Basic Biology of CMV: Application to Diagnosis, Therapy, and Prevention

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October 8, 2023, 2:00 PM
SJ Quinney College of Law
https://venues.utah.edu/venues/sj-quinney-college-of-law-conference-center-5/

Session Overview

- History of the cytomegalovirus
- Biology of the cytomegalovirus
- Medical importance of cytomegalovirus infections

Disclosures

- Grant support from Moderna vaccines

Cytomegalovirus: History

Prof. H. Ribbert

https://www.nli.org.il/en/a-topic/987007273250205171

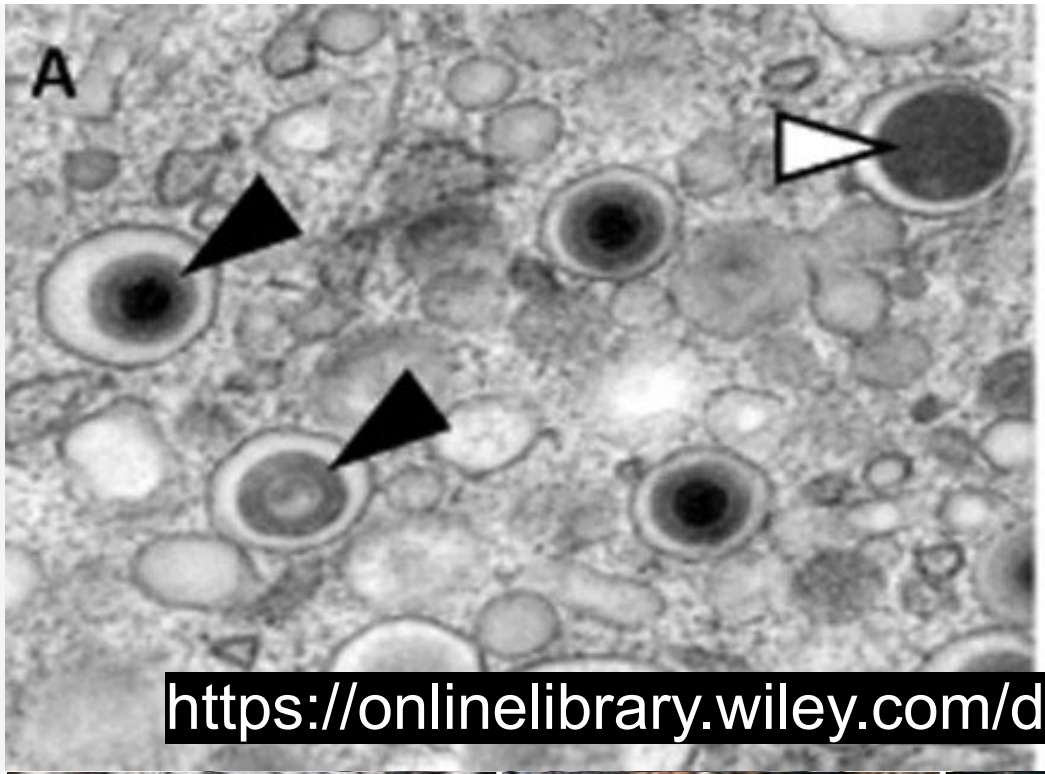
- Professor Hugo Ribbert (1855 – 1920)
- Bonn, Germany
- “Protozoal-type cells” in autopsy of a stillborn infant in 1881
- Growth restricted, microcephalic baby

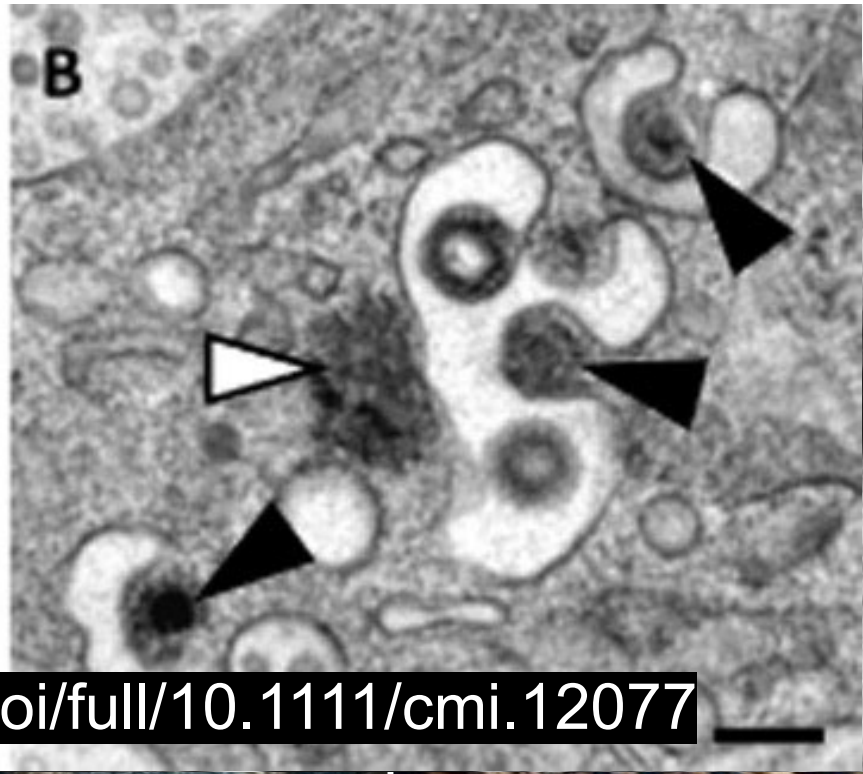
Prof. Albert Jesionek
University of Munich
1870 – 1935

https://www.altmeyers.org/en/dermatology/jesionek-albert-127665

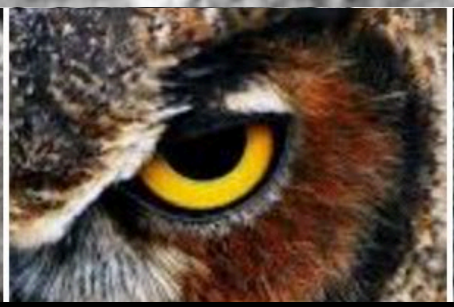
- Jesionek and Kiolemenoglou described similar cells as “protozoan like” cells in the lungs, kidneys and liver of an 8-month fetus
- These appear to be the first descriptions of typical cytomegalic cells with intranuclear inclusions
- “*Entamoeba mortinatalium*”

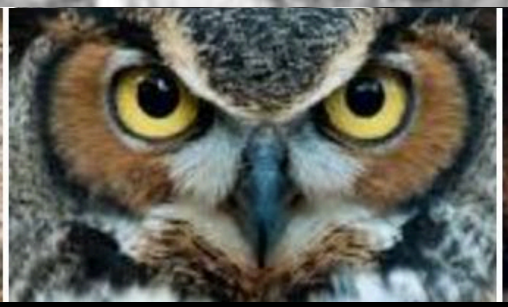
- Ribbert H (1904) Ueber protozoenartige Zellen in der Niere eines syphilitischen Neugeborenen und in der Parotis von Kindern. *Zbl All Pathol* 15:945–948
- Jesionek A, Kiolemenoglou B (1904) Ueber einen Befund von protozoenartigen Gebilden in den Organen eines hereditar-luetischen Foetus. *Muenchner Med Wochenschr* 51:1905–1907





https://onlinelibrary.wiley.com/doi/full/10.1111/cmi.12077





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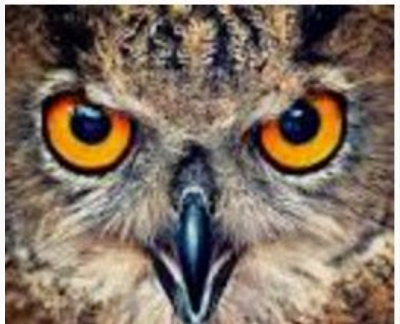
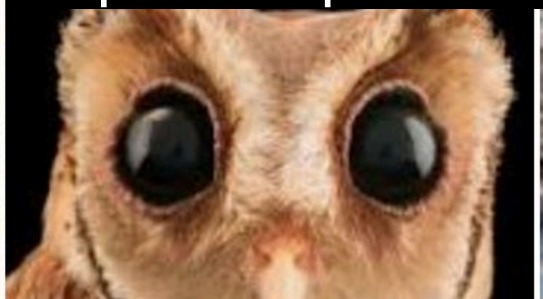
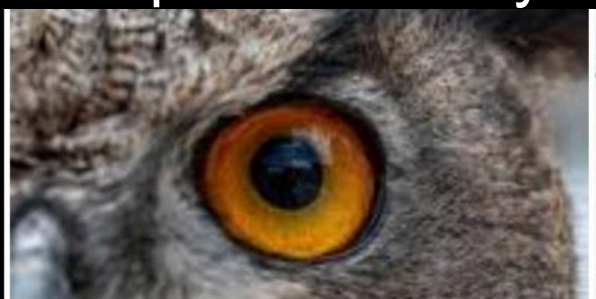
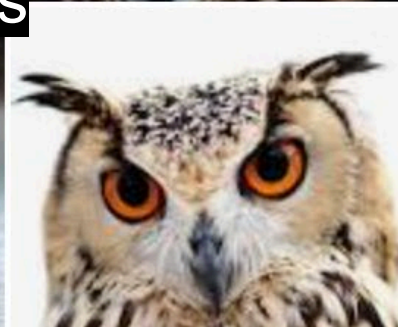






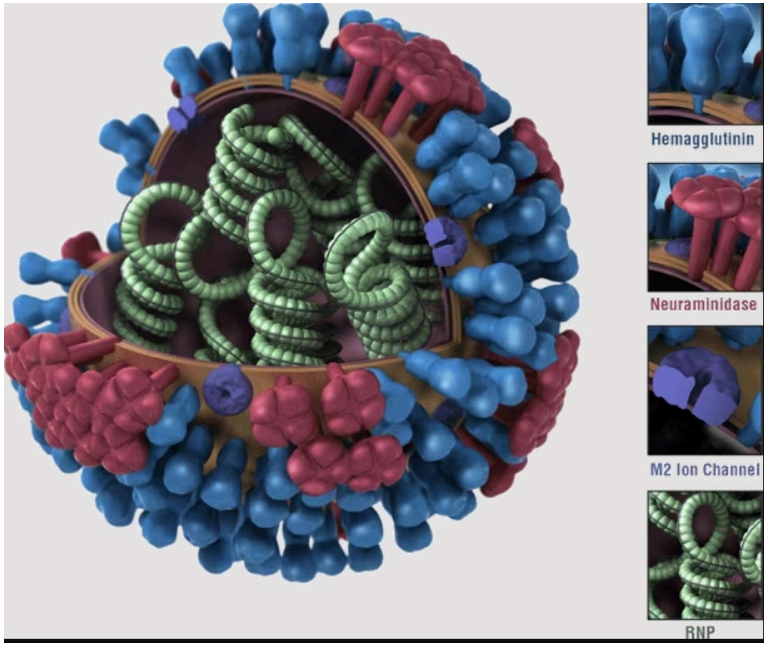


In 1907, Lowenstein described enlarged cells with intranuclear inclusions in parotid glands obtained from children less than 3 years of age.

Goodpasture (1921) noted that the inclusions appeared similar to those from the skin lesions of patients with varicella and herpes simplex infections. He proposed that the inclusions were viral rather than parasitic, and suggested the term "salivary gland virus" (SGV).

https://www.alamy.com/stock-photo-advert-for-berkefeld-filter-clean-water-1901-131022909.html?imageid=67C7639F-D600-4733-B39A-6DFB4C4E69AC&p=181734&pn=1&searchId=2bda0b25e9bc84f08192c5efef6d96d5&searchtype=0

Cole (1926) next put the Goodpasture hypothesis to the test. He obtained guinea pig salivary glands that had the characteristic inclusions and passed them through a Berkefeld filter. This was the first suggestion of a "filterable agent" (a virus) causing disease.



https://www.nps.gov/articles/influenza-at-camp-sherman.htm
https://www.cdc.gov/flu/images/h1n1/3D_Influenza_transparent_key_pieslice_med.gif?_=40931?noicon

The Journal of Pediatrics

VOL. 36 MARCH, 1950 No. 3

Original Communications

GENERALIZED CYTOMEGALIC* INCLUSION DISEASE

J. P. WYATT, M.D., J. SAXTON, M.D., R. S. LEE, B.S., AND H. PINKERTON, M.D.
ST. LOUIS, MO.

NOMENCLATURE

The lack of uniformity in the nomenclature of this disease may have delayed its recognition as an entity. Many of the names used have been cumbersome or inappropriate. The simplest and perhaps most universally used term, "inclusion disease," is not sufficiently specific, since inclusions are associated with many diseases. We therefore suggest that an adaptation of the term "cytomegalia," originally used by Goodpasture[18] to indicate the bizarre cytological alteration characteristic of the disease to be incorporated into its name. The term "cytomegalic inclusion disease" seems to be descriptive and unlikely to cause confusion. Since this term may well be applied to the localized and dormant type of infection so common in the salivary glands, it seems necessary to refer to symptomatic or fatal cases as "generalized cytomegalic inclusion disease."

Successful Cell Culture Isolation of Cytomegalovirus

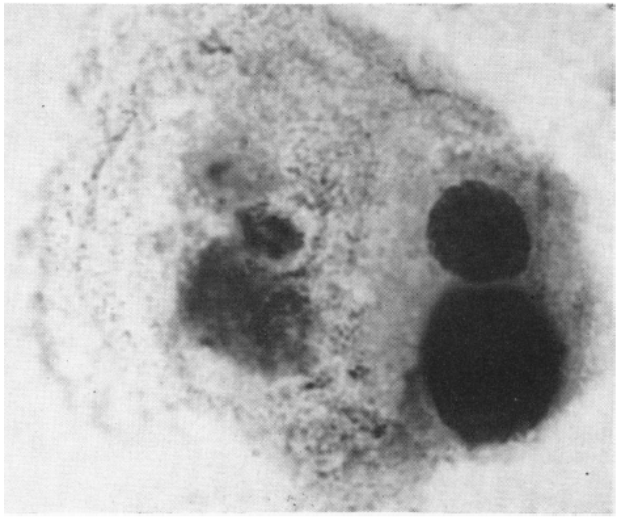
- Dr. Margaret Smith 1956
- Dr. Wallace Rowe 1956
- Dr. Thomas Weller 1957

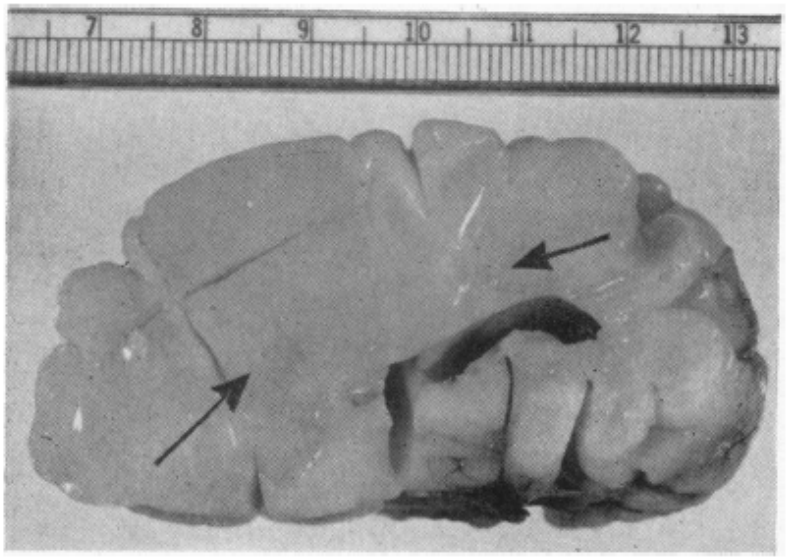
Med Microbiol Immunol. 2008 Jun;197(2):65-73

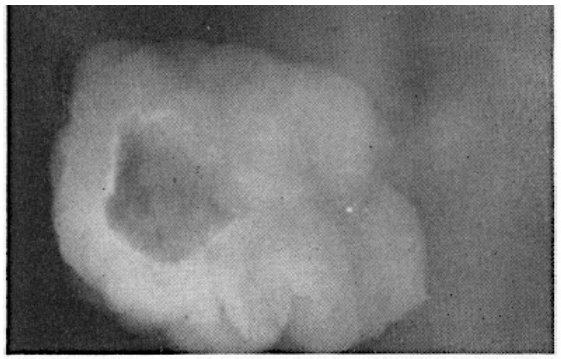
OBSERVATIONS ON CEREBRAL CYTOMEGALIC INCLUSION DISEASE OF THE FOETUS AND NEWBORN

BY

G. B. ELLIOTT and K. A. ELLIOTT
From the Department of Clinical Pathology, Calgary General Hospital, Alberta, Canada







periventricular cerebral necrosis. These are the first confirmatory observations of the suspicion that this virus infection of foetal brain occurs quite early *in utero*. Cytomegalic salivary gland virus infection appears largely harmless outside infancy but remains a risk to the foetus if first contracted by the mother during pregnancy. This disease appears to be a potentially preventable cause of mental defect and cerebral malformation which

PMID: 13889943, 1962

Cytomegalovirus: The Virus

Cytomegalovirus Has Co-Evolved with Humanity…

Med Hypotheses. 2010 Feb;74(2):222-4. doi: 10.1016/j.mehy.2009.09.033. Epub 2009 Oct 13.

Kissing as an evolutionary adaptation to protect against Human Cytomegalovirus-like teratogenesis.

Hendrie CA[1], Brewer G.

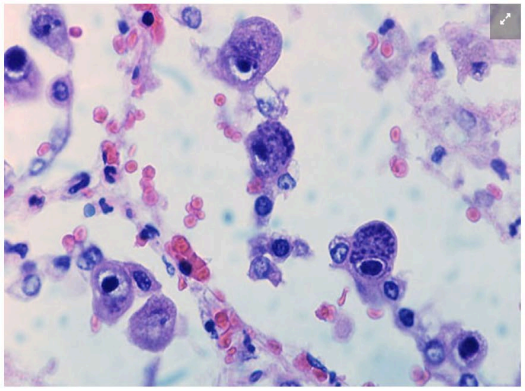
Author information

Abstract

Mouth to mouth sexual kissing is seen in more than 90% of human cultures. Various theories have been put forward to account for this but none offer a full explanation within an evolutionary framework. As mouth to mouth sexual kissing exposes each participant to the diseases of the other, it must confer significant benefit. Human Cytomegalovirus (HCMV) is a ubiquitous infection that carries a severe teratogenic risk if primary infection is acquired during certain critical periods. As HCMV is present in salivary gland epithelial cells and sheds from periodontitis induced lesions, female inoculation with a specific male's HCMV is most efficiently achieved through mouth to mouth contact and saliva exchange, particularly where the flow of saliva is from the male to the typically shorter female. The current hypothesis proposes that mouth to mouth sexual kissing enables females to control when they become infected with a particular male's HCMV and so protect their offspring from the threat of teratogenesis from primary infection during vulnerable times in their development. Females only gain this benefit if they also avoid becoming infected by other males. Hence HCMV induced teratogenesis is a strong viral pressure towards the development of monogamy as well as kissing as a behavioural strategy to protect against it.

KISSING EVOLVED TO SPREAD GERMS, NOT FEELINGS

By Clay Dillow November 2, 2009



Yale Rosen

The Love Bug

Cytomegalovirus is generally harmless unless introduced during pregnancy; British researchers now think the practice of kissing ones mate evolved as a means to spread and build immunity to the saliva-dwelling pathogen prior to a pregnancy.

HOME » NEWS » NEWS TOPICS » HOW ABOUT THAT?

Kissing was developed 'to spread germs'

It isn't the most romantic theory, but scientists believe kissing was developed to spread germs which build up immunity to illness.

2K 6 1 2K Email

Kissing helps to protect women Photo: GETTY IMAGES

8:00AM GMT 31 Oct 2009

They say the gesture allows a bug named Cytomegalovirus, which is dangerous in pregnancy, to be passed from man to woman to give her time to build up protection against it.

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In How About That?

Pictures of the day

Pictures of the day

Classification of Human Herpesviruses

Subfamily	Scientific name	Common name
Alphaherpesvirinae	Human herpesvirus 1 Human herpesvirus 2 Human herpesvirus 3	Herpes simplex virus type 1 Herpes simplex virus type 2 Varicella-zoster virus
Betaherpesvirinae	Human herpesvirus 5 Human herpesvirus 6 Human herpesvirus 6a Human herpesvirus 7	Cytomegalovirus - - -
Gammaherpesvirinae	Human herpesvirus 4 Human herpesvirus 8	Epstein-Barr (EB) virus Kaposi's sarcoma associated virus

http://www.jaymedelrosario.com/the-8-known-common-names-for-herpes-viruses-that-can-infect-humans-are/


Love may not last forever. But herpes does.
yourecards
someecards.com


"NOTHING LASTS FOREVER"
FALSE. DIAMONDS AND HERPES

Article

Cell

Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences

Petter Brodin,[1,2,3,11] Vladimir Jojic,[4,11] Tianxiang Gao,[4] Sanchita Bhattacharya,[3] Cesar J. Lopez Angel,[2,3] David Furman,[2,3] Shai Shen-Orr,[5] Cornelia L. Dekker,[6] Gary E. Swan,[7] Atul J. Butte,[6,8] Holden T. Maecker,[3,9] and Mark M. Davis[2,3,10,*]

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[3]Institute of Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA 94304, USA
[4]Department of Computer Science, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
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[9]Human Immune Monitoring Center, Stanford University School of Medicine, Stanford, CA 94304, USA
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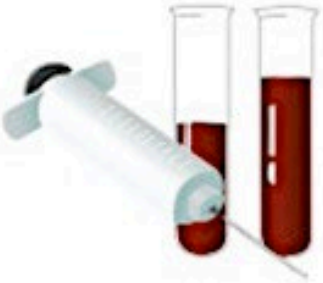
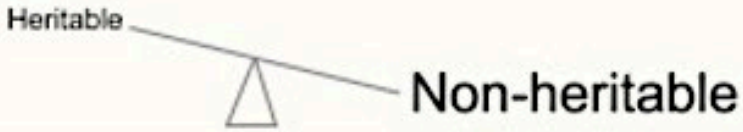
[11]Co-first author
*Correspondence: mmdavis@stanford.edu
http://dx.doi.org/10.1016/j.cell.2014.12.020

210 healthy twins

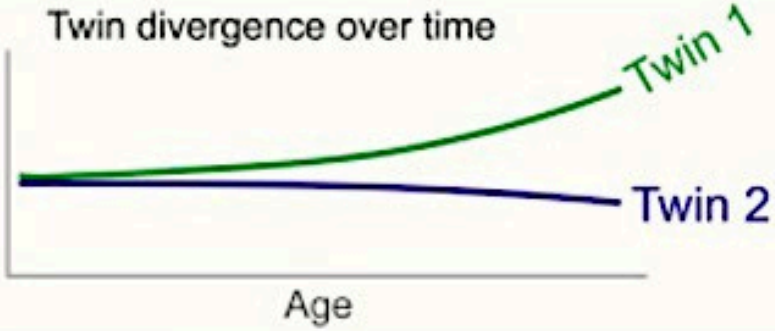


Immune cell frequencies
Cell signaling
Serum proteins
Flu vaccine responses

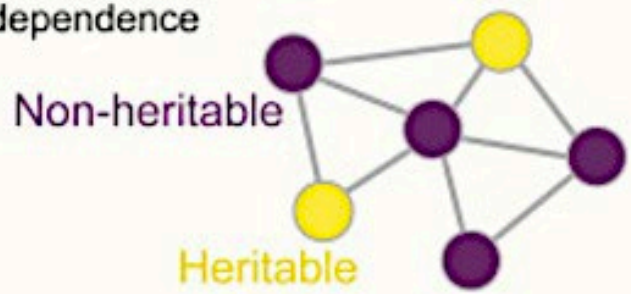
Immune variation explained



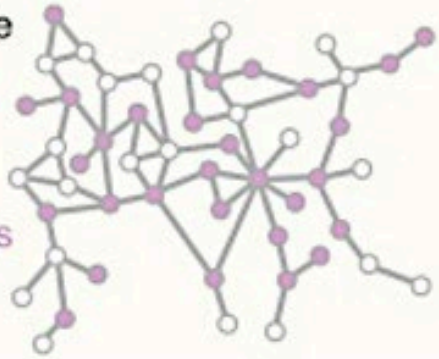
Twin divergence over time

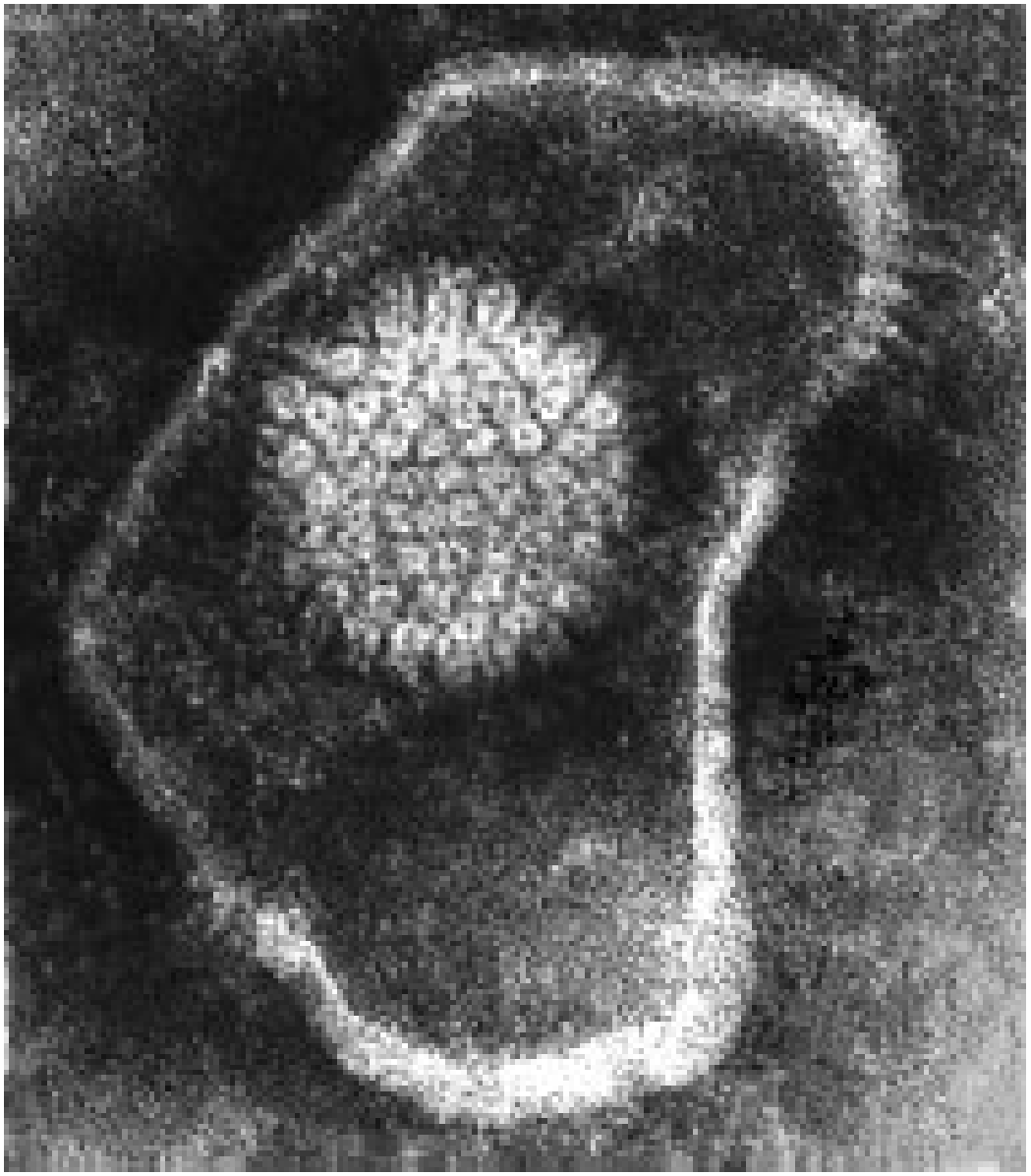


Inter-dependence

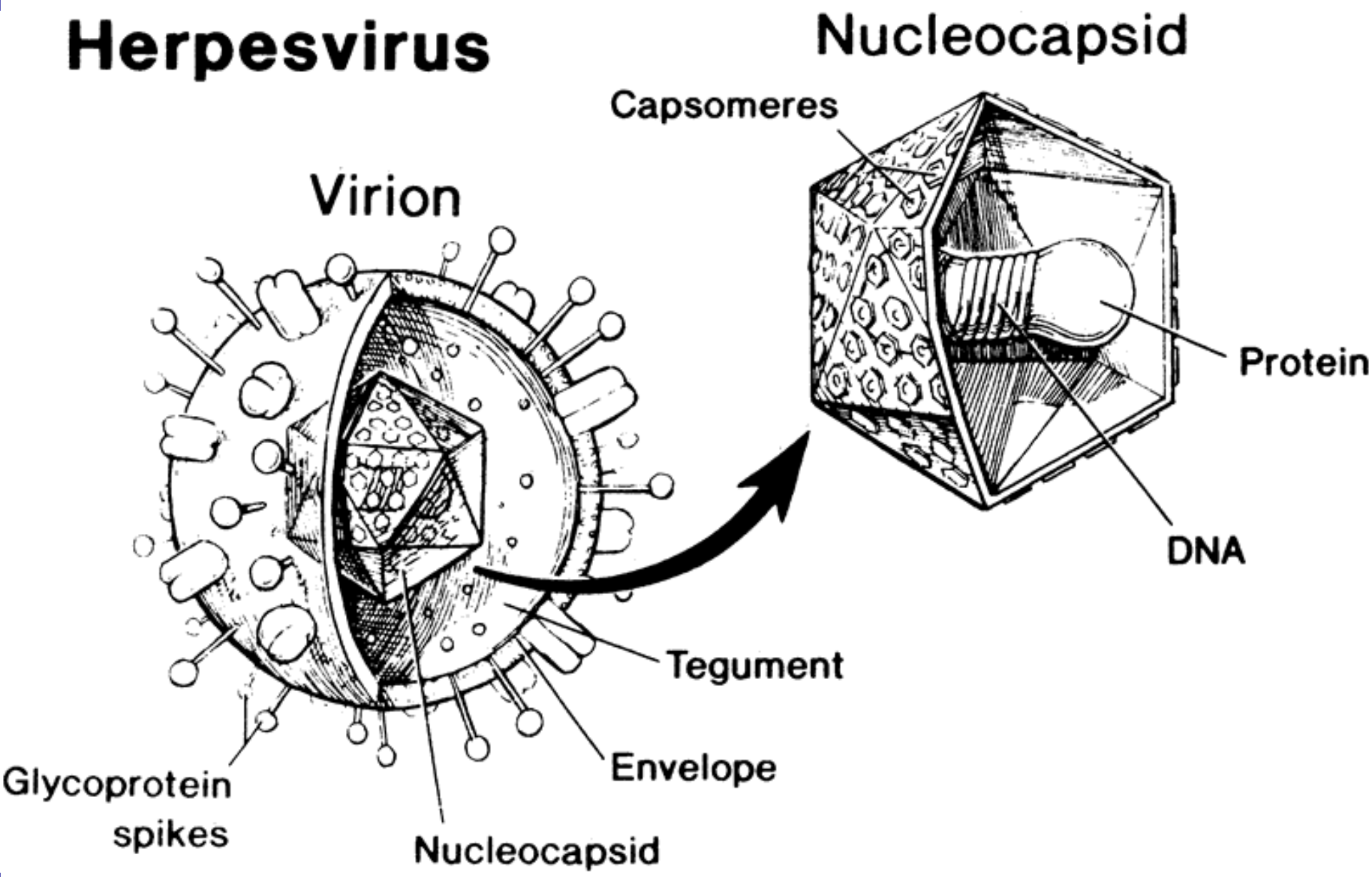


Broad, non-heritable influence





http://virology-online.com/viruses/hsv2.gif



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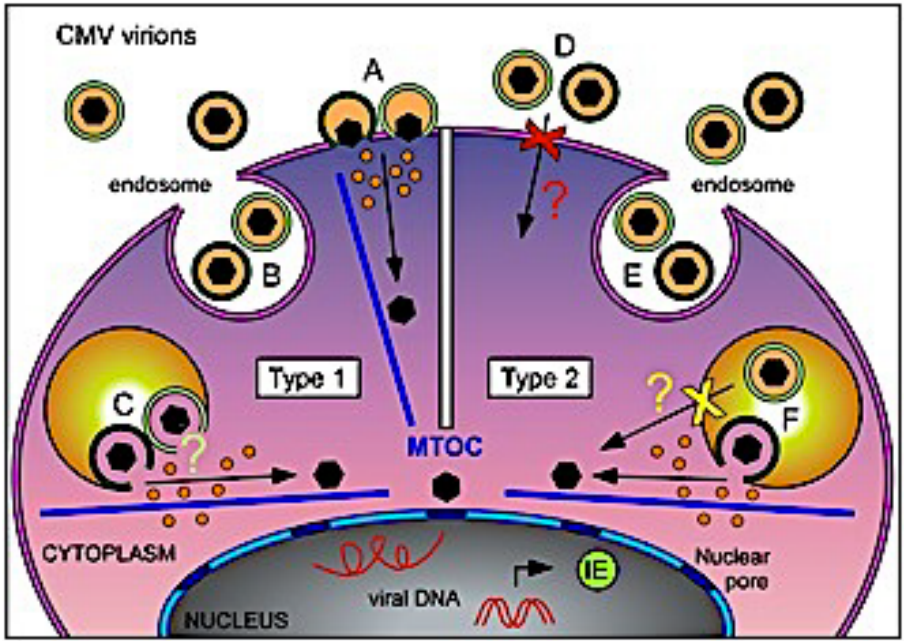
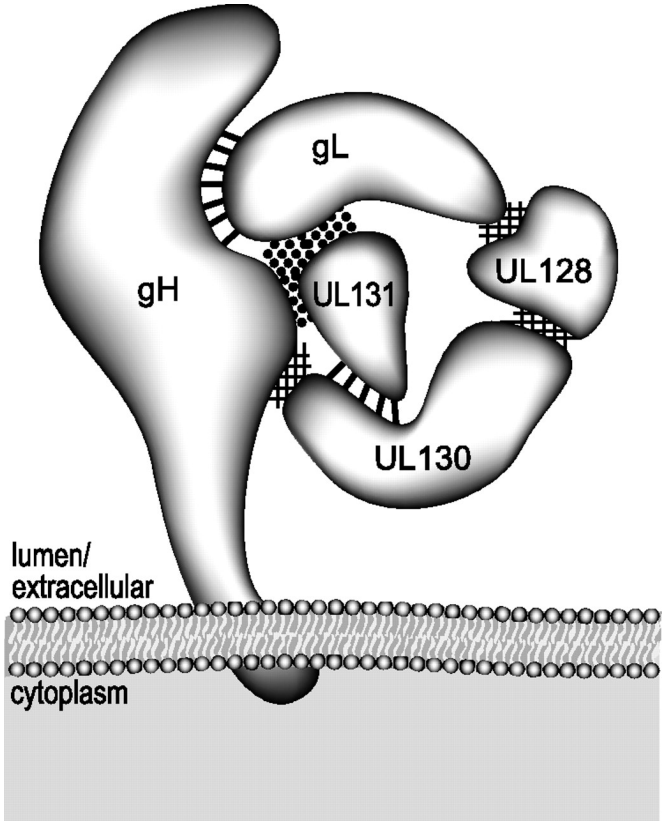
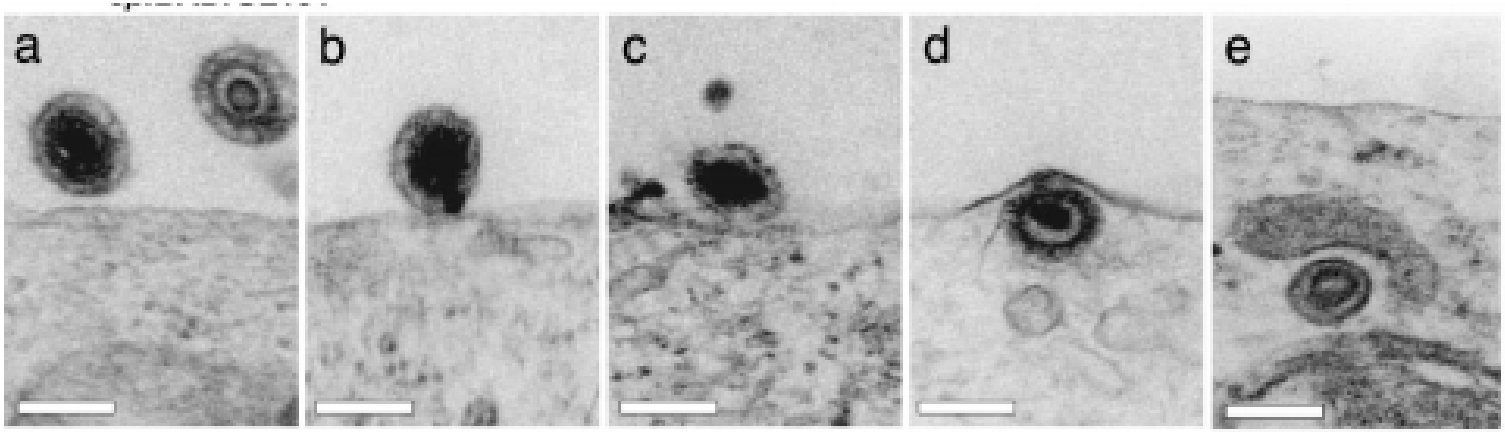
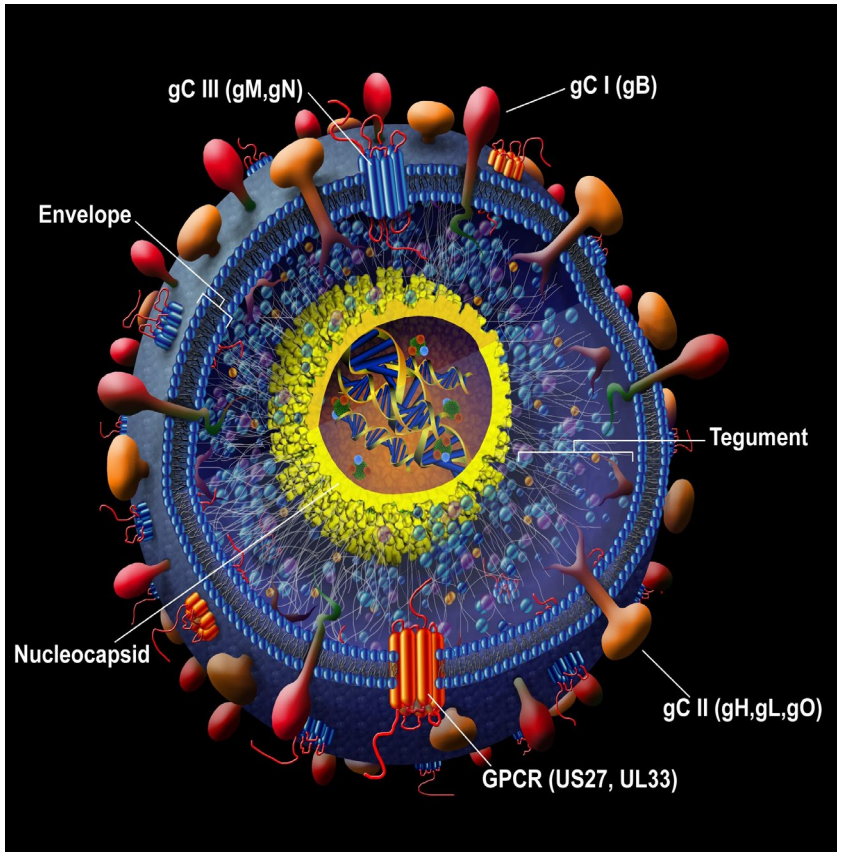






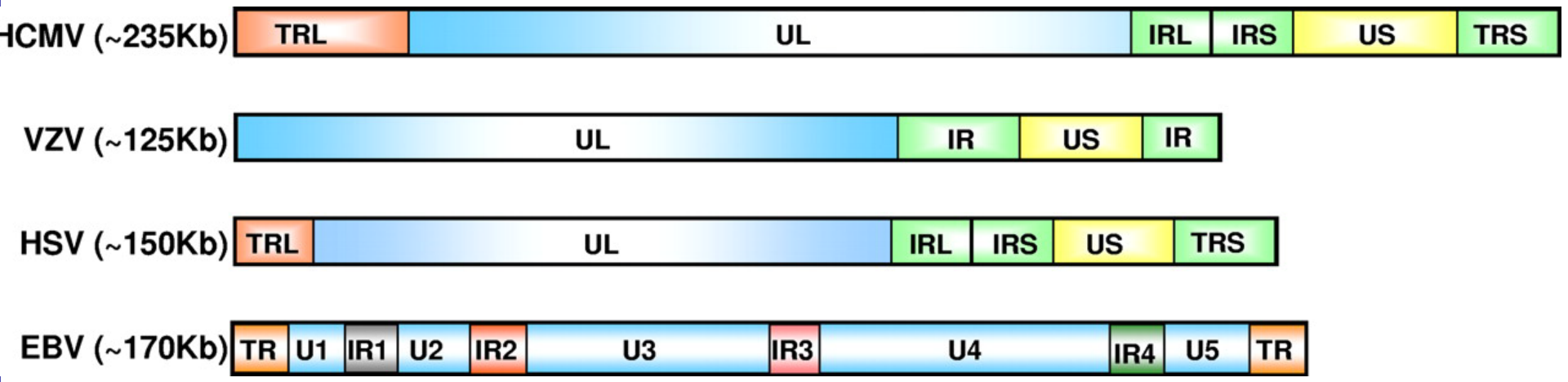
https://www.researchgate.net/profile/Laura_Hertel/publication/262814826/figure/fig3/AS:272599649353762@1442004229927/Figure-2-CMV-entry-routes-CMV-virions-can-enter-host-cells-by-fusion-of-the-envelope.png
http://jvi.asm.org/content/82/1/60/F10.large.jpg
http://www.pnas.org/content/104/50/20037.full.pdf

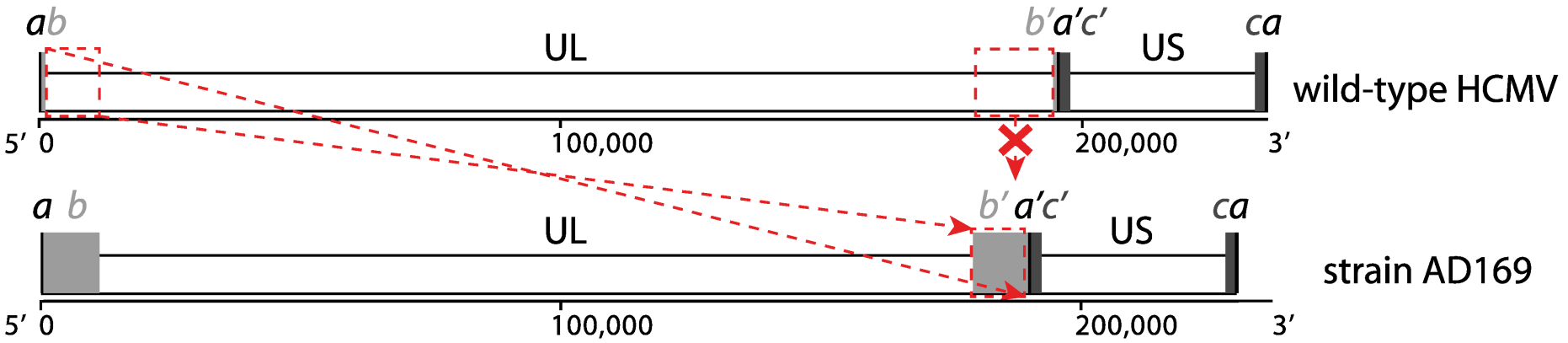


CMV Gene Product	Host Immune Response
Envelope Glycoproteins	
gB	Major target of neutralizing antibodies; target of CTLs
gH	Important target of neutralizing antibodies; target of CTLs
UL128-131	Associated with gH on viral envelope; target of neutralizing antibodies; important target for antibodies that neutralize infection at epithelial surfaces
gM/gN	Target of antibody neutralizing antibody responses
Structural proteins	
pp65	Major target of CTLs; target of non-neutralizing antibody responses
pp150, pp28	Target of CTLs and antibody responses
pp50	Target of CTLs
pp71, pp52	Targets of antibody responses
Nonstructural proteins	
IE1	Important target of CTLs; target of non-neutralizing antibody responses

Schleiss and Plotkin, *Vaccines*, 6th Edition, 2012, Chapter 43

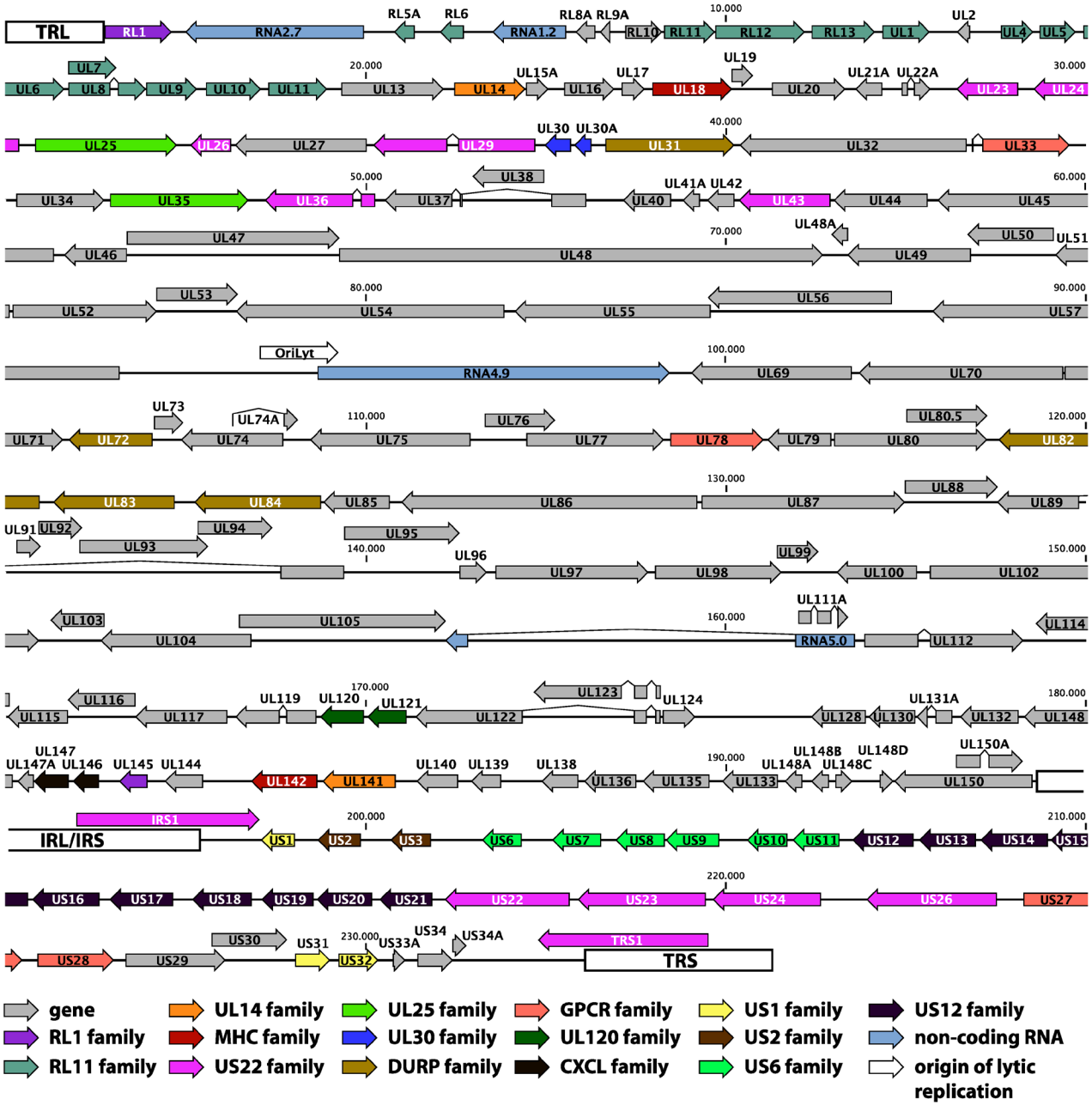
Cytomegalovirus Molecular Biology





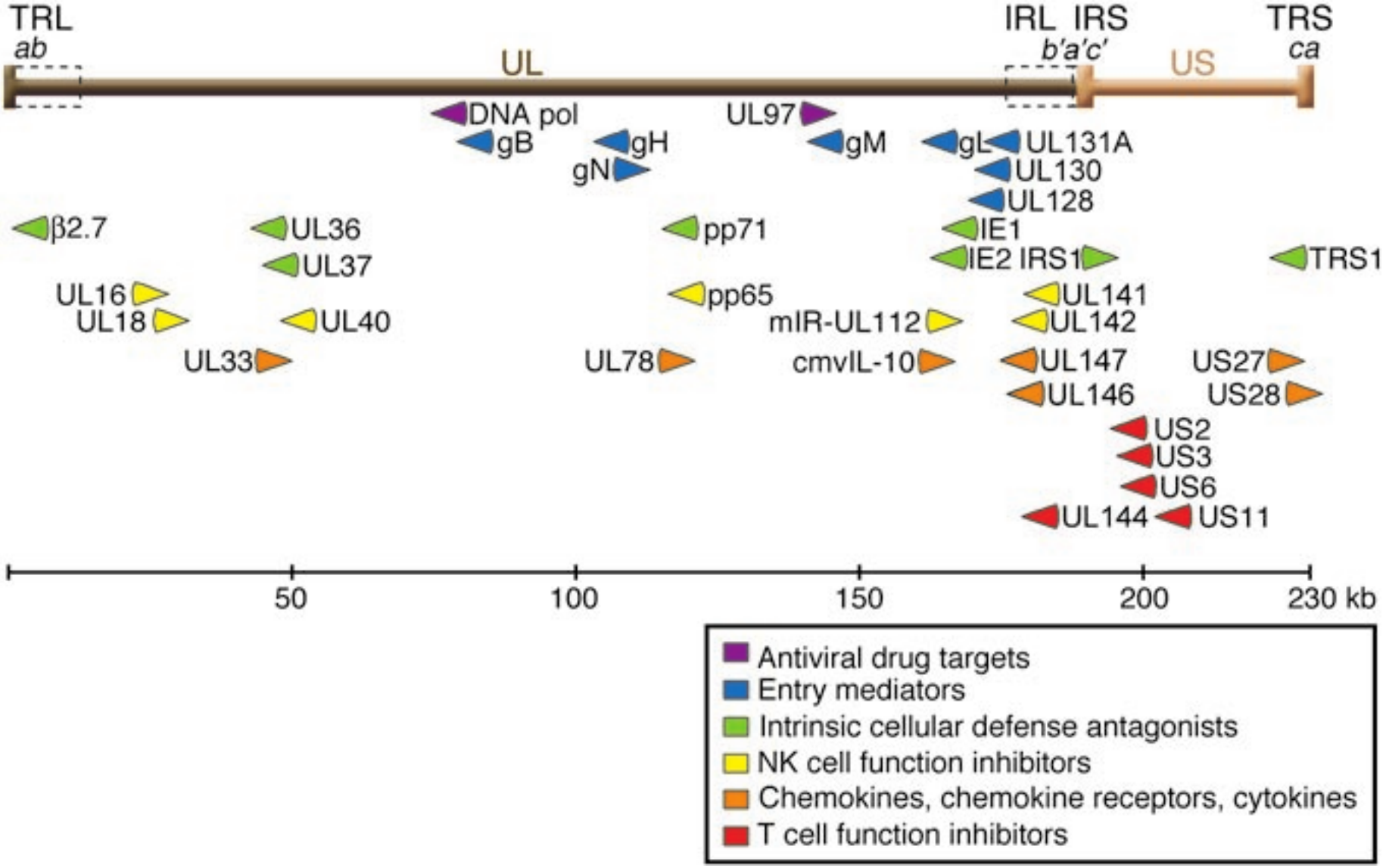
What does “UL” and “US” refer to?

http://cmr.asm.org/content/22/1/76/F1.large.jpg
http://www.mdpi.com/viruses/viruses-06-01049/article_deploy/html/images/viruses-06-01049-g001.png

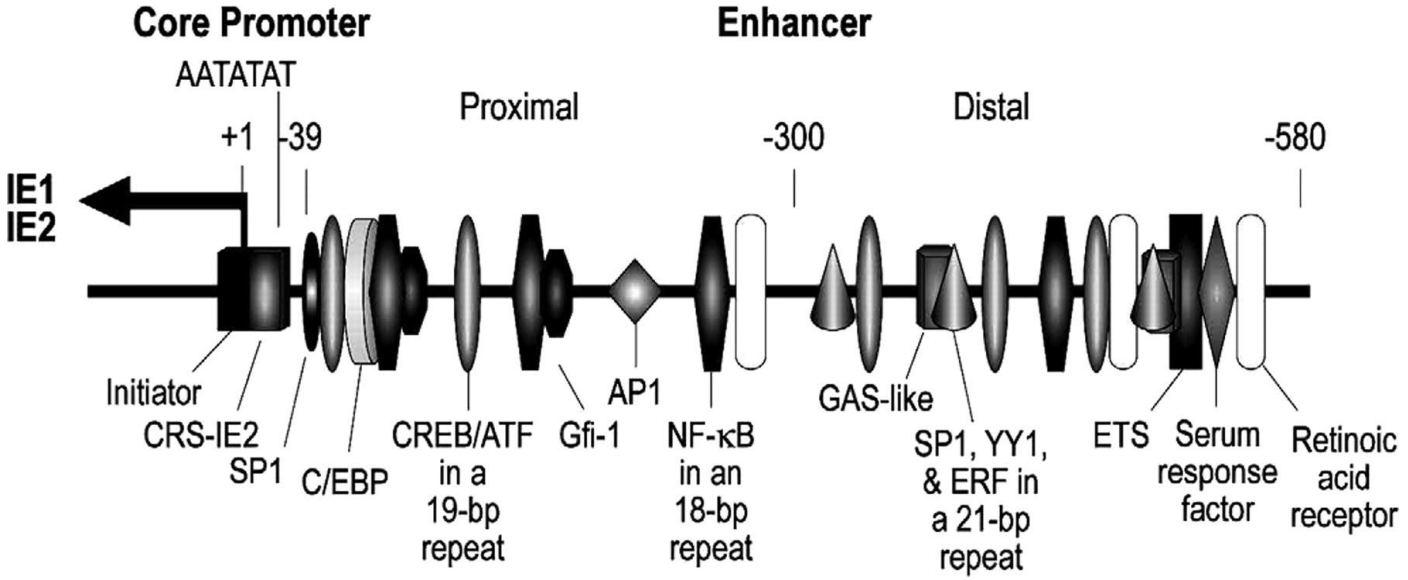


http://www.mdpi.com/1999-4915/6/3/1049/htm

CMV – Immune system evasion



Boeckh and Geballe, 2011, JCI



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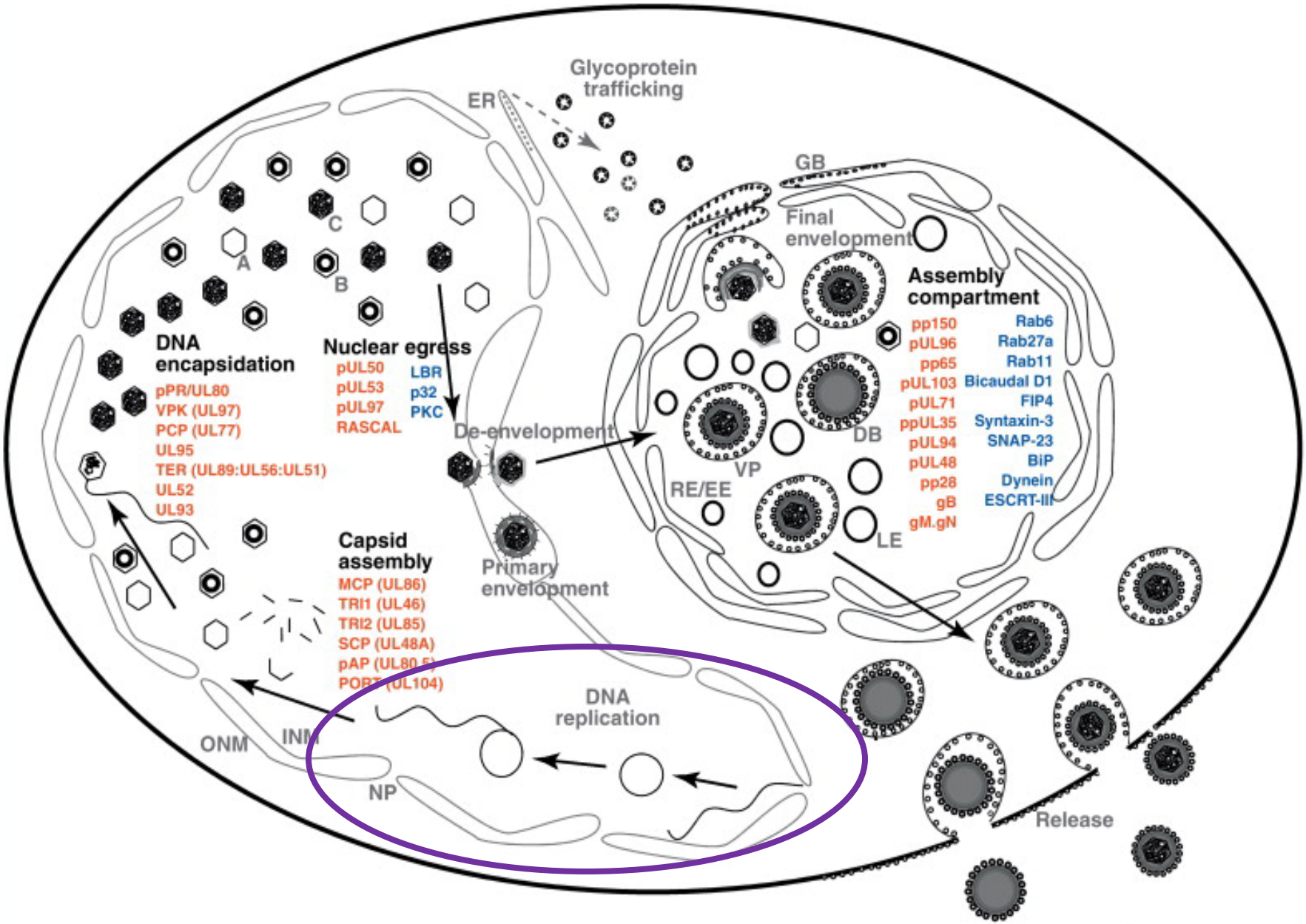
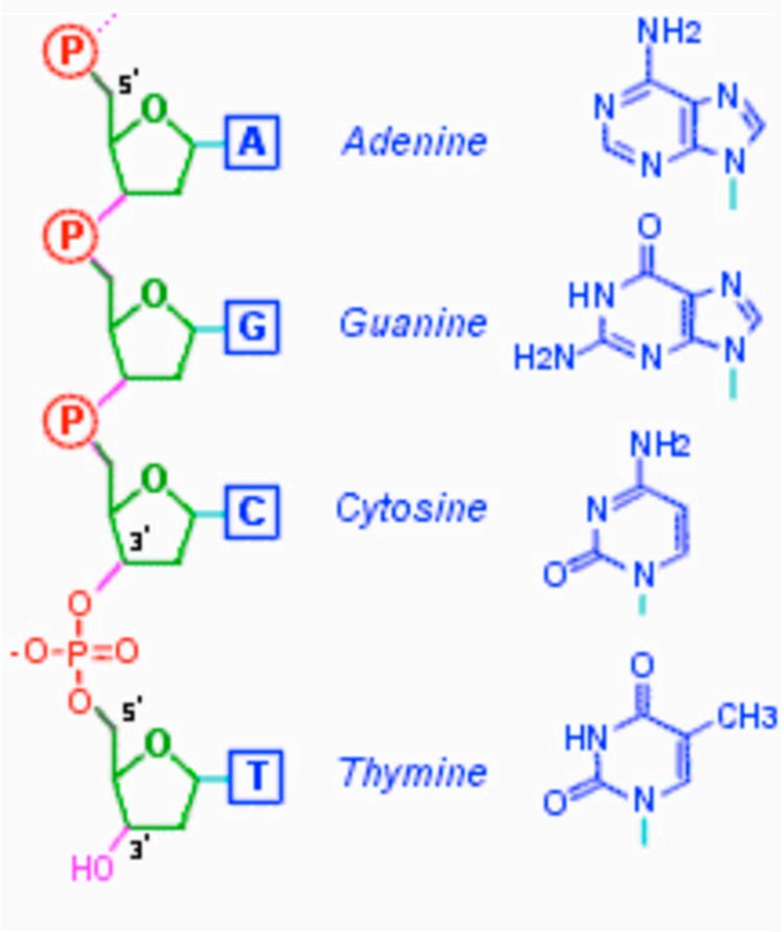


http://www.cell.com/trends/microbiology/fulltext/S0966-842X(12)00081-9

Antiviral Therapy for Herpesviruses – the 1980s…

- Viruses use cellular machinery to replicate.
- Antiviral therapy runs substantial risk of cytotoxicity, malignancy, teratogenesis.
- Therapies that interfere with the virus life cycle will also interfere with cellular physiology.



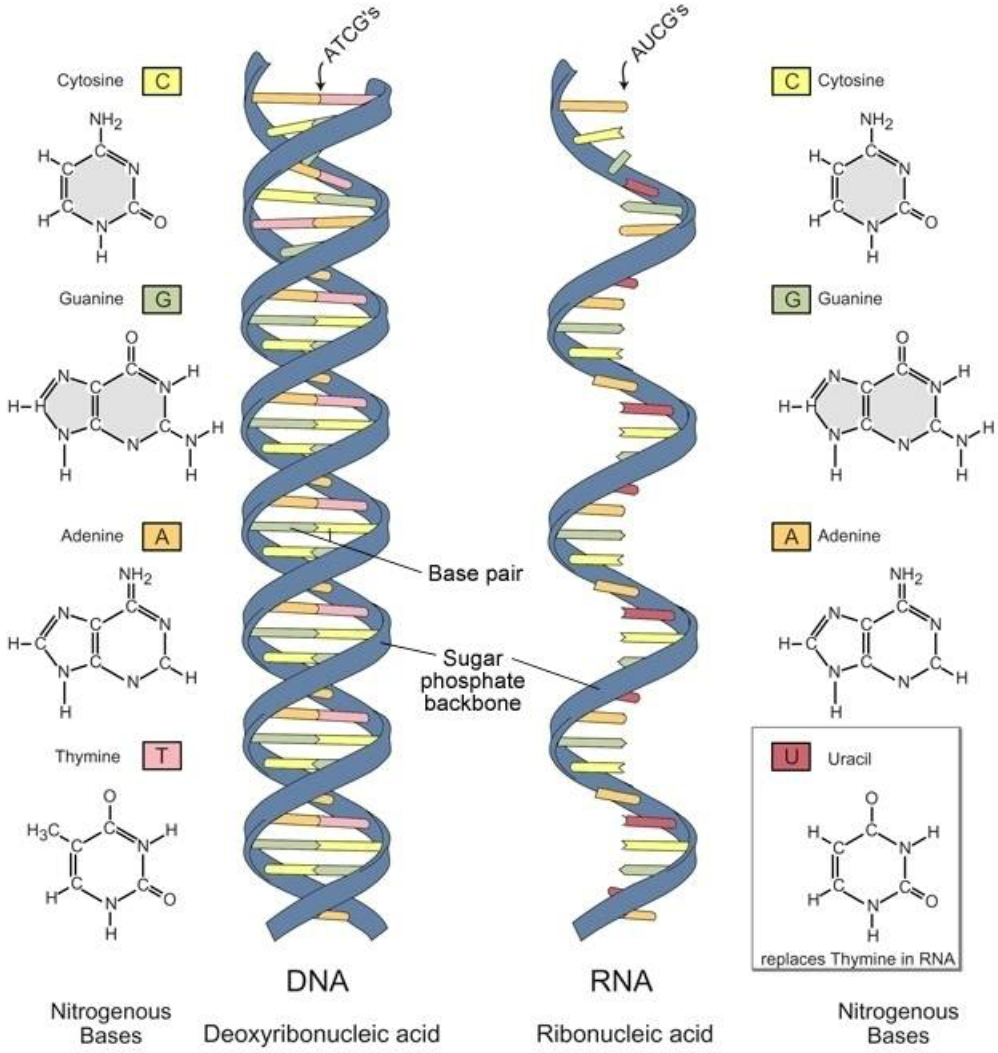
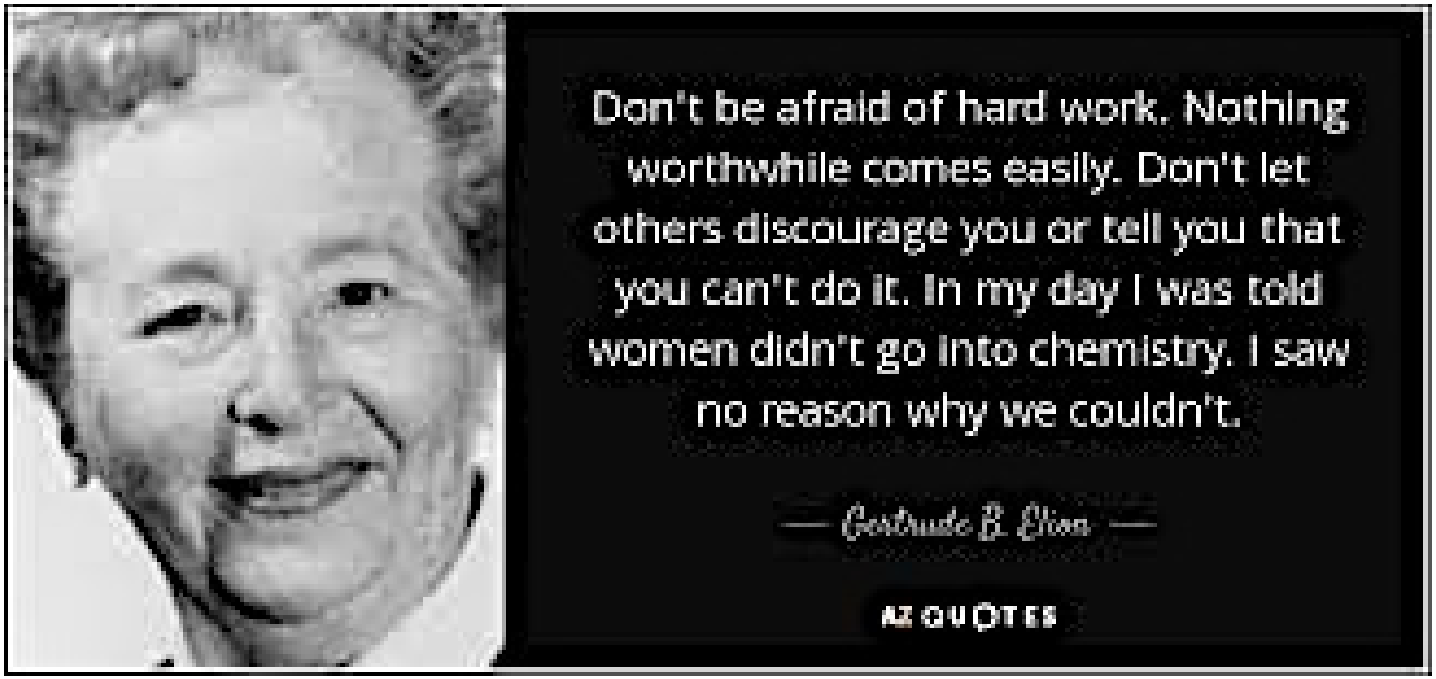
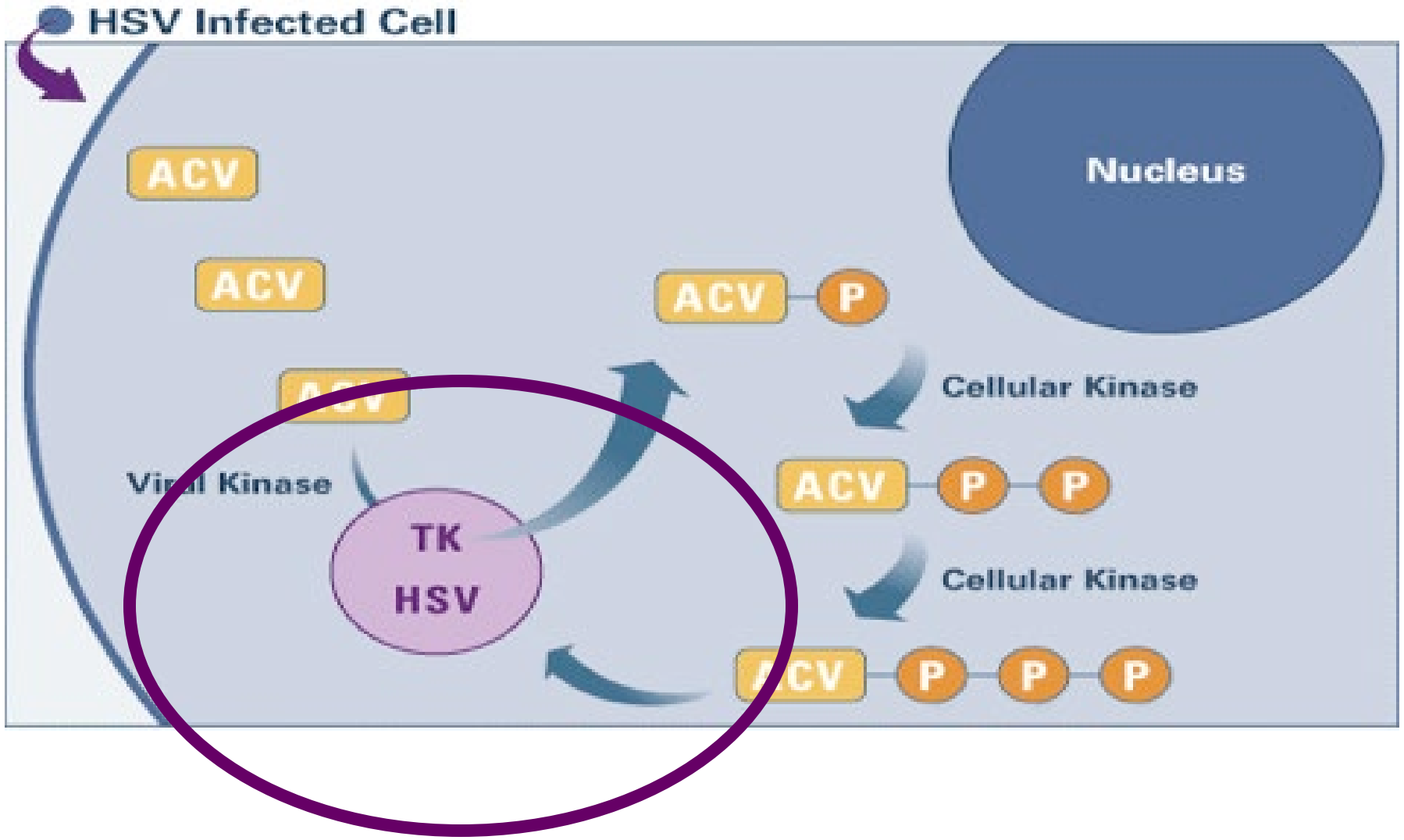


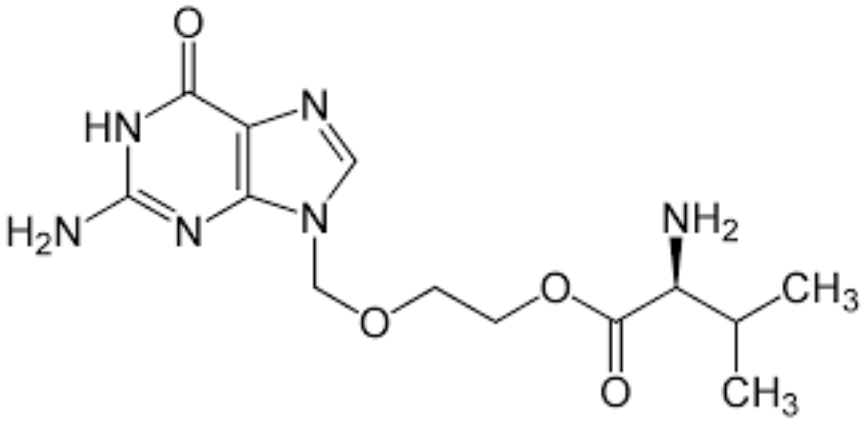
Image adapted from: National Human Genome Research Institute.


Don't be afraid of hard work. Nothing worthwhile comes easily. Don't let others discourage you or tell you that you can't do it. In my day I was told women didn't go into chemistry. I saw no reason why we couldn't.
— Gertrude B. Elion —
AZ QUOTES



https://sites.google.com/site/hlth106/acyclovir/acyclovir


We're In Love,
And She Has Herpes.
VALTREX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CH3
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CH3


I won't let
genital herpes
ruin my life!
Valtrex may cause extreme masterbation and blindness. Do not take Valtrex near puppies and babies.
VALTREX

JOGC Journal of Obstetrics and Gynaecology Canada
Journal d'obstétrique et gynécologie du Canada

Guideline No. 420: Cytomegalovirus Infection in Pregnancy

Isabelle Boucoiran, MD • Mark Yudin, MD • Vanessa Poliquin, MD • Sheila Caddy, MD • Soren Gantt, MD • Eliana Castillo, MD

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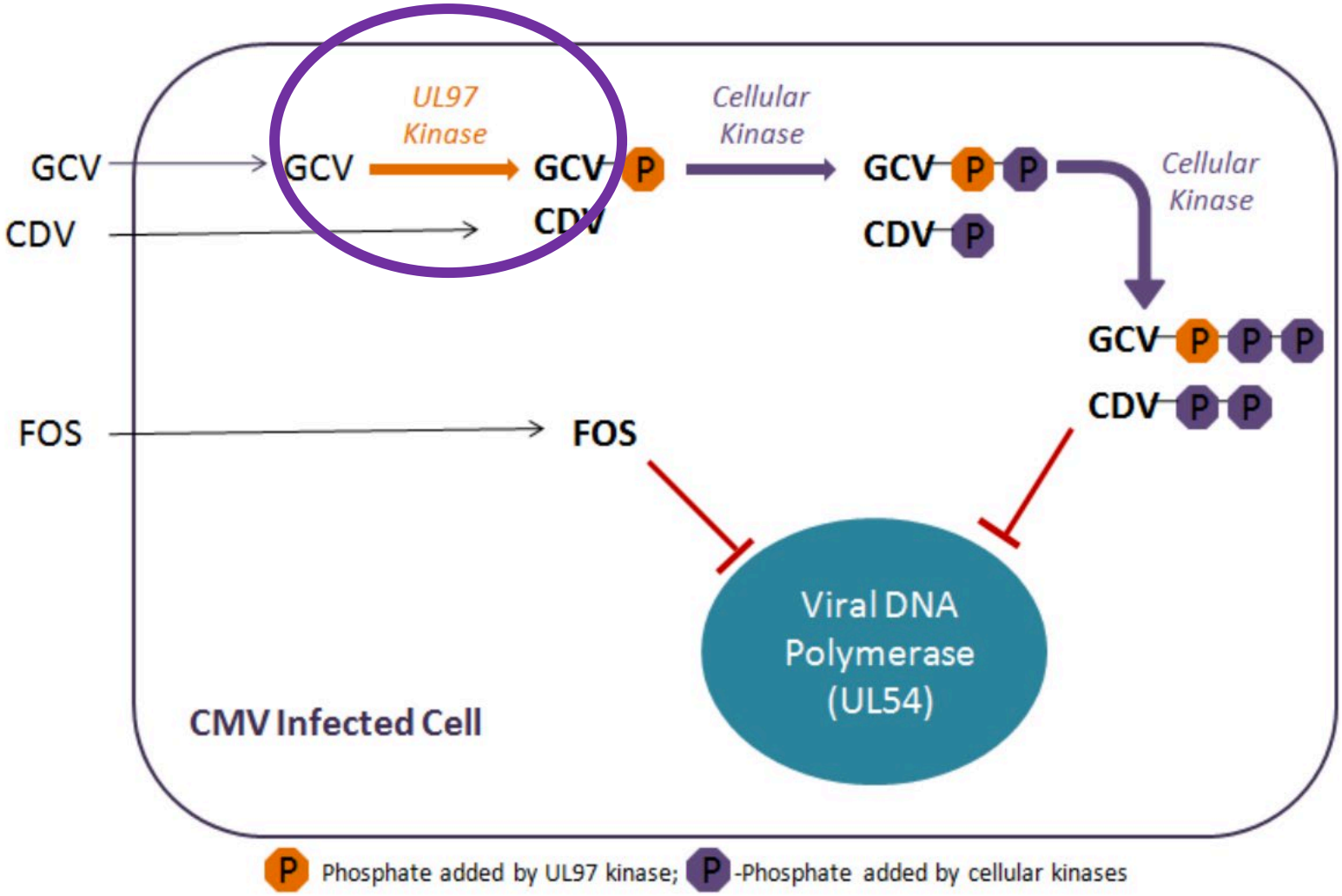
Maternal Antiviral Therapy to Treat or Prevent Congenital CMV Infection

Valacyclovir appears safe for use in pregnancy, even in the first trimester.[82,83] At a dosage of 8 g per day, it results in therapeutic concentrations in amniotic fluid and fetal blood.[84]



http://sites.utexas.edu/pharmacotherapy-rounds/files/2015/09/gordon11-01-13.pdf

Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 2767–2770, May 1983
Medical Sciences

Unique spectrum of activity of 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine against herpesviruses *in vitro* and its mode of action against herpes simplex virus type 1

(antiviral chemotherapy/acyclovir analog/DNA polymerase/thymidine kinase)

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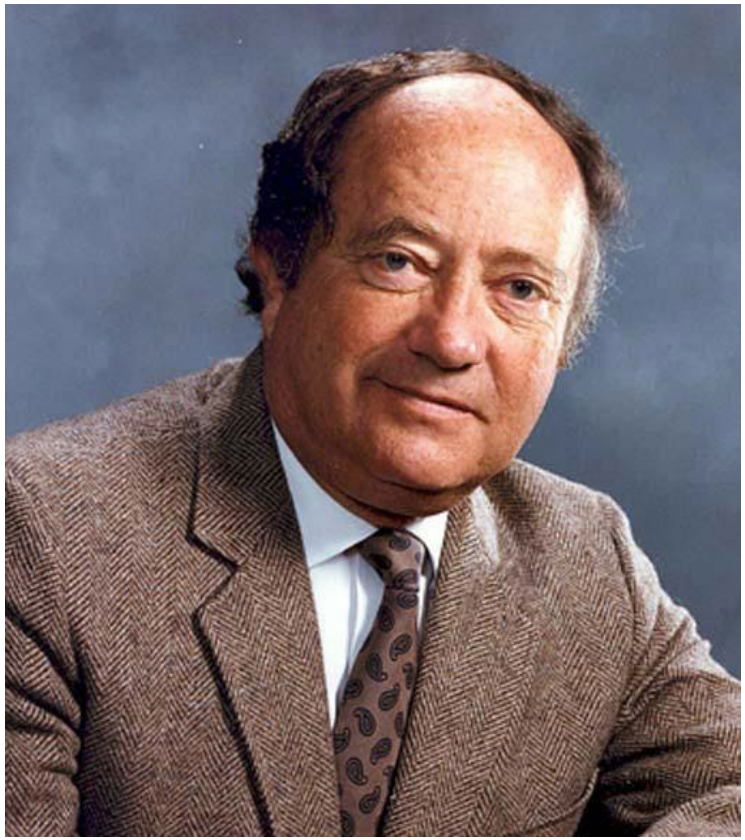
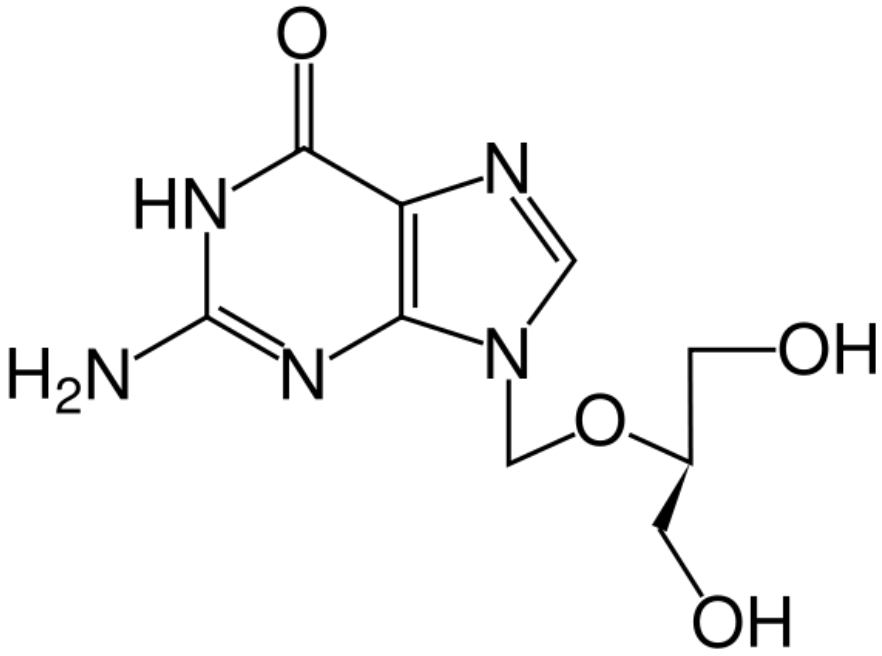
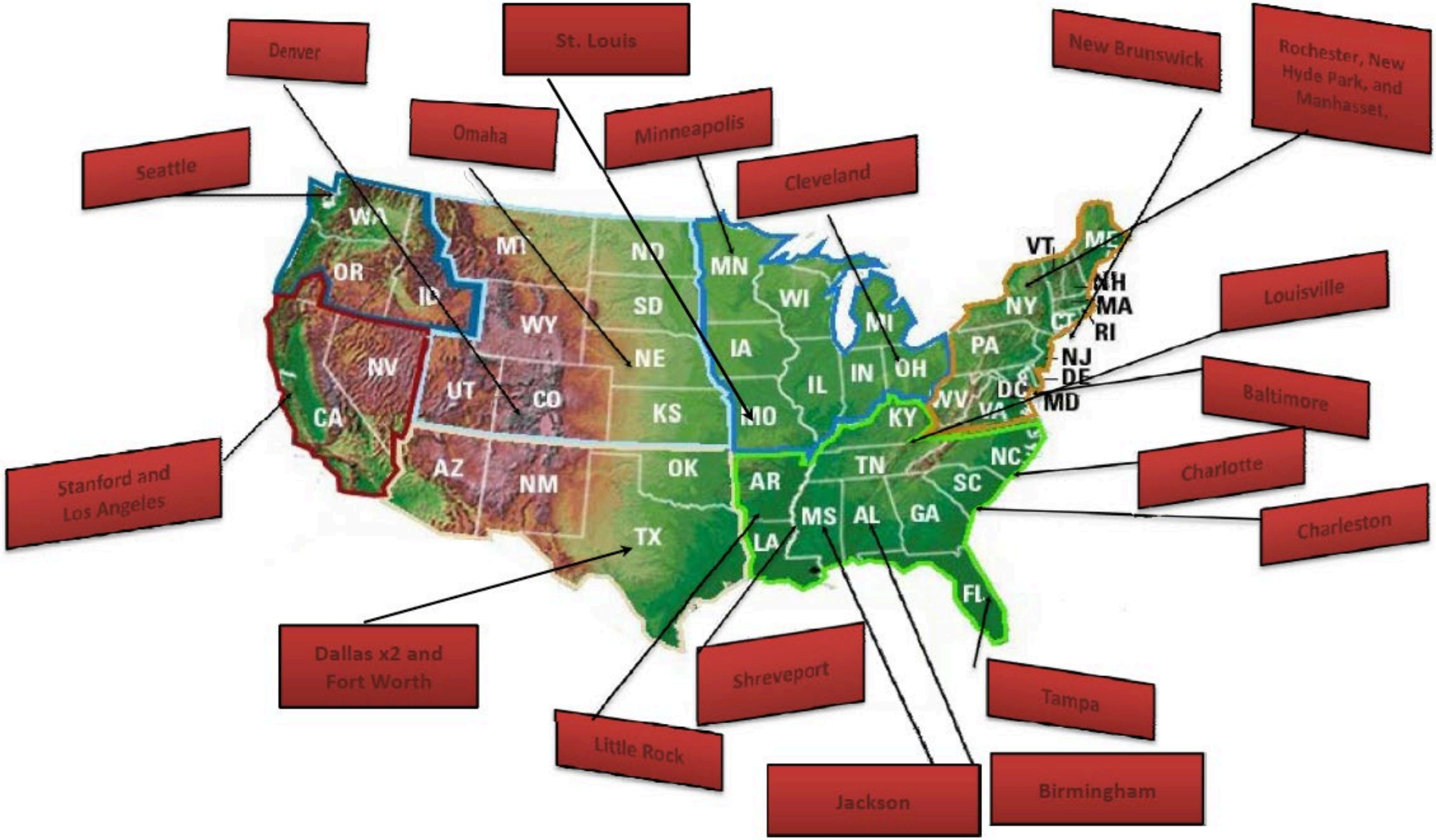
Communicated by Ernest L. Eliel, January 31, 1983







CASG 112 Active Sites

Drugs of the Future 2013, 38(5)

CCC: 0377-8282/2013
DOI: 10.1358/dof.2013.38.5.1946425

MONOGRAPH

LETERMOVIR

Rec INN

Treatment of Human Cytomegalovirus Infection
Antiinfective Agent

AIC-246

2-[8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4(*S*)-yl]acetic acid

InChI: 1S/C29H28F4N4O4/c1-40-20-6-3-5-19(16-20)35-11-13-36(14-12-35)28-34-27-21(7-4-8-22(27)30)23(17-26(38)39)37(28)24-15-18(29(31,32)33)9-10-25(24)41-2/h3-10,15-16,23H,11-14,17H2,1-2H3,(H,38,39)/t23-/m0/s1

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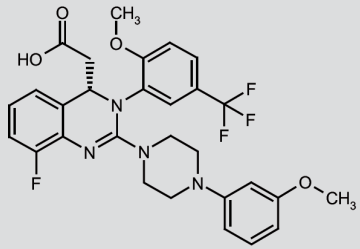
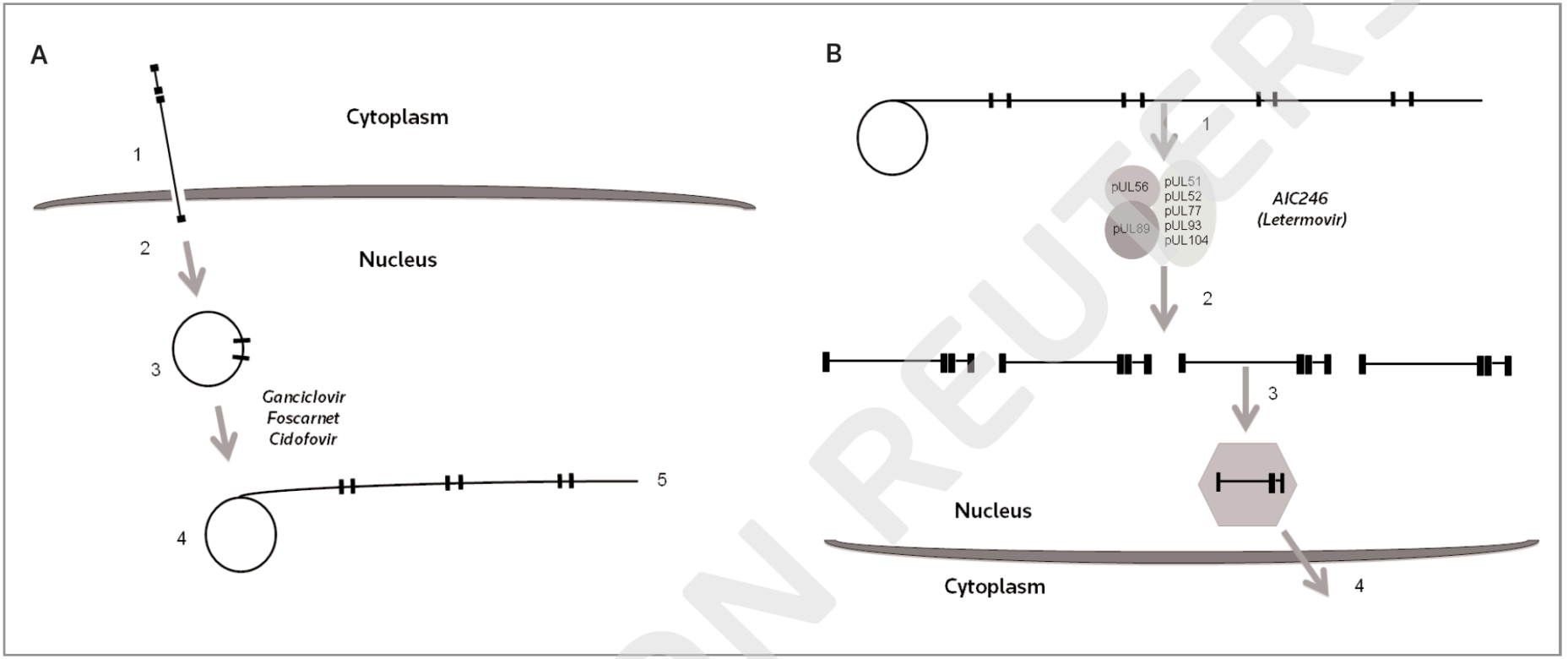



A
Cytoplasm
1
2
Nucleus
3
Ganciclovir
Foscarnet
Cidofovir
4
5
B
1
pUL56
pUL89
pUL51
pUL52
pUL77
pUL93
pUL104
AIC246
(Letermovir)
2
3
Nucleus
Cytoplasm
4

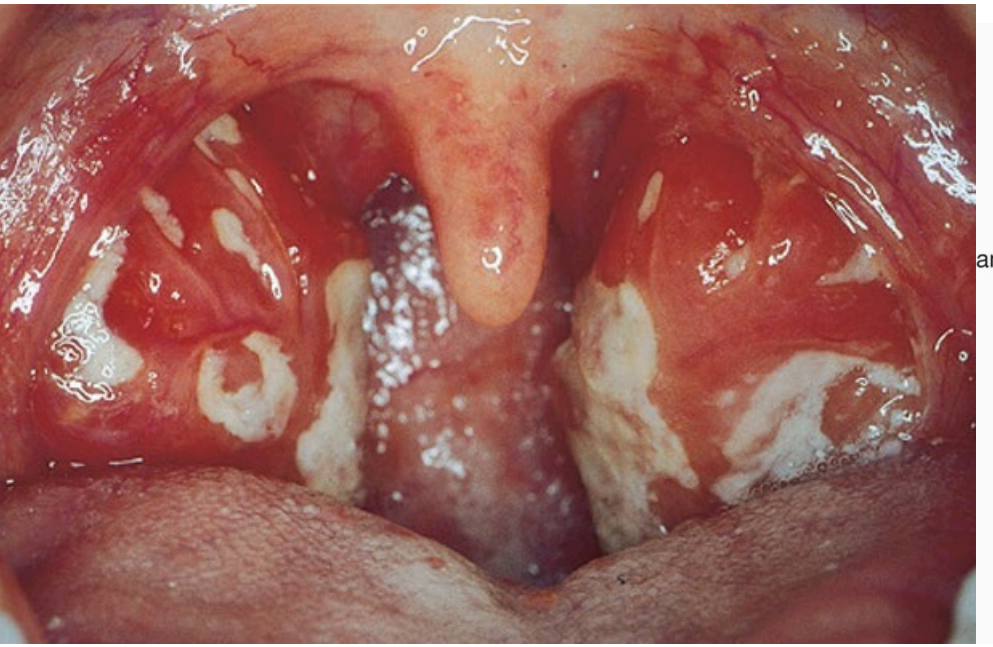
Cytomegalovirus: Disease

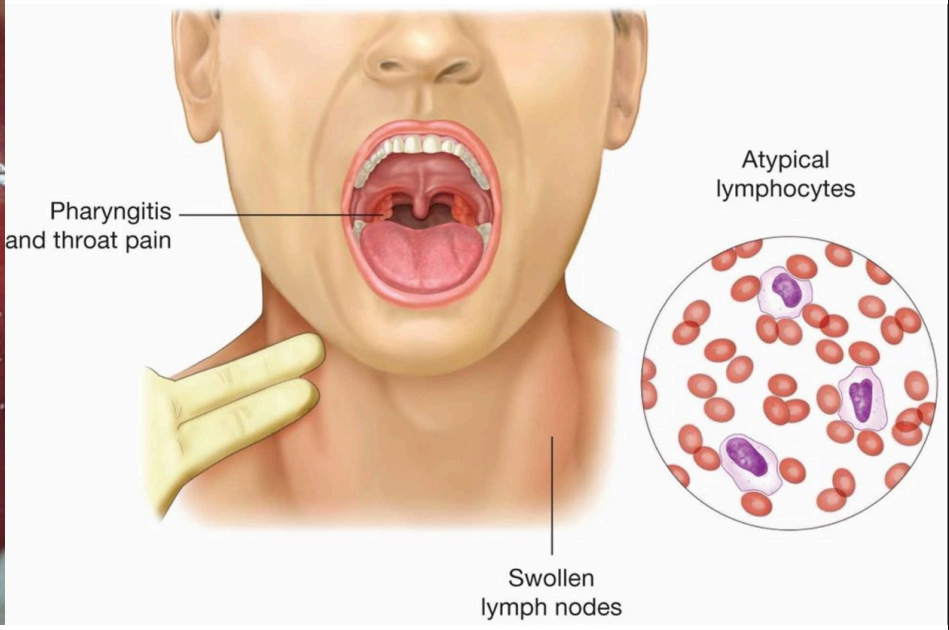
Cytomegalovirus Disease

- Mononucleosis
- Transplant Patients
- HIV
- Congenital Infection
- Long-term Health Consequences?

2010s Dogma: Outside of Transplantation and Newborns, CMV is not a "Pathogen"

- An incidental finding.
- No short-term diseases attributable to CMV.
- No long-term disabilities or health consequences.
- No role for therapy/prevention.





http://www.healthline.com/health/mononucleosis#Overview1

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Cytomegalovirus Reactivation in Critically-Ill Immunocompetent Patients

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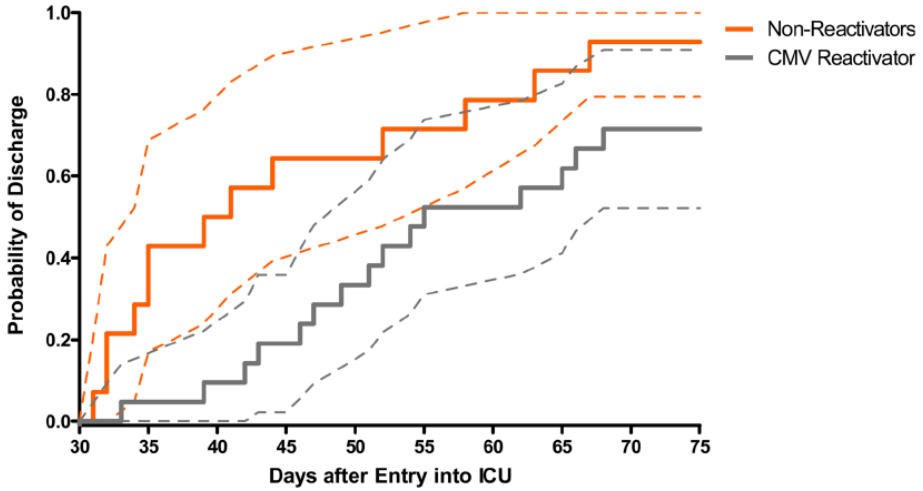
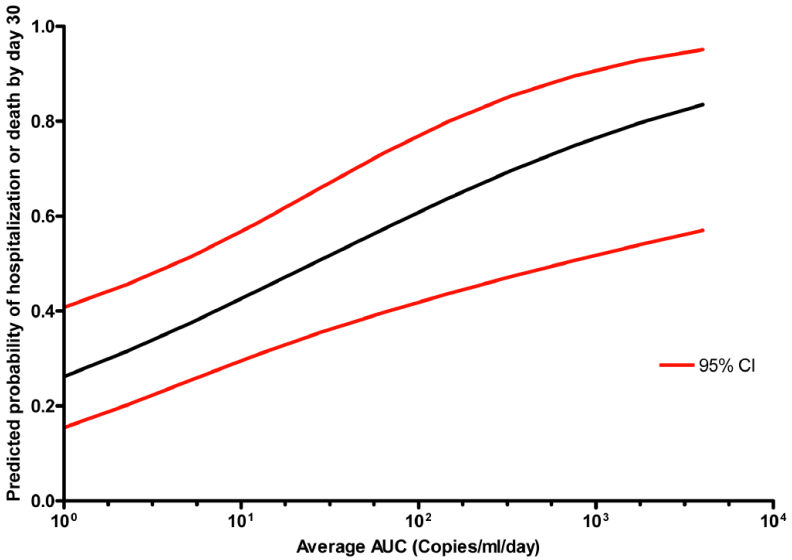
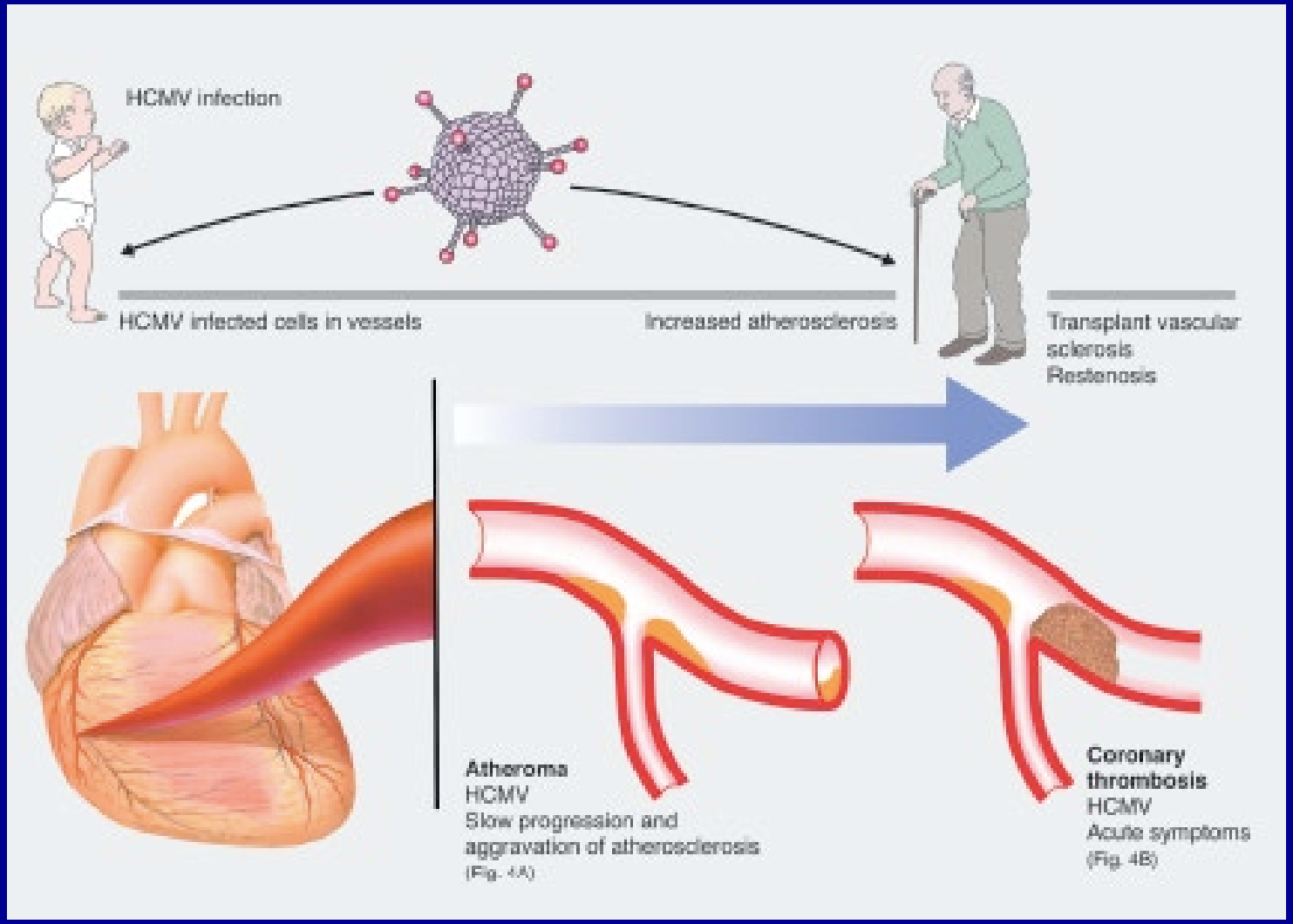
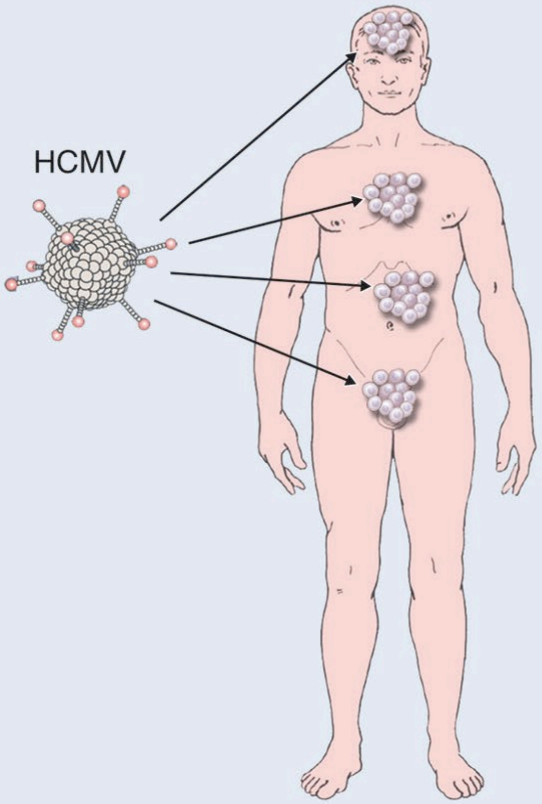




Does Cytomegalovirus Play a Causative Role in the Development of Various Inflammatory Diseases and Cancer?



Söderberg-Nauclér C. *J Intern Med*. 2006;259:219-246.



Malignant glioblastoma

Breast cancer

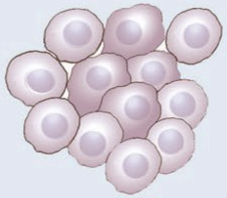
Colon cancer

Lymphoma

Prostate cancer

HCMV infection

Oncomodulation



Cancer

- HCMV may influence cell cycle progression
- HCMV IE86 binds to and inactivates p53
- HCMV –> ↑expression of proto-oncogenes
- HCMV affects epigenetic patterns?

=> control of cellular differentiation, gene expression, DNA replication

Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

Current Opinion in Virology

Does public perception of exposure risks and transmission mechanisms drive antiviral vaccine awareness? What if cytomegalovirus was transmitted by mosquitoes?

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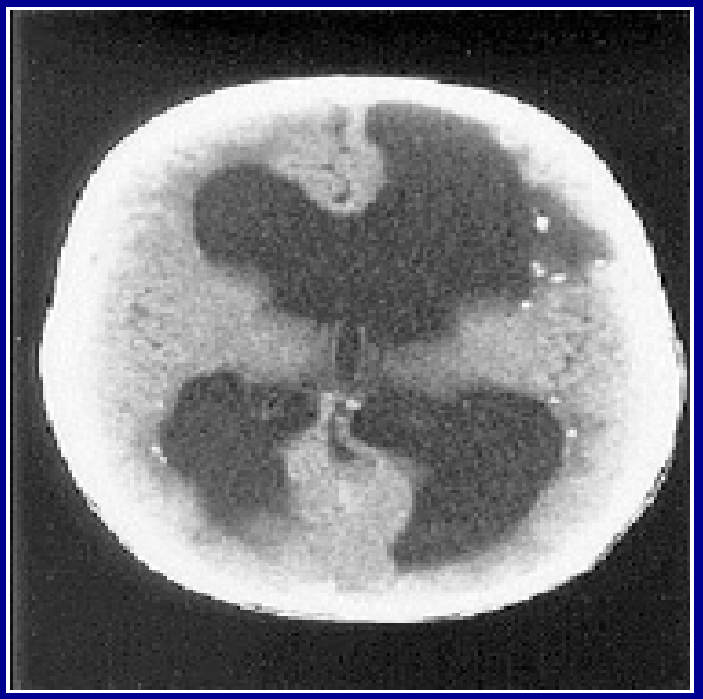
Congenital Cytomegalovirus Infection

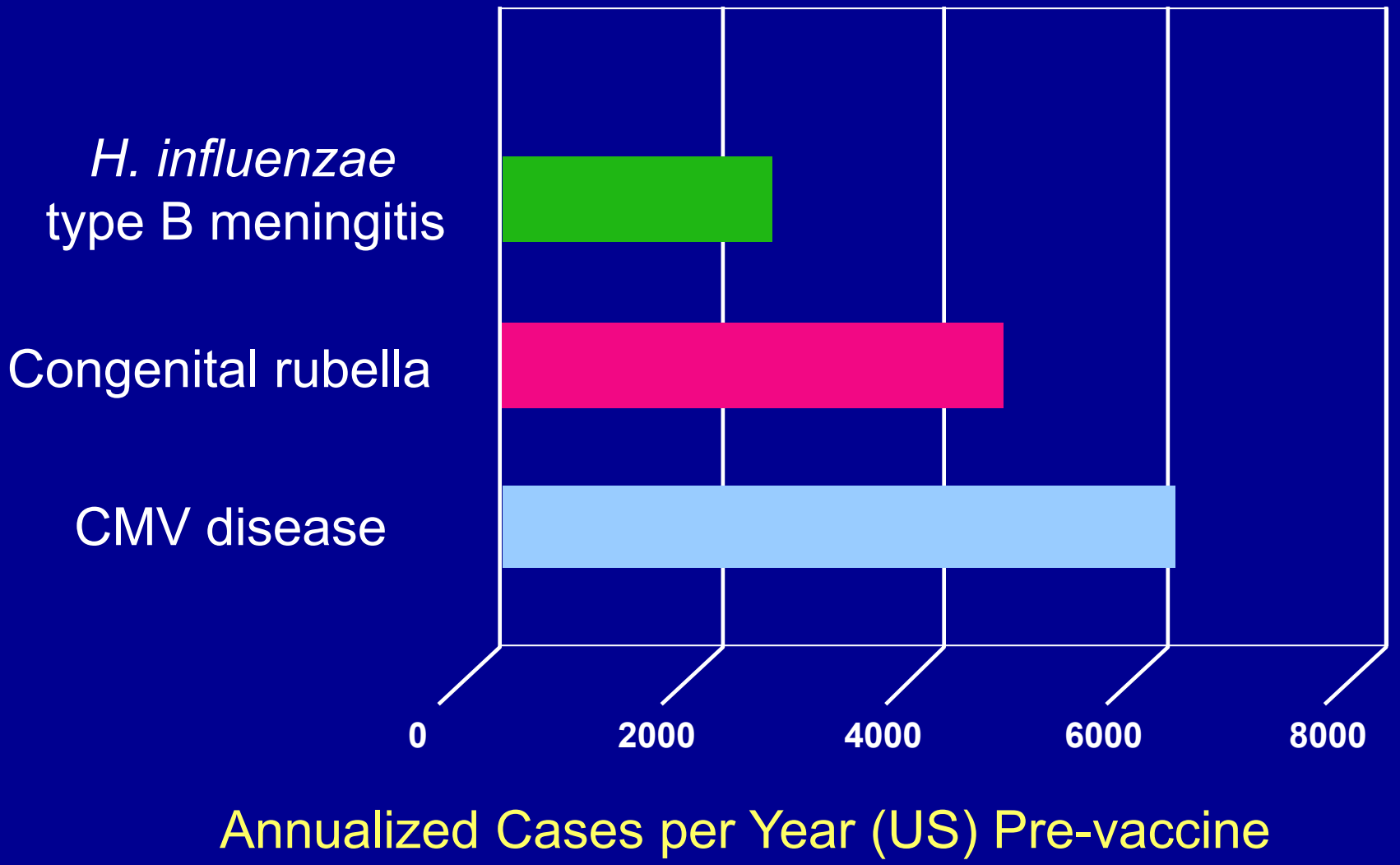
- Most common congenital viral infection in developed world (1% of all deliveries)
- Most pregnant women have no symptoms that trigger concern about possibility of CMV
- Leading cause of sensorineural hearing loss and developmental delay
- Lack of awareness among women, obstetricians, primary care physicians and lay public

Congenital CMV Infection

- The most common infectious cause of neurodevelopmental abnormalities in the United States (seizures, CP, MR, SNHL)



Infectious Causes of Neurologic Damage in Infancy

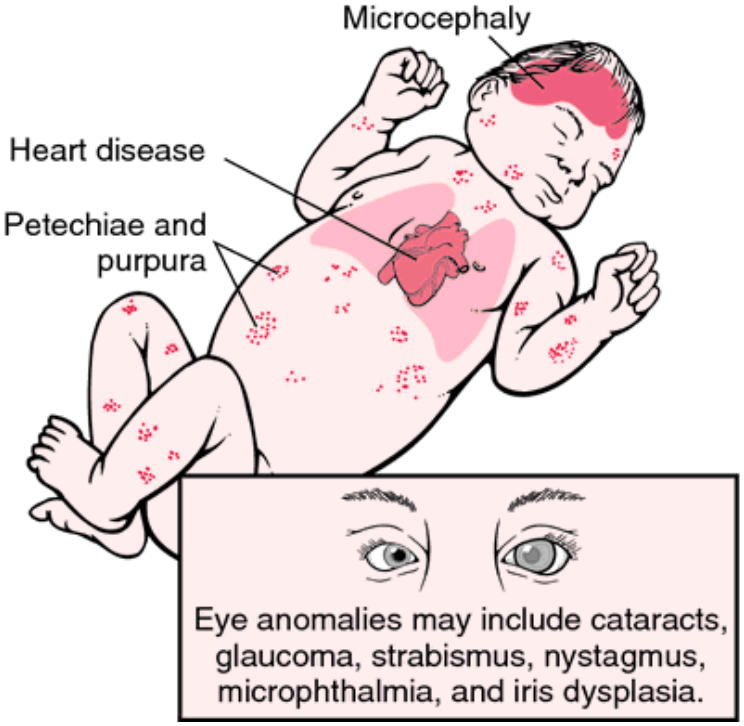


Public Health Impact of Congenital CMV Infection in USA

	Estimated
Number of live births	4,000,000
Rate of congenital HCMV infection	1/100
Number of infected infants	40,000
Symptomatic at birth (10%)	4,000
Fatal disease (10%)	40
Sequelae (60%)	2,400
Asymptomatic at birth (90%)	36,000
Sequelae (10%)	3,600
Total number with sequelae	6,000


RUBELLA
Is her unborn baby safe from rubella?
Clinical manifestations of congenital rubella as observed in 344 infants, correlated with time of maternal rubella
Birth defects occur in about 50 per cent of babies born to mothers who contract rubella during their first trimester of pregnancy.


LIFE
GERMAN MEASLES AND PREGNANCY
Current U.S. epidemic will damage
2NeatBooks.com


Microcephaly
Heart disease
Petechiae and purpura
Eye anomalies may include cataracts, glaucoma, strabismus, nystagmus, microphthalmia, and iris dysplasia.

Newborn Screening for CMV– the 2000s…

- Most infants with CMV will be normal.
- Screening raises undue anxiety in families.
- Nothing can be done to improve the prognosis.
- Antiviral therapy will be too toxic.

Diagnosis: Mothers and Infants

- Antibody
- Antibody Avidity
- Culture
- Antigenemia
- Nucleic Acid (DNA) Detection
  - Blood spots
  - Urine
  - Saliva

TORCH Titers

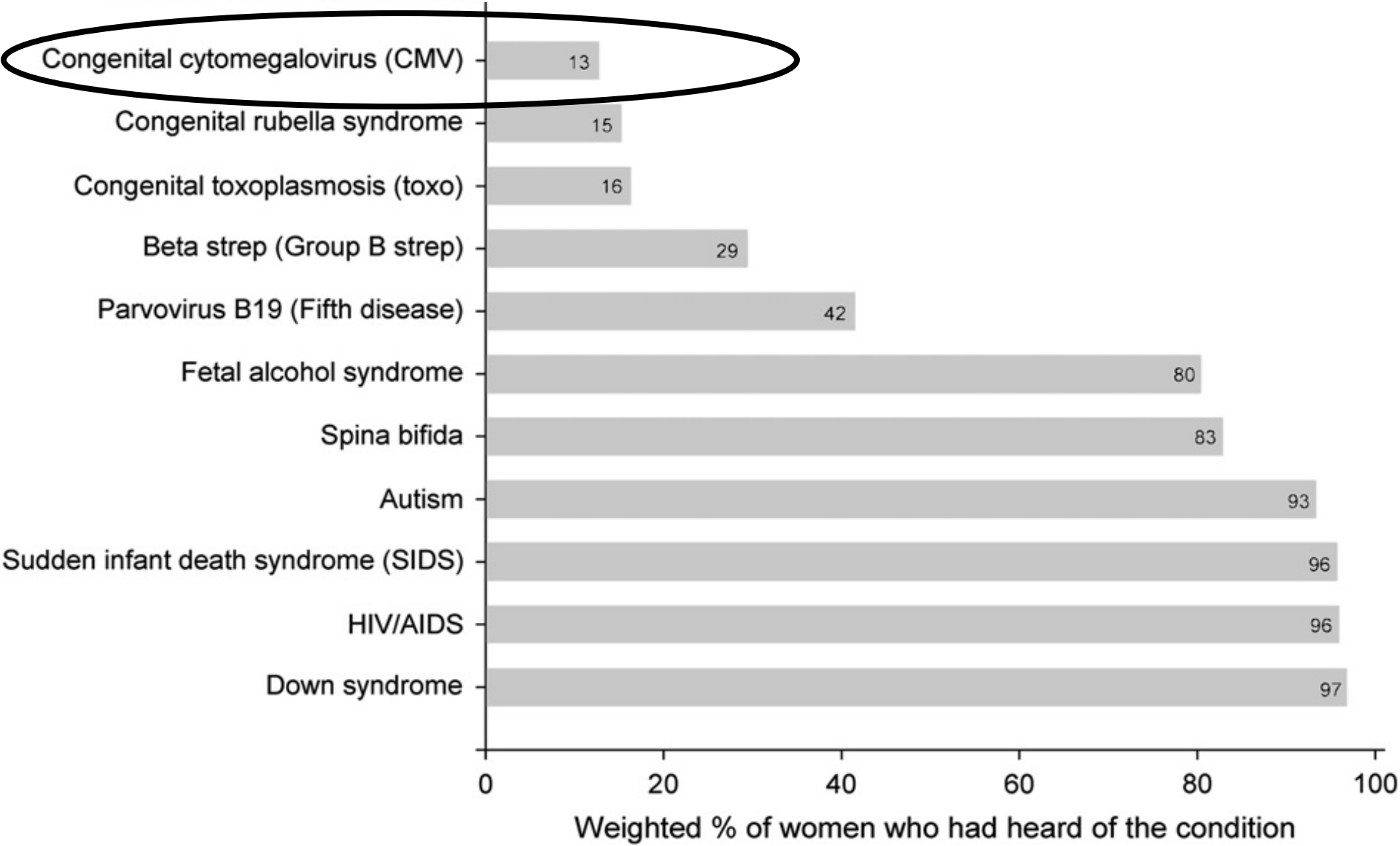
CMV Prevention– the 2010s Dogma…

- No measures are known to prevent acquisition.
- Immunity prior to pregnancy is protective.
- People won't change behaviors.
- A vaccine is the only answer.

Awareness of and behaviors related to child-to-mother transmission of cytomegalovirus ☆

Michael J. Cannon [a,*], Kyresa Westbrook [a], Denise Levis [a], Mark R. Schleiss [b], Rosemary Thackeray [c], Robert F. Pass [d]

Preventive Medicine 54 (2012) 351–357



Debate

Highly accessed | Open Access

Washing our hands of the congenital cytomegalovirus disease epidemic

Michael J Cannon[1,2] and **Katherine Finn Davis**[1,3]

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3 Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Georgia, USA

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BMC Public Health 2005, **5**:70 doi:10.1186/1471-2458-5-70

- Thoroughly wash hands with soap and warm water after activities such as:
  - Diaper changes
  - Feeding or bathing child
  - Wiping child's runny nose or drool
  - Handling child's toys
- Do not share cups, plates, utensils, toothbrushes, or food
- Do not kiss on or near the mouth
- Do not share towels or washcloths
- Clean toys, countertops and other surfaces that come in contact with urine or saliva.

- **CMV infection is neither preventable nor treatable...**
- **It is not certain that infections in pregnant women can be prevented by avoiding exposure...**
- **It is doubtful whether parents will comply with these behavioral measures in non-study settings...**
- **There is very little evidence for the efficacy of these strategies and even less for their practical implementation...**
- **The only effective prevention strategy relies upon the development of a vaccine...**
- **The quest for a CMV vaccine is also driven by the absence of good alternative strategies. Susceptible women can be identified by serologic testing before pregnancy, but avoiding CMV exposure is difficult, since women may have sexual partners with CMV infection or may be exposed to young children during the pregnancy (Arvin and Dekker)**

The Case for Screening Newborns for Congenital CMV

- 10-15% of infants born with CMV will have neurodevelopmental sequelae
- Anti-viral treatments are available
- Therapy alters neurodevelopmental outcome in symptomatic infants
- Most infants who develop SNHL pass the newborn hearing screen

Legislative News and Views - Rep. Kelly Fenton (R)

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Vivian Act Introduced in Legislature to Promote Education, Awareness and Detection of Congenital CMV Virus

Thursday, May 11, 2017

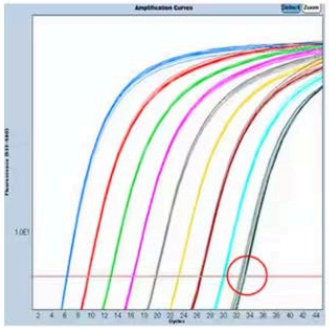
Tweet

SF 2383/HB 2653
March, 2017

Subd. 3. **Commissioner duties.** (a) The commissioner shall make available to health care practitioners and women who may become pregnant, expectant parents, and parents of infants up-to-date and evidence-based information about congenital CMV that has been reviewed by experts with knowledge of the disease. The information shall include the following:

(1) the recommendation to consider testing for congenital CMV in babies who did not pass their newborn hearing screen or in which a pregnancy history suggests increased risk for congenital CMV infection;

Minnesota Newborn Screening Program Commences DBS CMV Screening on 2/8/2023



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NIH National Institute of Allergy and Infectious Diseases

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

NIH R01HD098866
R01 HD079918
R21 AI158019

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