Infectious cause for non-infectious disease

Cytomegalovirus:review of BDORT and medical literature

- Yoshiaki Omura M.D.. discovered the BDORT in 1977 and used it to reveal the previously described
- “resonance phenomenon” and
- The “therapeutic effect”,
- ”selective drug uptake enhancement method”.

With these techniques, Dr. Omura has discovered substances and pathogenic organisms that have a role in chronic disease and proposed treatments for those conditions.

A significant pathogen in chronic disease detected by BDORT is the Cytomegalovirus.

Albert Einstein said:

- “I have no special talents. I am only passionately curious.”

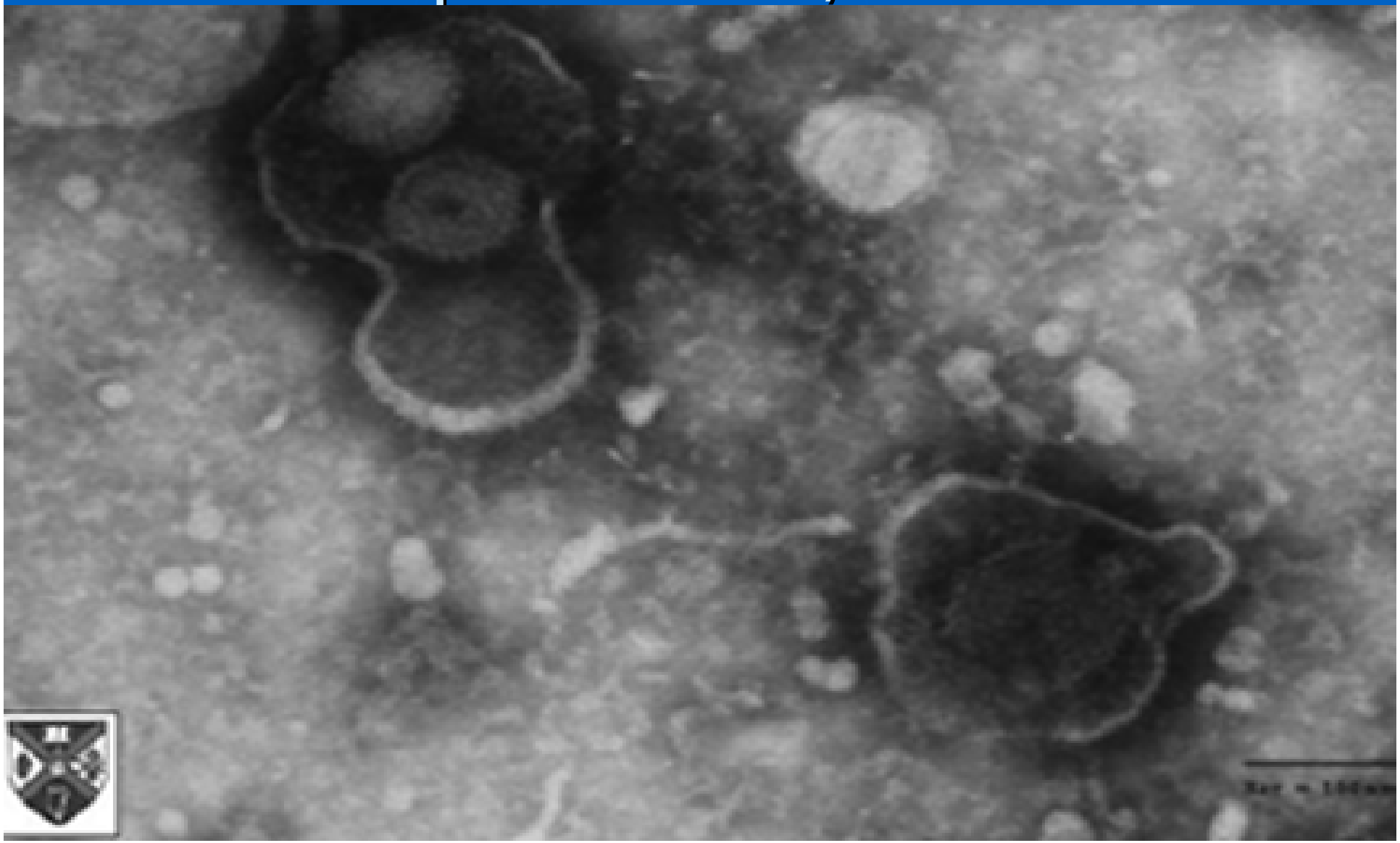
OVERVIEW

- Cytomegalovirus (CMV) causes asymptomatic infections, serious congenital infections, heterophile-negative mononucleosis in adults, and fever hepatitis syndrome in neonates transplant recipients.

EPIDEMIOLOGY

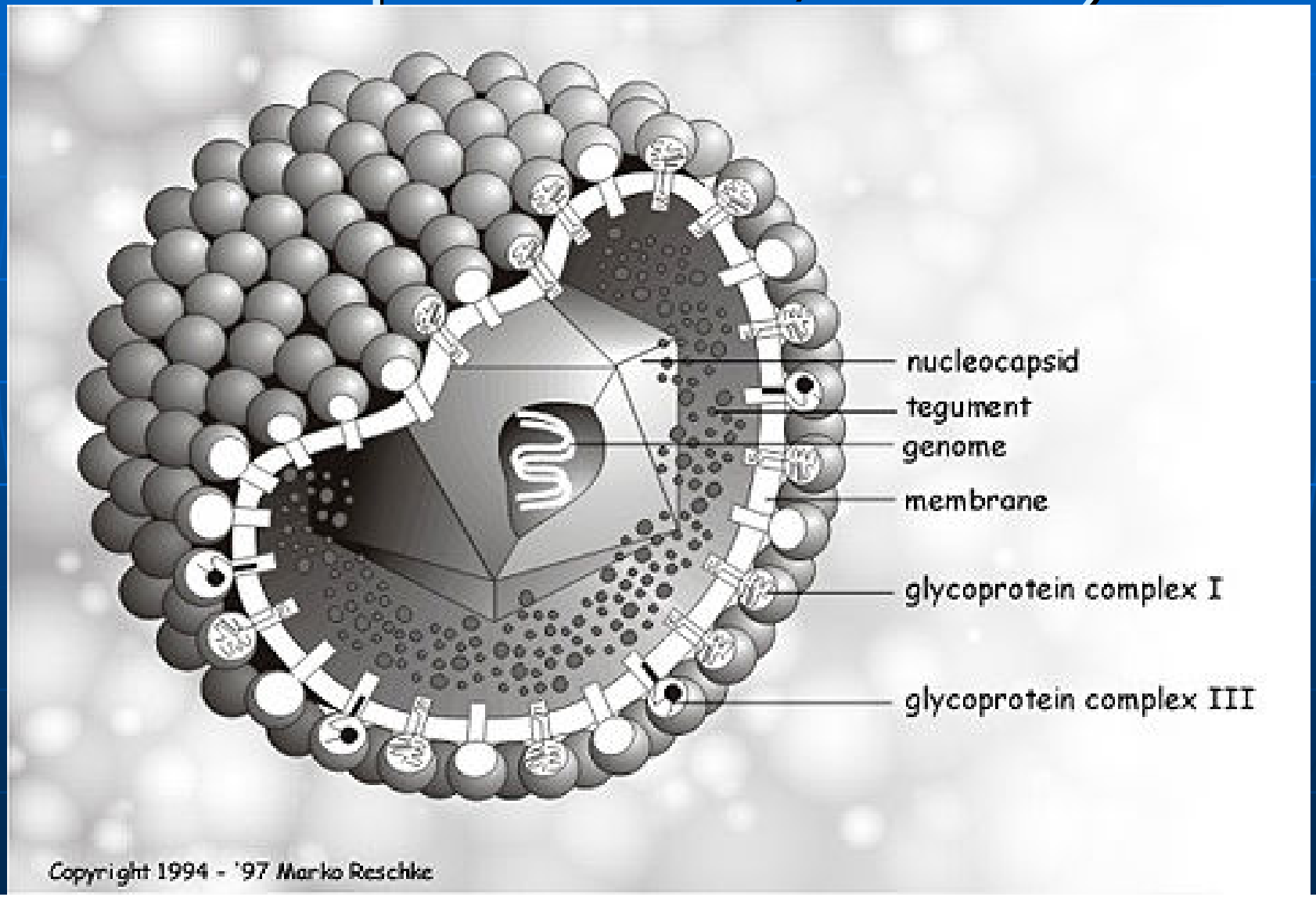
- **Incidence:** CMV is ubiquitous, and at least 80% of adults (worldwide) have antibody to it. Infection rates are highest below age 6 and are elevated for young adults. The rate of CMV infection in adolescents of well-developed countries is about 10-15%, increasing to about 50% when 35 years old.

Etiology: CMV is the Human Herpes Virus 5; HHV-5

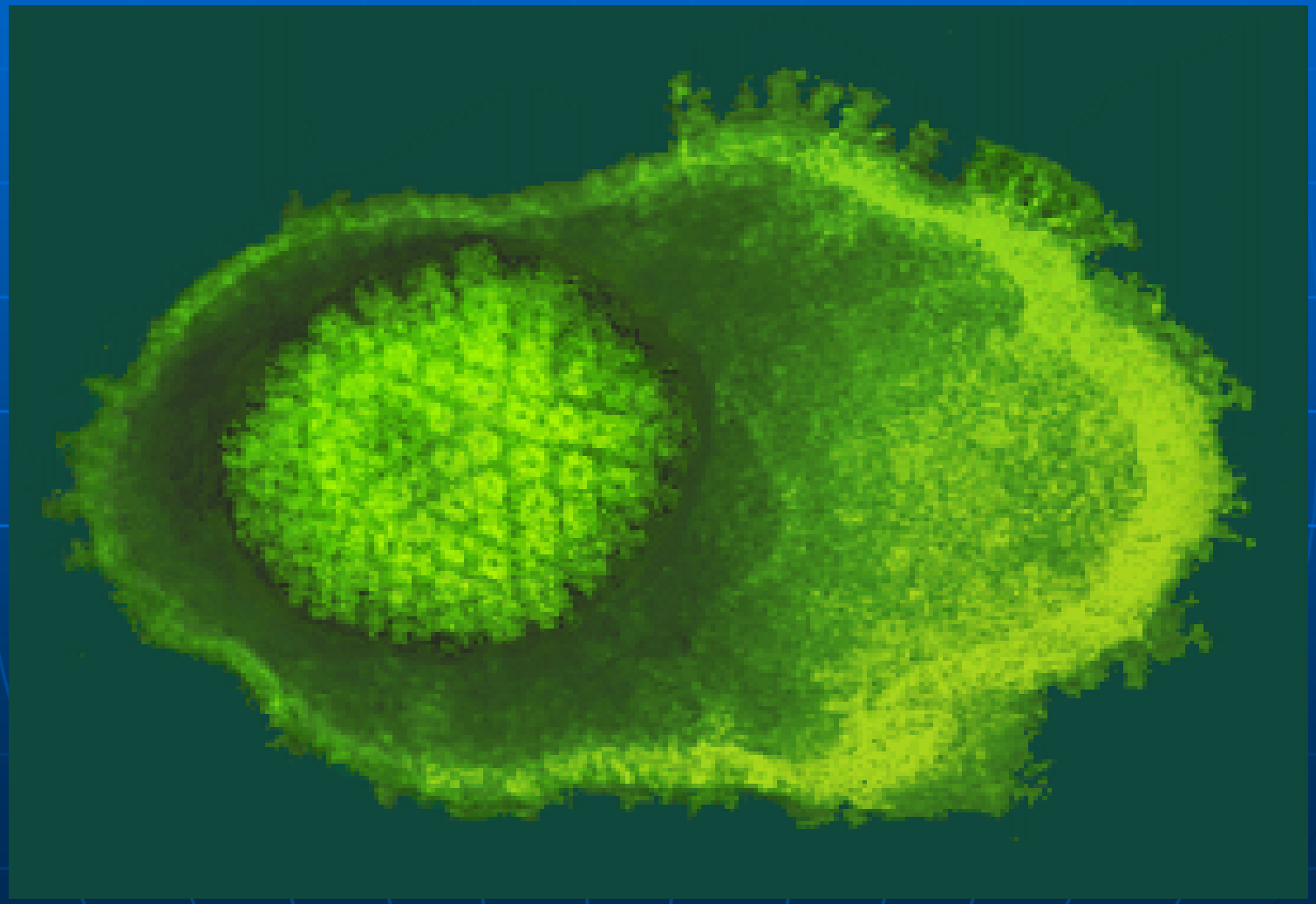


CMV Lifecycle

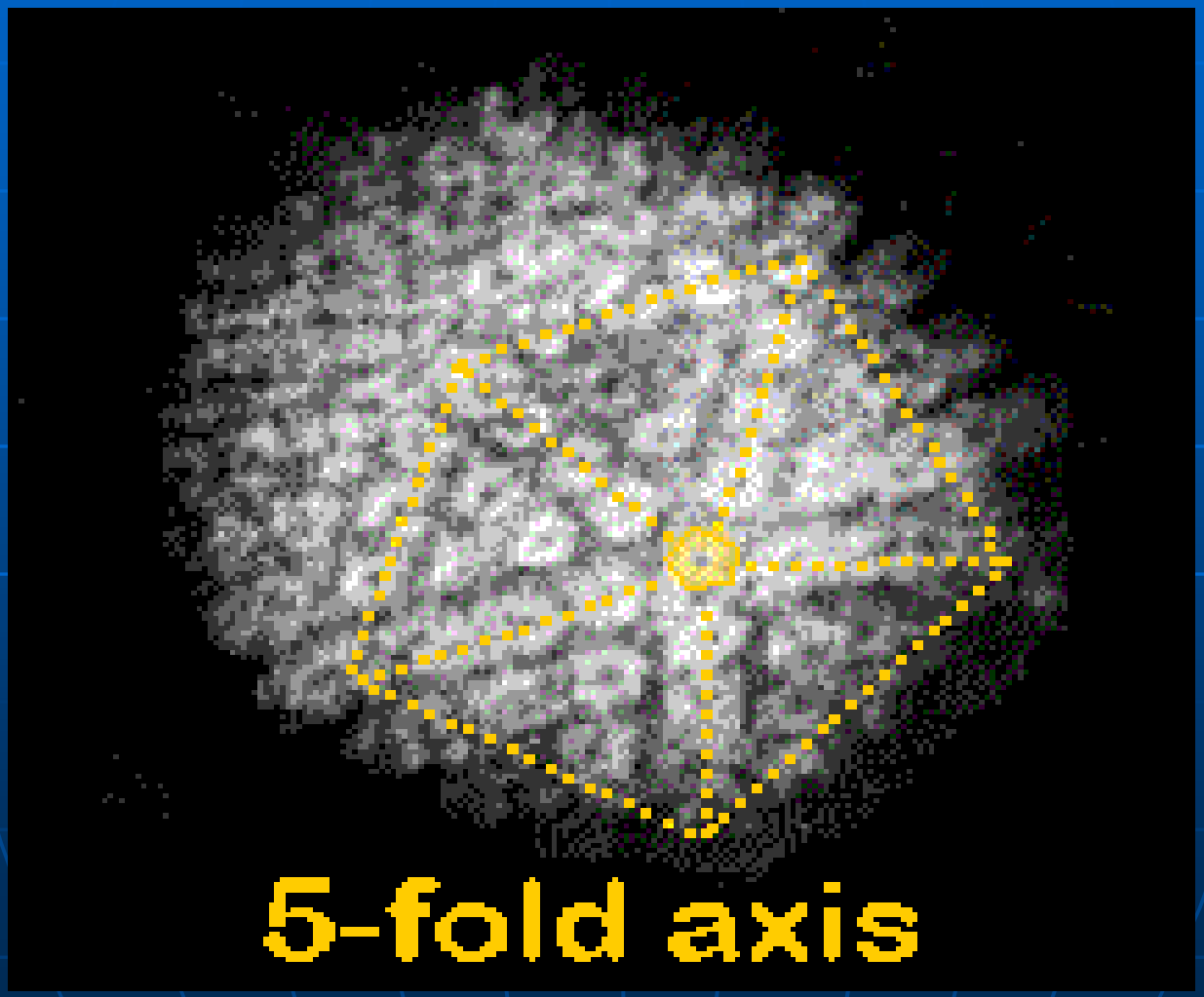
CMV, a herpes virus (Human Herpes Virus 5; HHV-5)



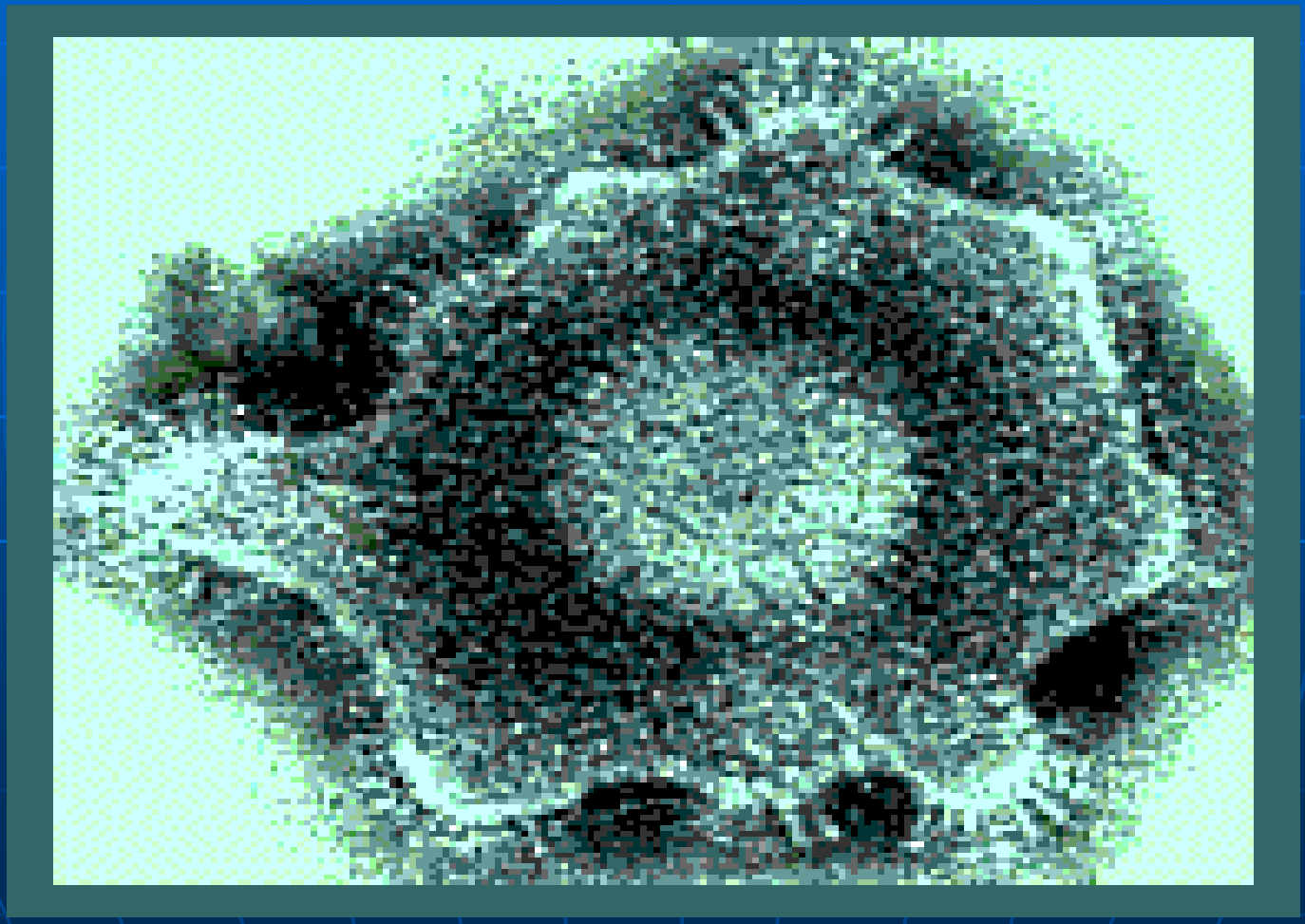
CMV electronmicrograph



CMV capsid structure



CMV micrograph 2



Source:

- CMV has been isolated from urine, blood (harbored within leukocytes), throat washings, saliva, tears, breast milk, semen, stools, amniotic fluid, vaginal and cervical secretions, as well as tissues taken for transplantation.

Routes of transmission:

- **Congenital infection:** virus ascends from the cervix (viral reactivation in immune mothers) or invades from the maternal blood (mothers with primary infection).
- **Perinatal infection:** Approximately 20% of pregnant women at term harbor CMV in their cervix; mostly reactivation. Neonates may acquire CMV during passage through the birth canal or later from breast feeding.

Infection in adults

- **Oral**
- **Sexual transmission**
- **Postneonatal CMV infection** rates are increased under crowded living conditions, with some role for sexual transmission.
- **Posttransfusion infection.**
- **Infection following transplantation.** CMV may be transmitted by organ transplantation. Sero-positive recipients may reactivate the virus due to immunosuppressive therapy.

- **Major means by which CMV is transmitted; sexual route (heterosexual and homosexual), transfusions, and transplants.**

PATHOGENESIS

- Usually CMV infections are subclinical.
- CMV infects epithelial cells and lymphocytes.
- CMV is highly cell-associated and spreads to coalescing cells. This close cell-interaction protects the virus from antibody inactivation.

Pathogenesis

- **Latency:** Eventually CMV attains a latent state and persistent infection within T-cells, endothelial cells and monocyte-derived macrophages.
- Cell-mediated immunity is required for resolution of symptoms and also contributes to symptoms. Antibodies role is limited.
  Suppression of cell-mediated immunity allows recurrence of symptoms and can result in severe disease

Pathogenesis

- **Immunosuppression:** The virus also has the ability to induce immunosuppression in the body.

MANIFESTATIONS

- **Congenital infection.** 0.2% to 2% of all newborns are infected with CMV. Fetuses can be infected via their mother's bloodstream during a primary infection of the mother or by virus ascending from the cervix (during a recurrence). Symptoms of a congenital infection are usually less severe or can be prevented in the fetus of a seropositive mother. Approximately 10-15% (4000 per year) of infants infected *in utero* via a primary maternal infection show classic CMV inclusion disease and may exhibit teratogenesis:
-

MANIFESTATIONS

- **Neonatal infection.** As many as 20% of pregnant women harbor CMV in their cervix at term and are likely to experience reactivation of CMV during their pregnancy. 50% of the neonates born through an infected cervix acquire CMV and become excreters of the virus at 3-4 wks. CMV infection from maternal milk or colostrum. Healthy infants who acquire CMV at birth usually show **NO** symptoms of disease.
- **CMV is the most common viral cause of congenital defects.**


term newborn was covered with reddish purple 0.5-1 cm nonblanching macules and papules.found to have microcephaly and hepatomegaly. A skin biopsy showed extramedullary hematopoiesis, and head US showed diffuse calcifications. typical of cytomegalovirus or TORCH infection in the newborn.

MANIFESTATIONS

- Microcephaly
- thrombocytopenia with petechiae or purpura
- intracerebral calcification
- hepatosplenomegaly
- chorioretinitis rash seizure disorders
- jaundice
- mental retardation
- hearing loss (1-3% of cases)
- interstitial pneumonia

Infection in immunocompetent hosts

- Infection is usually asymptomatic in infants &children. or“Flu”or pseudo-mononucleosis
- Complications of infection are uncommon in immunocompetent hosts, but include:
  - Guillain-Barre syndrome.
  - Meningoencephalitis
  - Pericarditis
  - Mycocarditis
  - Thrombocytopenia
  - Haemolytic Anemia.
  - Gastrointestinal ulceration.

- **Infection in children and adults.**
- Only 10-15% of adolescents are infected with CMV however this number increases to 50% by 35 years of age.
- CMV is sexually transmitted. 13 to 23% of women visiting venereal disease clinics have CMV isolated from their cervix.
- CMV concentrations in semen is the highest of all body secretions

- Young adults who are infected with CMV are generally asymptomatic, but may develop an infection resembling infectious mononucleosis similar to Epstein-Barr called heterophile-negative mononucleosis syndrome: sore throat without exudative tonsillitis fever atypical lymphocytosis abnormal liver function tests virus splenomagaly and abnormal lymphocytes in the blood.

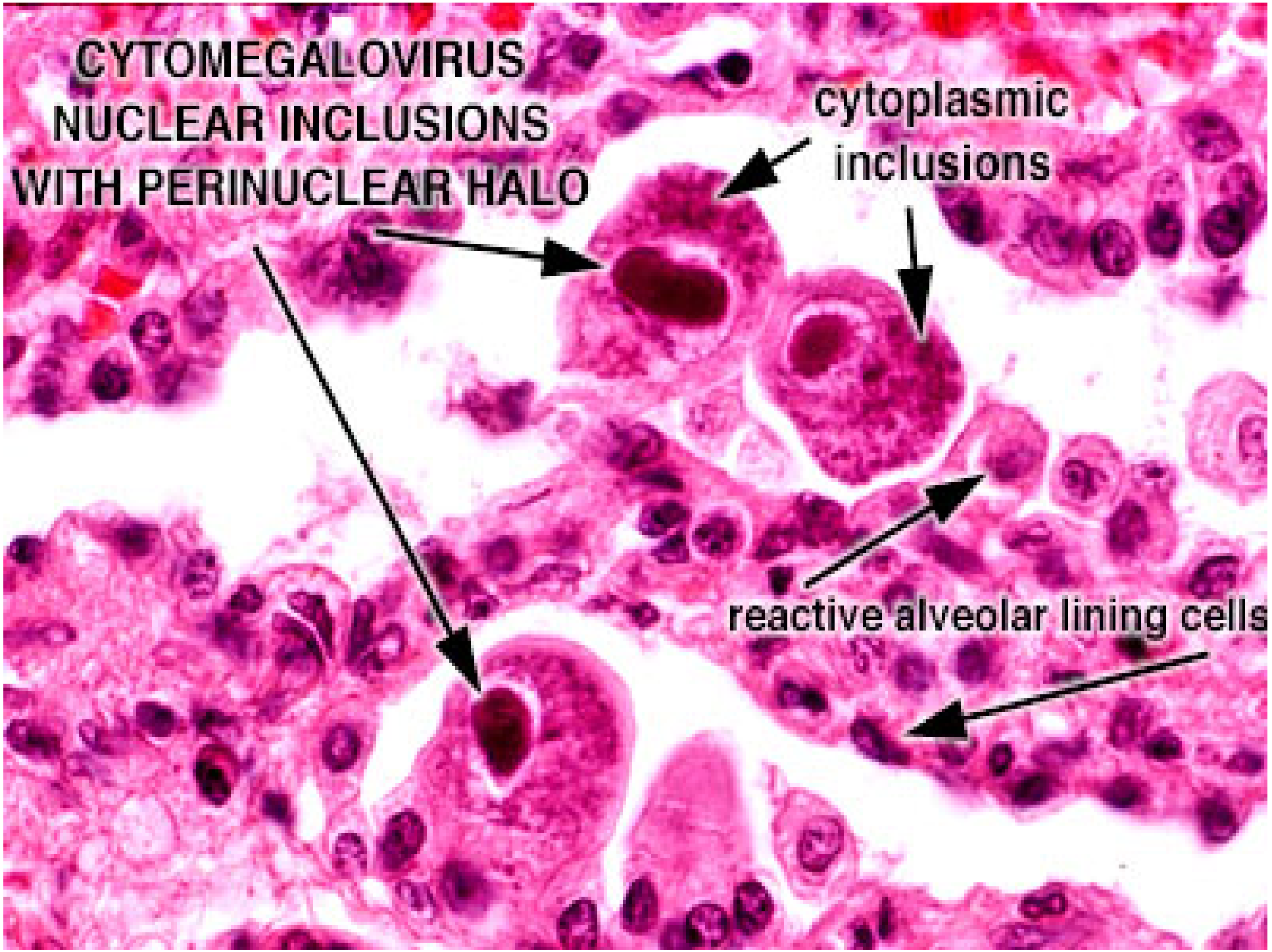
- **Transplant patients and posttransfusion infection.** usually asymptomatic. Common manifestations include; In adults: mononucleosis-like syndrome after 3-5 weeks. pneumonia, hepatitis

Immunocompromised patients. Both reactivation and primary infections can occur in this group of patients.

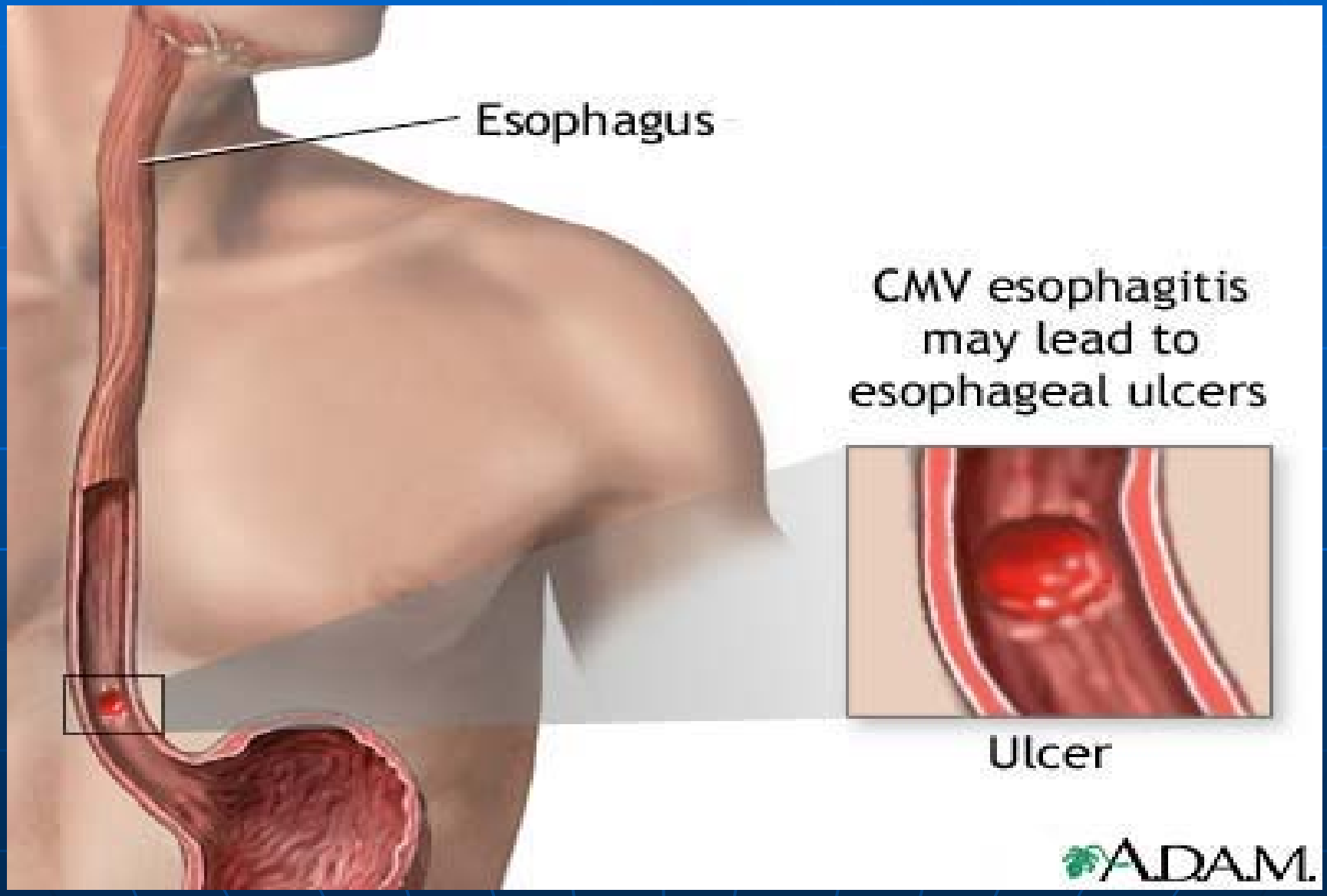
- **Interstitial pneumonia** the immunosuppressed-can be fatal if not treated. Other manifestations include:
- **hepatitis,**
- **encephalitis,**
- **esophagitis** (10% of AIDS patients),
- **colitis** (10% of AIDS patients),
- **pancreatitis,**
- **cholecystitis**,
- **chorioretinitis** (10-15% of AIDS patients; The first signs of CMV retinitis are vision problems such as moving black spots.),
- **necrotizing adrenalitis**

CMV Pneumonia

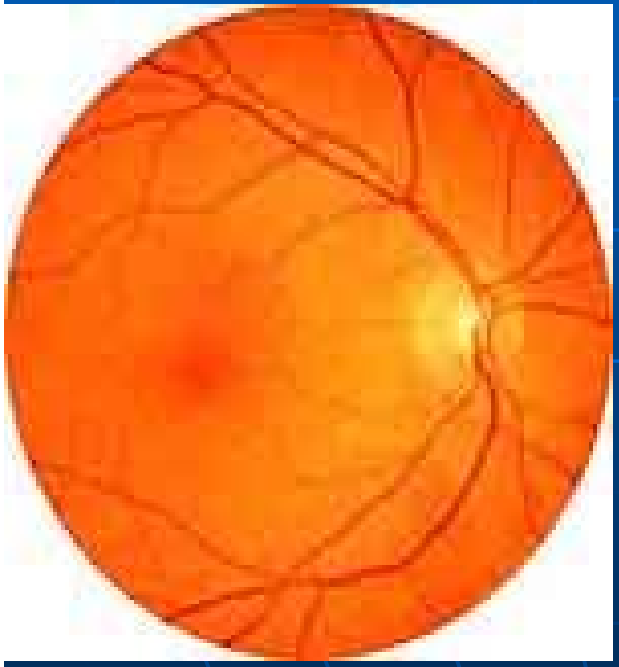
- CMV infection coexists with other opportunistic infections, particularly PCP. Controversy extent CMV actually contributes to lung pathology
- Diagnosis: CMV inclusions on lung biopsy specimens.
- CXR:bilateral, reticular, interstitial disease.
- CT scans bilateral or focal heterogeneous opacities, ground-glass or consolidative changes, in many individuals, well-defined
- solitary or multiple nodules measuring up to 3 cm in diameter. Differentiation of this infection from PCP not be possible.


CYTOMEGALOVIRUS
NUCLEAR INCLUSIONS
WITH PERINUCLEAR HALO
cytoplasmic
inclusions
reactive alveolar lining cells

esophagitis (10% of AIDS patients),



CHORIORETINITS-(10-15% of AIDS patients;first signs CMV retinitis-vision problems e.g. moving black spots.),

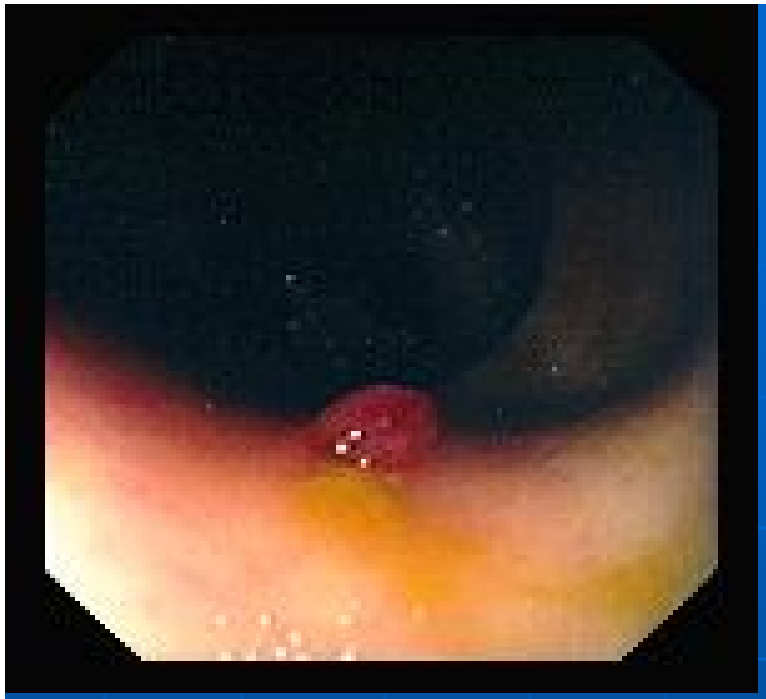


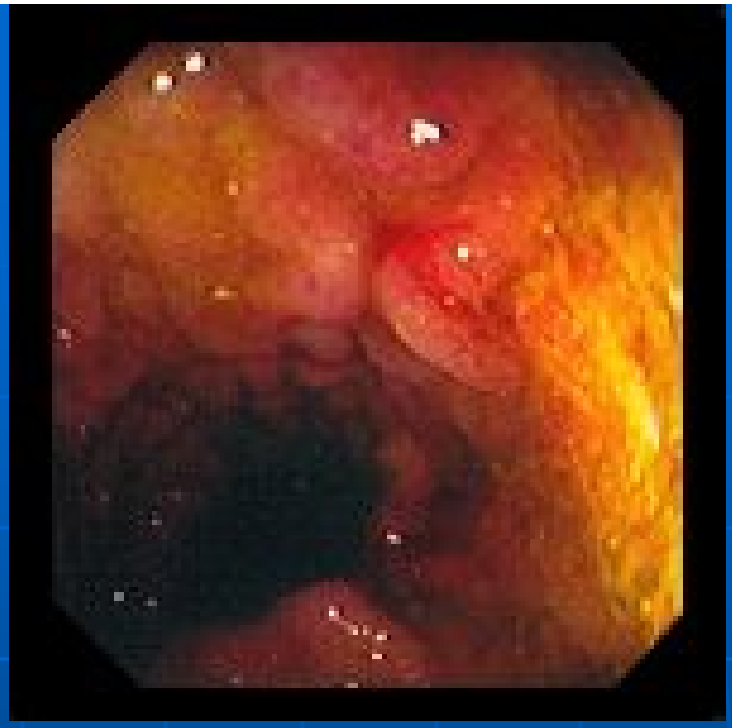
normal

CMV

CMV Colitis

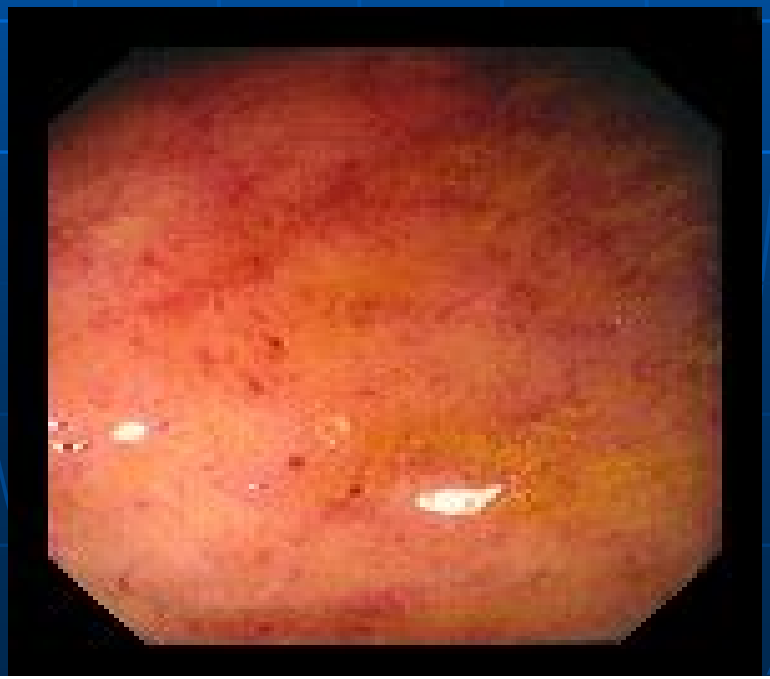
- **34 year-old man, infected with HIV, who presented with diarrhea. Sigmoidoscopy revealed mucosal inflammation with focal mucosal hemorrhage, edematous folds and polypoid lesions. Biopsies demonstrated viral inclusions consistent with cytomegalovirus.**

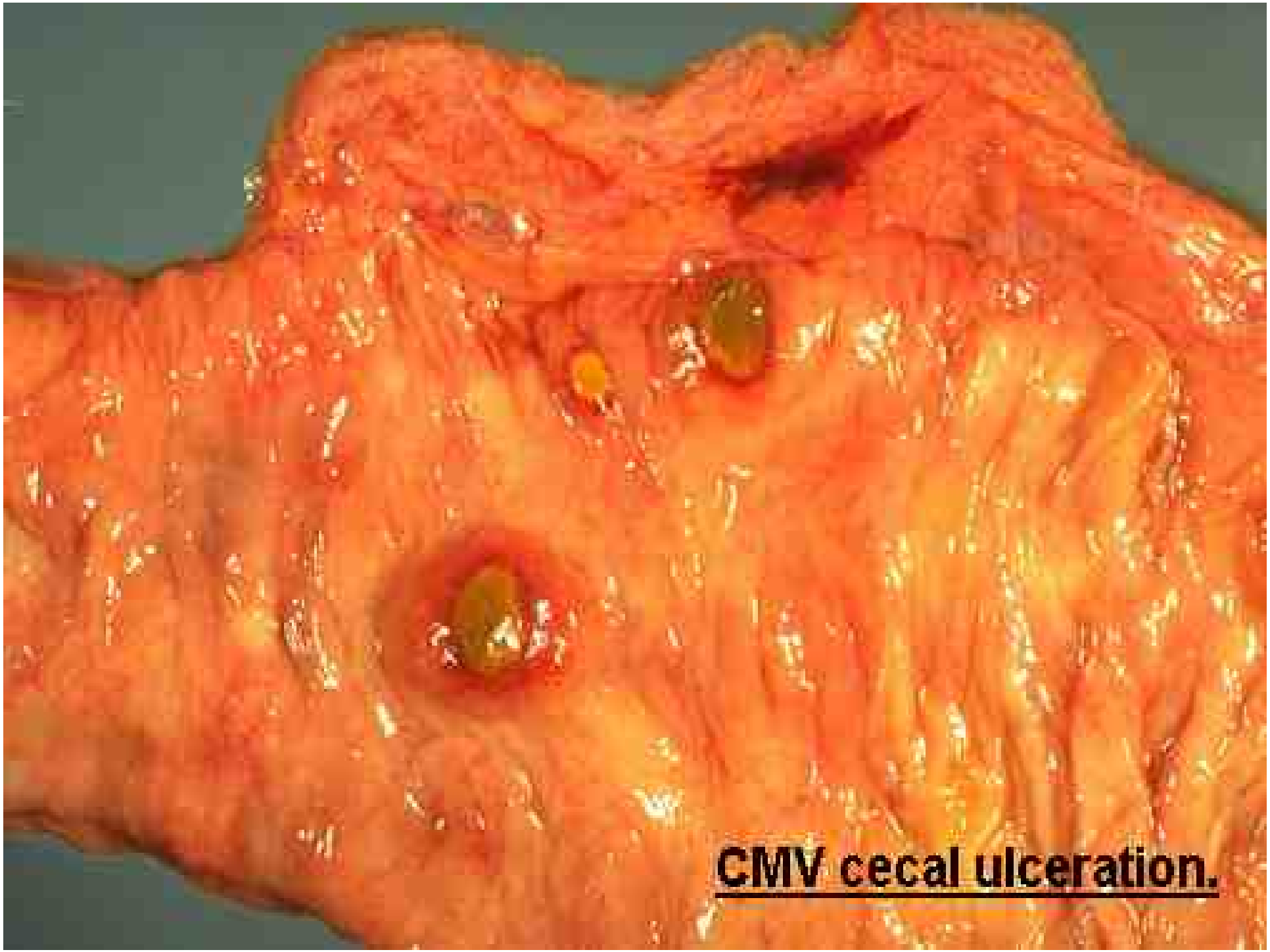




PSEUDOPOLYP

CMV COLITIS




CMV cecal ulceration.

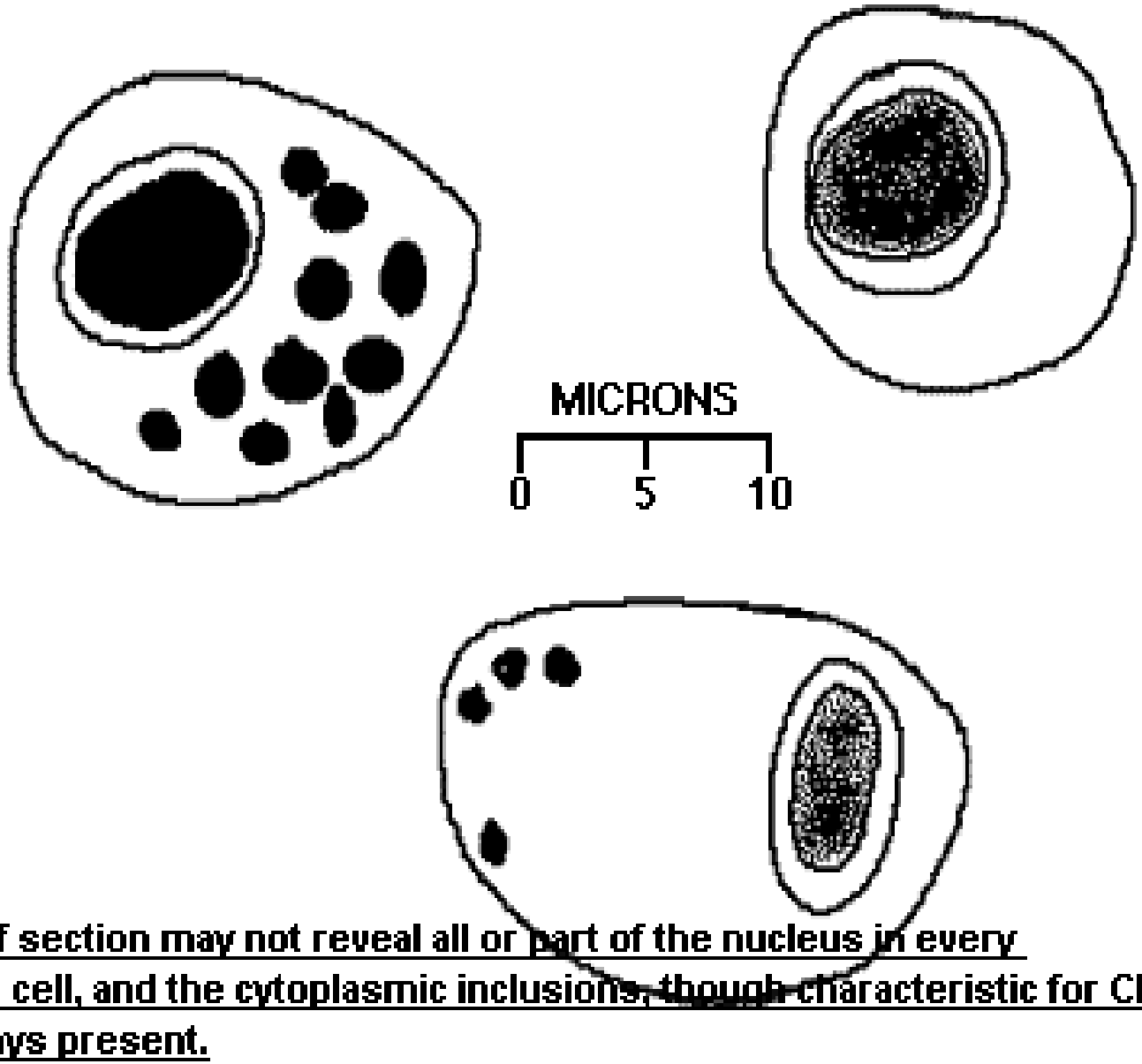
DIAGNOSIS

- **Cytology:CMV-induced large-inclusion bodies in urine sediment diagnoses CMV infection in neonates, however 1/3 false negatives.**

Histology.

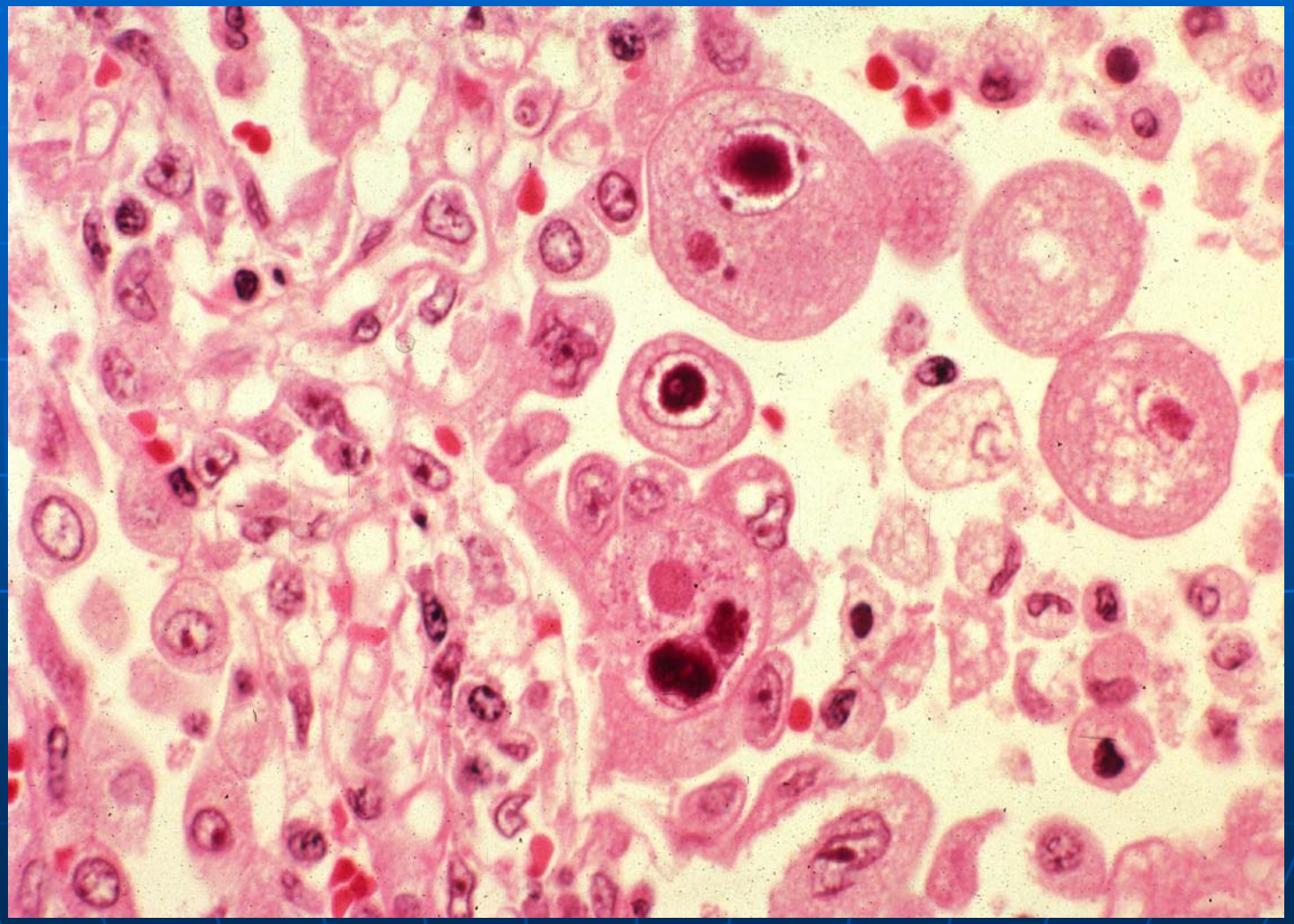
- The owl's eye appearance of CMV infected cells can easily be seen in tissue or organ preparations from any part of the body. Cells are enlarged and contain intranuclear and intracytoplasmic inclusions and peripheralized chromatin

CYTOMEGALOVIRUS

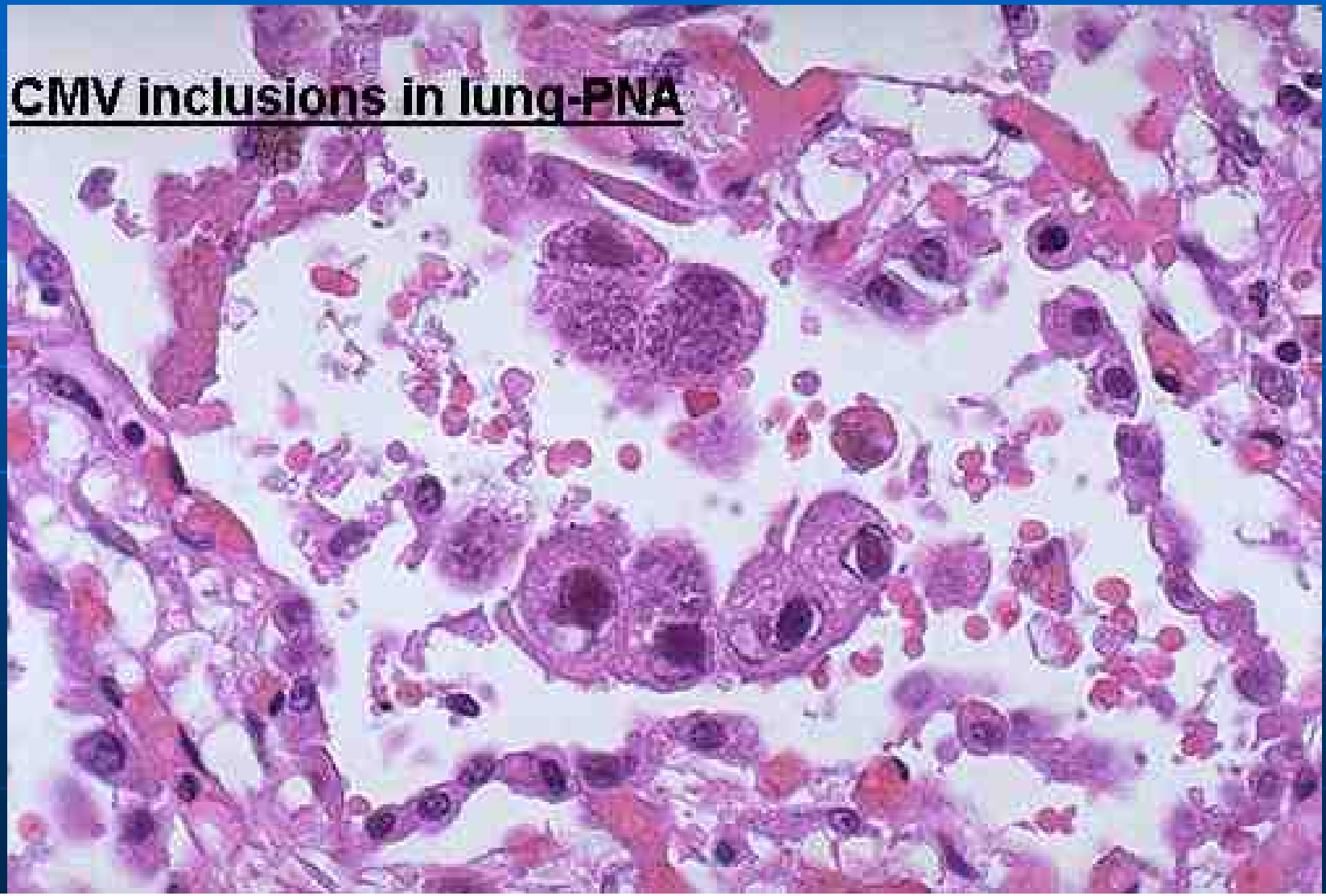


the plane of section may not reveal all or part of the nucleus in every cytomegalic cell, and the cytoplasmic inclusions, though characteristic for CMV, are not always present.

“Owl eye” sign



intracytoplasmic inclusions and peripheralized chromatin



Culture

- The ability to culture CMV from the patient gives the most reliable diagnosis. CMV can be found in most body fluids and cultured on diploid fibroblast lines with positive results in 1-4 weeks. However, positive results can be visualized in 16-36 hours after inoculation by applying monoclonal antibodies and immunofluorescent staining.

Serology.

- **CMV infected patients exhibit a negative heterophile antibody test. Complement fixation can be used to detect CMV-IgM antibodies in infants infected with CMV *in utero.***

THERAPY

- The most effective treatment for CMV infections is ganciclovir (dihydroxy propoxymethyl guanine), an analog of acyclovir and foscarnet.
- Hyperimmune human anti-CMV immunoglobulin has been used to reduce CMV disease associated with renal transplants.

Drug treatment of CMV:

- **Ganciclovir**
  - Ganciclovir is related to aciclovir but it is more active against cytomegalovirus. It is also much more toxic than aciclovir[6].
  - Oral ganciclovir provides much lower serum levels than intravenous, and so oral ganciclovir is mainly restricted to use as prophylaxis for CMV disease.
  - For the treatment of CMV pneumonia, ganciclovir is administered with immunoglobulin[7].
  - Other uses of ganciclovir include treatment of gastrointestinal disease in patients who have received transplants and in patients who are HIV positive.
  - Ganciclovir has also been used to treat CNS disease, including encephalitis and neuropathy, but with mixed results.
- **Valganciclovir**
  - Used for the initial treatment and maintenance treatment of CMV retinitis in AIDS patients.
  - Also licensed for preventing CMV disease following solid organ transplantation from a cytomegalovirus-positive donor.
- **Foscarnet**
  - Also active against cytomegalovirus. It is more toxic and therefore used as a second-line agent.
- **Acyclovir prophylaxis**
  - High-dose valacyclovir, penciclovir, famciclovir, and acyclovir have been used for CMV prophylaxis in patients who have received organ transplants.
- **Cidofovir prophylaxis**
  - Has been used for the treatment of refractory CMV retinitis in patients positive for HI

Prognosis

- The prognosis of patients with CMV hepatitis is generally good. Most patients recover completely.
- Symptoms can persist, usually in the form of fatigue, for several months after primary infection.

- Because patients who develop CMV disease are immunocompromised, their prognosis is determined by their underlying disease.

PREVENTION

- Safe sex practices as well as blood and tissue screening will help limit the spread of CMV.
- An attenuated CMV vaccine is under development. It is targeted at preventing the most serious forms of CMV illness: primary infection of immunosuppressed patients and congenital infections.

Prevention & prophylaxis

- Antiviral agent (acyclovir or ganciclovir) have been shown to be effective in reducing the risk of cytomegalovirus infection following solid organ transplantation
- Ganciclovir, acyclovir and valacyclovir have been used for and early treatment in patients who have received allogeneic marrow transplants. prophylaxis
- Acyclovir has also been used in patients who have received other types of transplants.

How BDORT can help

- BDORT may be useful for detection of localized CMV infections
- May be useful in cancer treatment
- May detect CMV although sero-negative- due to intra-cellular latent infection

Acupunct Electrother Res 1997;22(3-4):167-74 (ISSN: 0360-1293)
Ayuzawa S et al ;Dept Neurosurg Univ Tsukuba, Ibaraki, Japan.

Information from Industry

A patient with a whiplash, including pain and weakness of the right upper extremity and the symptoms of Barre-Lieou syndrome, diagnosed Bi-Digital O-Ring Test **indicated strong abnormal response around right side of his neck shoulder,** including vertebral artery and acupuncture point GB 21, ***positive resonance to Cytomegalovirus*** and Strep faecalis were detected. Antibiotic and anti-viral agents, as well as Ku-Oketsu-Zai, a type of Oriental herbal medicine for overcoming blood stagnation or stasis,. Infection at the site of the vertebral artery and the peri-arterial sympathetic nerve plexus was considered as a cause of In addition we especially noted, in this clinical case, that the patient's impaired **grasping force *dramatically improved*** from 8 kg to 52 kg in a very short time ***when the patient held suitable medicine selected with Bi-Digital O-Ring Test drug compatibility test.*** We assume that the drug action was transferred electromagnetically, by which the pathological electromagnetic oscillations caused by trauma and following infections were scavenged.

CMV neuropathy

- **Cytomegalovirus multifocal neuropathy in AIDS: analysis of 15 consecutive cases.**

  Roullet E, Assuerus V, Gozlan J, Ropert A, Said G, Baudrimont M el Amrani M, Jacomet C, Duvivier C, Gonzales-Canali G, et al.

  Department of Neurology, Hopital Saint-Antoine, France.

  A severe multifocal neuropathy caused by cytomegalovirus (CMV-MN) can occur in the late stage of human immunodeficiency virus (HIV) infection.

CMV and Guillan-Barre

- **Journal of Neurology, Neurosurgery, and Psychiatry, 1997, Vol 62, 641-643**
- **Cytomegalovirus infections and anti-GM2 antibodies in Guillain-Barre syndrome**
- **BC Jacobs,** et.al.Department of Neurology, University Hospital Dijkzigt and Erasmus University, Rotterdam, The Netherlands.
- To investigate whether antecedent cytomegalovirus (CMV) infections in patients with Guillain-Barre syndrome are associated with the presence of specific antiganglioside antibodies, acute phase serum samples from 130 patients with Guillain-Barre syndrome and 200 controls were tested. Anti-GM2 IgM antibodies were found more often in patients with Guillain- Barre syndrome with CMV infection (22%) than in patients without the infection (2%) (P = 0.003).
- **CMV infections may elicit anti-GM2 antibodies in susceptible patients, which may contribute to the pathogenesis of Guillain-Barre syndrome associated with CMV.**

Ann Neurol. 2000 Feb;47(2):274-5.

Correlation between cytomegalovirus infection and IgM anti-MAG/SGPG antibody-associated neuropathy.

Yuki N et.al. Department of Neurology, Dokkyo University School of Medicine, Shimotsuga, Tochigi, Japan.

IgM anti-myelin-associated glycoprotein (anti-MAG)/sulfated glucuronyl paragloboside (SGPG) **antibody is found in some patients with chronic polyneuropathy (CP). An antigen-driven process is considered to induce this autoantibody, but the agent has yet to be identified.** It has been reported that sera from cytomegalovirus (CMV)-infected patients contained anti-SGPG antibody. To clarify the mechanism of the production of the anti-MAG/SGPG antibody, we investigated CMV DNA in sera from 26 patients with IgM anti-MAG/SGPG antibody-positive CP. Twenty-three (88%) had CMV DNA. The positive frequency was significantly higher than the frequencies in sera from patients with IgM anti-MAG/SGPG-negative CP, the other disease controls, and the normal control subjects. There were no statistical differences in the frequencies of Epstein-Barr virus DNA between anti-MAG/SGPG-positive and anti-MAG/SGPG-negative CP and between anti-MAG/SGPG-positive CP and each disease control. Moreover, no herpes simplex virus 1 DNA was detected in the sera from patients with anti-MAG/SGPG-positive CP.

- **The strong correlation of anti-MAG/SGPG-positive CP with the presence of serum CMV DNA suggests that CMV infection induces the IgM anti-MAG/SGPG antibody.**

Acupunct Electrother Res 2003;28(1-2):35-68 (ISSN: 0360-1293)Omura Y; Shimotsuura Y; Ohki M using the Bi-Digital O-Ring Test Resonance Phenomena between 2 identical substances, one can non-invasively detect the approximate location on the body of abnormally increased risk factors in just 2 minutes, by detecting the resonance with L-Homocystine, However, in our study, when the clinical significance of CRP and L-Homocystine was compared, we found that

- **CRP often was not increased when there was extensive infection of Mycobacterium Tuberculosis as well as asymptomatic infection by Cytomegalovirus,** Herpes Simplex Virus Type I, Human Herpes Virus Type 6, Borrelia Burgdorferi, or Chlamydia Trachomatis in **the heart (and other parts of the body),**
- **Once the pathogenic factors were identified, the effective medication was given, and the Selective Drug Uptake Enhancement Method** (originally discovered by the first author in 1990) was applied after the effective drug was administered, to selectively deliver the medication to the pathological area, while reducing drug uptake to the normal parts of the body. As a result, the therapeutic effect was markedly accelerated.
-

Cytomegalovirus-associated heart muscle disease

- **Eur Heart J 1995 Dec;16 Suppl O:46-9** (ISSN: 0195-668X) Schonian U; **Department of Cardiology, Philipps University, Marburg, Germany.Human cytomegalovirus** (CMV) can persist in many **organs after primary infection.** Not only is it
- **suspected to cause morbidity during reactivation in patients under immunosuppression, but it**
- **may also induce long-term latency by chronic disease**, e.g. in the myocardium. Endomyocardial biopsies of 27 patients with active myocarditis, 35 patients with healing, 41 patients with healed and 25 patients with ongoing myocarditis according to the Dallas Criteria and 52 patients with dilated cardiomyopathy (DCM) and the biopsies of 25 healthy heart donors were studied for persisting CMV-DNA by polymerase chain reaction (PCR) and in-situ hybridization (ISH). CMV-DNA could be assessed in 5-14% of patients in the different stages of myocarditis and in 22% of patients with DCM.
- **CMV persists in all cell types including myocytes, whereas in the controls it is only found in interstitial cells. CMV antigens could not be detected in the myocardium with our methods. It must be assumed that infection by CMV is more a persistent or latent than an active infection.**

Relate prev. infection with CMV & HSV1 to CoronaryHeart Disease

- **Arch Intern Med 2000 Jul 10;160(13):2027-32** (ISSN: 0003-9926) Sorlie PD; Nieto FJ; Adam E; Folsom AR; Shahar E; Massing M National **Heart**, Lung, and Blood Institute, National Institutes **of** Health,. **RESULTS: The population with the highest antibody levels of CMV (approximately the upper 20%) showed an increased relative risk (RR) of CHD and diabetes**
- **no association of CHD with the highest herpes simplex virus 1 antibody levels**
- **CONCLUSIONS: High levels of CMV antibodies are significantly associated with incident CHD. Infection with CMV, particularly in more susceptible disease states such as diabetes, may be an important risk factor for CHD.**

Coronary restenosis&CMV

- Am J Cardiol 1998 Apr 1;81(7):866-8 (ISSN: 0002-9149) Blum A **Cardiology Department, Tel-Aviv Medical Center, Israel.cytomegalovirus (CMV) DNA was found in atherosclerotic coronary arteries in restenotic lesions**, and prior infection with CMV could be a strong independent risk factor for restenosis patients with high antibody titer (> or = 1:800)
- higher restenosis rate than seropositive patients with a low antibody titer (< or = 1:400) (p <0.05).
- High antibody titers against CMV (IgG) may be a strong marker for coronary artery disease, and might predict post-coronary angioplasty restenosis.
- **These findings support the infectious theory of atherosclerosis (especially with prior CMV infection), and also suggest that a chronic immunologic response has a role in atherosclerosis and restenosis**

Statins, CAD & CMV

- **Circulation 2003 Jan 21;107(2):258-63** Horne BD et al Cardiovascular Department, LDS Hospital, Salt Lake City, **Seropositivity to cytomegalovirus (CMV) and elevated C-reactive protein (CRP) may jointly predict increased mortality rates in patients with coronary artery disease (CAD).**
- Therapy with statins reduces lipid levels but may also have other beneficial (eg, antiinflammatory) effects
- prospectively evaluated the effect **of** statins on CMV-and CRP-associated **death** among patients with significant, angiographically defined CAD.), and CMV(+)/**high** CRP.
- **CONCLUSIONS: The survival benefit of statins interacted with CMV seropositivity and high CRP to significantly reduce mortality rates among patients with CAD.**
- This finding supports the hypothesis that statins have beneficial, "lipid-independent," antiinflammatory effects. The mechanism **of** statin benefit associated with CMV seropositivity remains to be determined.

- **Acupunct Electrother Res 1995 Aug-Dec;20(3-4):195-** Omura Y; Beckman SL Heart Disease Research Foundation, New York, USA.
- **...Infection ...with implication for cancer.The authors found that antibiotics used to treat various infections often were ineffective in the presence of abnormal localized deposits of heavy metals like Hg and Pb, which were often observed to co-exist with Chlamydia trachomatis, Herpes Simplex Types I & II**
- **Cytomegalovirus(CMV), and other micro-organisms. We also found Chinese parsley accelerates the excretion of Hg, Pb, and A1 from the body though the urine. Our subjects were given a course of antibiotics (Doxycycline for Chlamydia trachomatis infection) or anti-viral agents**
- **(EPA with DHA for Herpes Family Viruses) together with Chinese parsley. infection, or anti-viral agents (EPA with DHA) for Herpes Family Viruses,**
- **drug uptake enhancement methods to selectively increase delivery of the drugs to the affected areas, and Chinese parsley tablets to remove the heavy metal deposits, the last traces of the**
- **infections and clinical symptoms disappeared completely.**

CMV and Cancer

- Cancer Treat Rep. 1977 Mar-Apr;61(2):139-46.**Cytomegalovirus and cancer of the prostate: in vitro transformation of human cells.Geder L et.al.**
  Urogenital tissue specimens were maintained in culture for 2 years. Epithelioid growth was enhanced with use of collagenase digestion rather than trypsinization. Twenty of 34 prostate cancer cell cultures survived more than ten in vitro passages, during which time four of 20 demonstrated epithelioid morphology. One epithelioid line (T-157) survived 32 in vitro passages. The cells demonstrated lack of contact inhibition in culture, were slightly positive in acid phosphatase tests, and reacted positively with cytomegalovirus (CMV)-immune sera in indirect immunofluorescence (IF) tests. These cells, which were proven to be of human male origin, failed to yield infectious virus and could be re-isolated from a nodule induced by the cells when injected sc into weanling athymic nude mice. The serum of the patient from which the tumor cells were derived demonstrated high CMV antibody titers and reacted with the virus-specific membrane and intracellular antigens of CMV-transformed human cells in IF tests.
- A CMV strain isolated from one of the normal prostate cell cultures established an in vitro long-term persistent infection of human embryo lung cells which resulted in the development of two transformed cell lines.
- The transformed cells possessed CMV antigenic markers and induced non-differentiated tumors when transplanted into athymic nude mice.
- The results constitute further evidence of the transforming capacity of CMV, and suggest that the virus may be oncogenic in its natural (human) host.

Mark Twain said:

- “It is better to deserve honors and not have them than to have them and not deserve them.”

Albert Einstein said:

"We have to do the best we can. This is our sacred human responsibility."