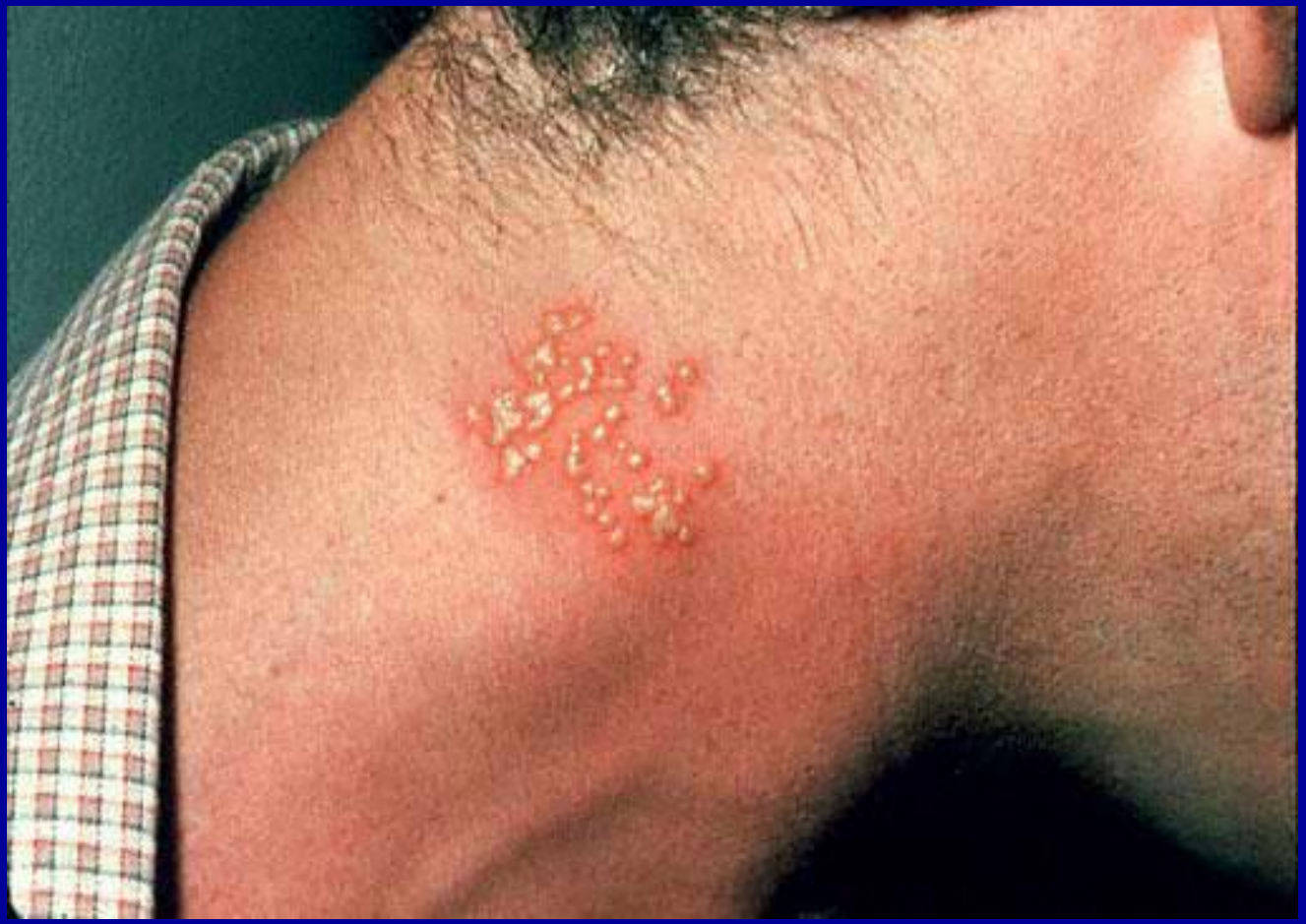
CUTANEUOS HSV INFECTION



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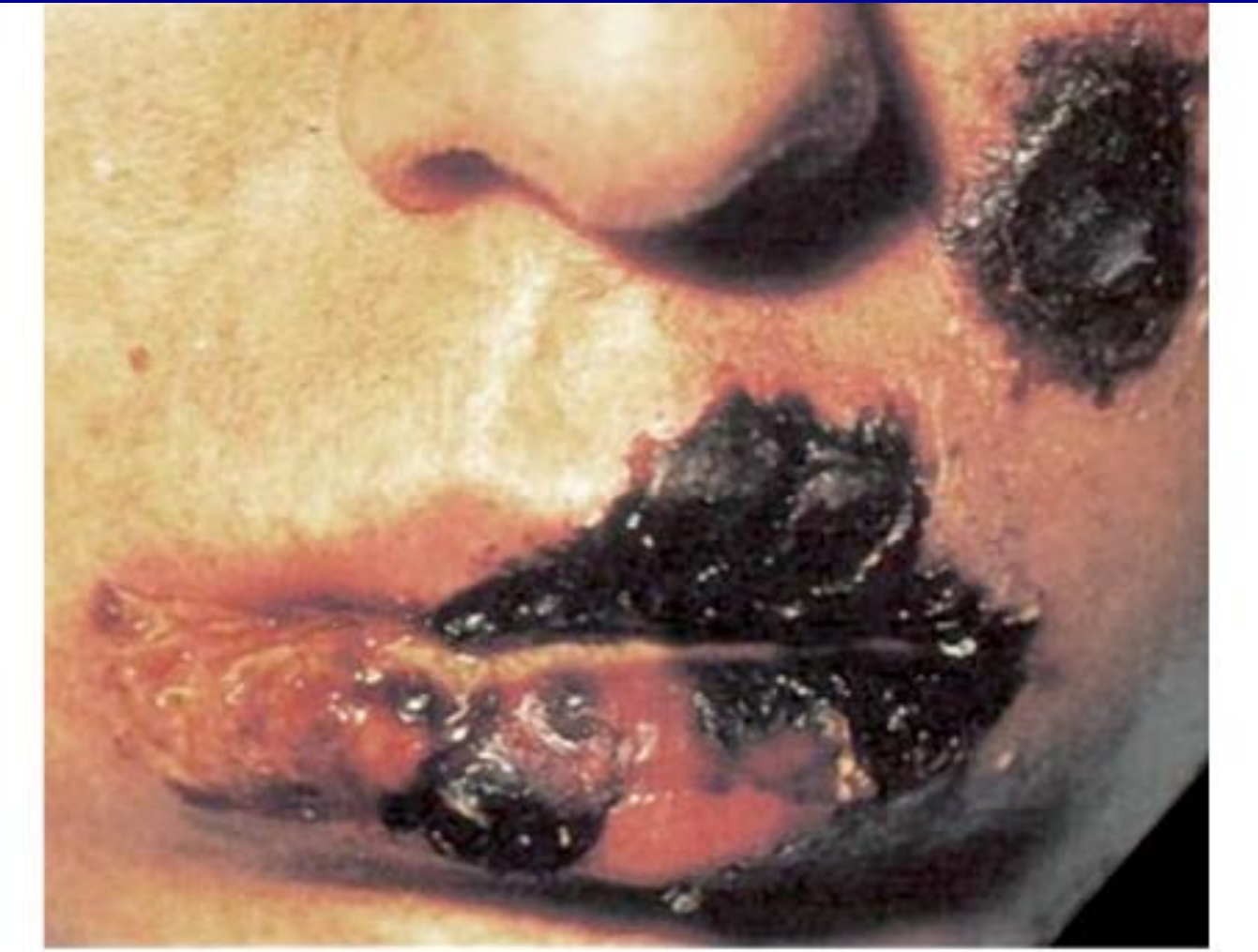


Severe mucocutaneous herpes simplex type 1 infection in a bone marrow transplant patient

Clinical manifestations

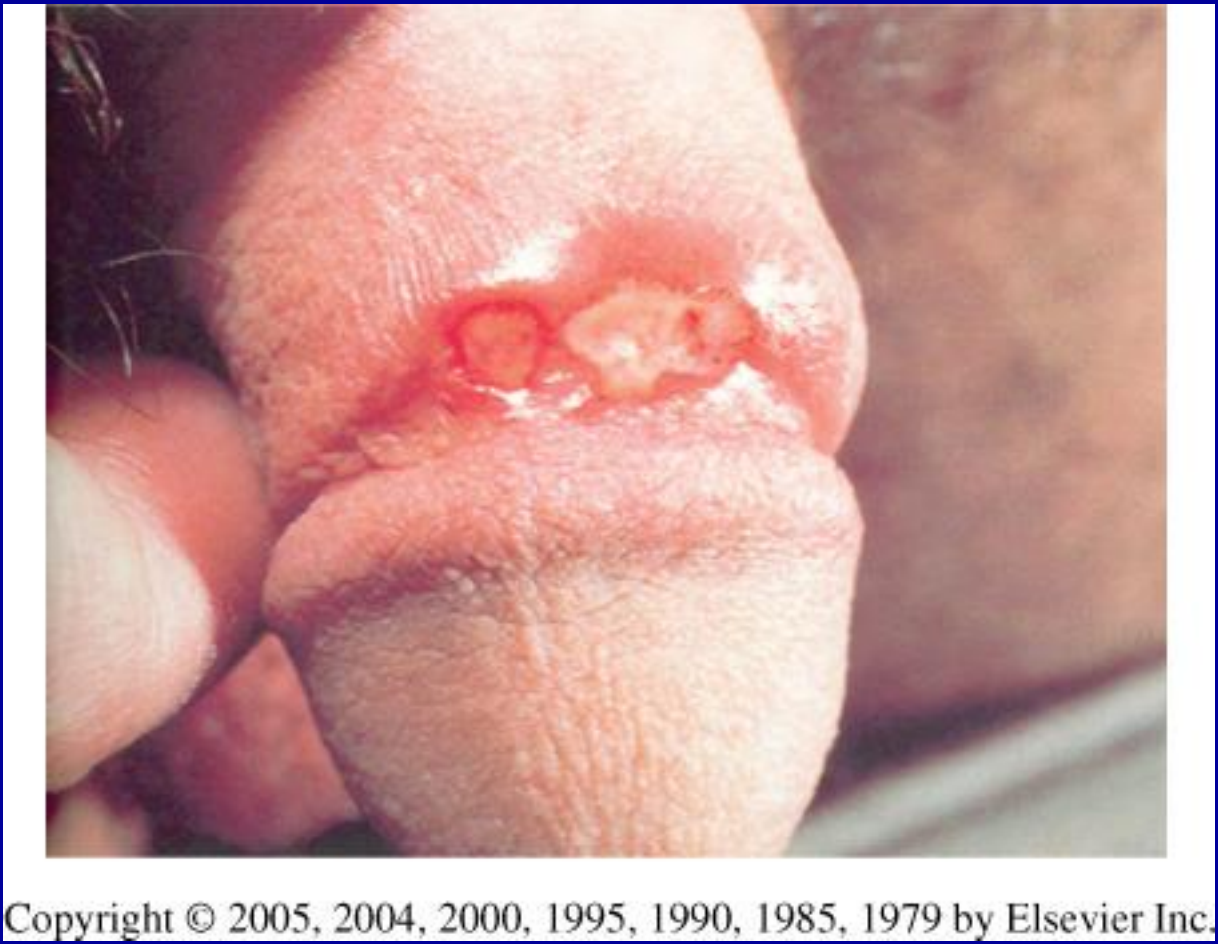
- Primary genital infection
  - Primary infections are usually associated with fever, dysuria, localized inguinal adenopathy and malaise
  - Vesicles and ulcers
  - Lesions persists ~ 3 weeks
- Recurrent genital infections
  - typically limited – three to five – vesicles
  - Duration typically 7-10 days

- **In one study, 74% of initial genital herpes infections due to HSV-1 and 63% of initial genital herpes infections due to HSV-2 in women were asymptomatic**

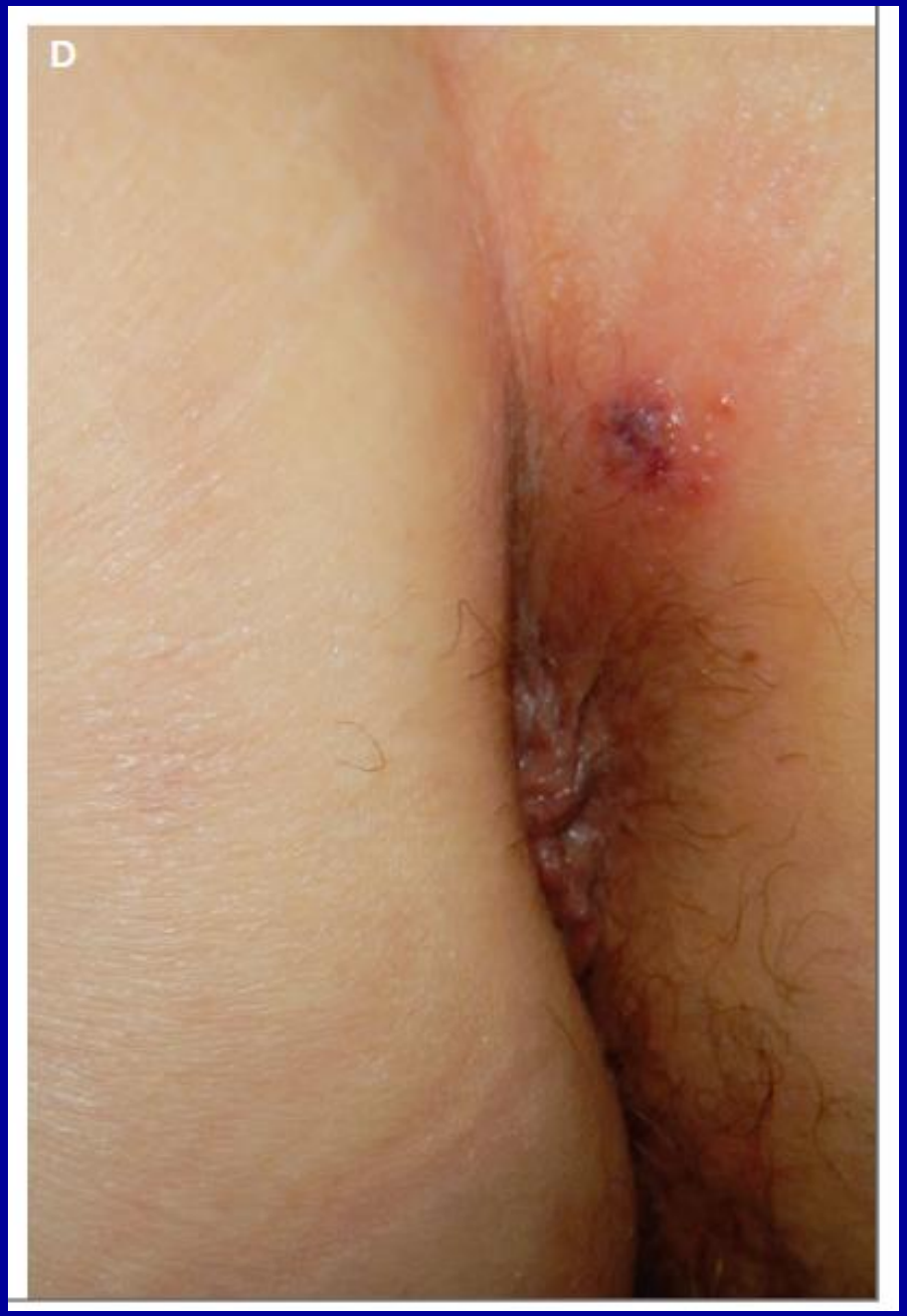
- **Initial HSV-2 genital infection in persons with preexisting HSV-1 antibodies is often asymptomatic**

- **Only 10 to 25% are symptomatic**

- **Asymptomatic people shed virus one day in 5. The only way to know it to get tested.**



Herpes simplex virus lesion on penis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TREATMENT

- Acyclovir (guanosine analog) is standard therapy for HSV infections

- Valaciclovir and famciclovir have enhanced oral bioavailability (more powerful) Can have greater effect and be taken less often.

- Mechanism of action:
  - **Acyclovir is preferentially monophosphorylated by viral thymidine kinase** – (3000 times) **-** selectivity for HSV infections (and VZV) Meaning what?
  - The viral thymidine kinase acts on acyclovir instead of on Beta proteins, so viral replication is disrupted; viremia and infectivity decreased tremendously.
  - It does not eliminate the source (ds DNA in host cells)

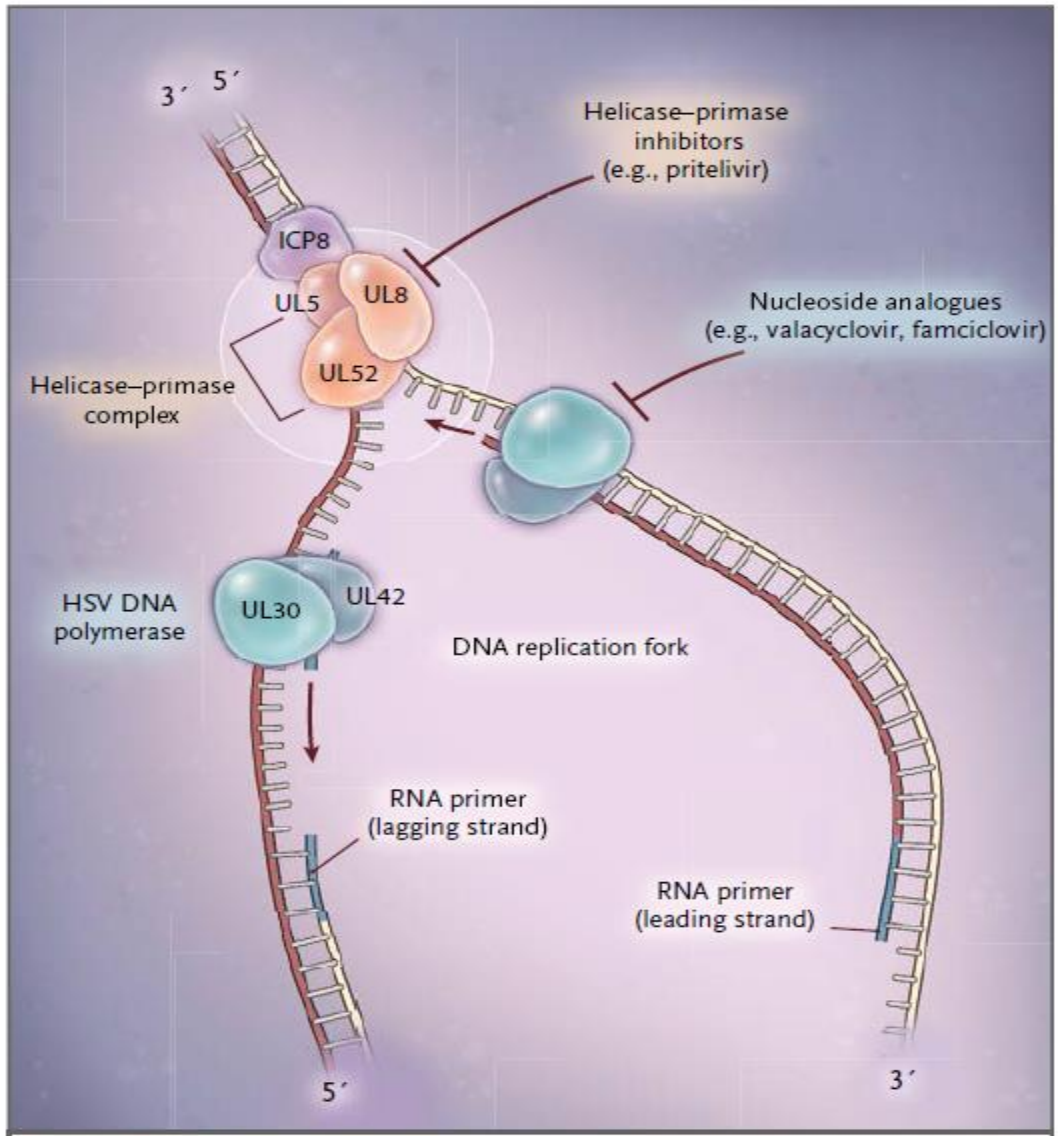

Figure 1. Model of the Action of Helicase–Primase Inhibitors.

A polymerase (UL30), together with its accessory subunit (UL42), functions in concert with three subunits of the helicase–primase complex (UL5, UL8, and UL52) and the DNA binding protein ICP8 to direct the synthesis of viral DNA. Pritelivir directly interferes with this process by inhibiting the helicase–primase complex and thereby preventing the formation of viral DNA.

Genital herpes:

- Can be treated with topical, oral or intravenous acyclovir
- Topical application reduces the duration of viral shedding and the time of healing, but are least effective
- Intravenous is most effective, but require hospitalization (severe local disease or systemic infections)
- Long-term oral administration of acyclovir efficiently suppresses genital herpes in patients with frequent recurrences
- IMPORTANTLY, asymptomatic shedding of virus can continue despite effective suppression with acyclovir (possibility of person-to-person transmission)

Suppressive therapy

- Suppressive therapy does reduce genital outbreaks of HSV2 by 80%

- It also reduces asymptomatic viral shedding from 27% to 6%

Herpes labialis

- **Topical therapy is of no value**

- **Oral administration:**
  - **For an outbreak, reduces length of time to complete healing by about 25% if administered quickly (i.e. one or two days after outbreak)**
  - **Prevents recurrence of outbreaks by more than half.**