Gliomas & CMV

Disclaimer

This paper has been prepared by someone with no medical background, someone with no authority to comment apart from the fact that her father is currently suffering from a brain tumour.

Contents

Introduction

In the Australian state of NSW malignant brain tumours affect 7.3 in every 100,000 males and 5.7 in every 100,000 females[A-1], they are relatively uncommon.

There have been many theories as to what causes brain tumours, ranging from exposure to electromagnetic fields to the use of mobile phones, however to date a cause that can explain the majority of cases has not been formally established.

The purpose of this paper is to discuss the possibility of a link between a common virus Cytomegalovirus (CMv) and brain tumours, a hypothesis put forward by Professor Charles Cobbs, neurosurgeon at the University of San Francisco California in 2002[A-2].

Charles Cobbs Hypothesis

Essentially Charles Cobbs suggested that Cytomegalovirus might play an active role in the development of malignant gliomas.

As a neurosurgery resident, Cobbs had observed that his patients diagnosed with malignant gliomas were mostly older, well-educated and from higher socioeconomic backgrounds.

He believed that their "hyper-hygienic" lifestyles had possibly left their immune systems susceptible to more common viruses, such as the human cytomegalovirus (CMv) a herpes virus so ubiquitous that it infects 4 of 5 Americans.

During off-hours, and without formal research funding, Cobbs and a lab partner analyzed dozens of brain tumor samples: all of them were riddled with CMv.

In 2002, the doctor published his novel finding in a leading medical journal ‘Cancer Research’ where it was quickly dismissed by many of his peers.

However in February 2008, brain cancer researchers at Duke University Medical Center published the first peer-reviewed report that confirmed Cobbs' discovery, followed by two reports from independent labs at the M.D. Anderson Cancer Center at University of Texas in Houston and the Karolinska Institute in Stockholm, Sweden.

In October 2008, the National Brain Tumor Society sponsored a first-of-its-kind gathering in Boston of the world's top virologists and glioma experts to examine the possible link between CMv and the deadly brain tumors. With the exception of one investigator, all agreed that the current evidence demonstrates a strong association between the presence of CMv infection and malignant gliomas.

From the San Francisco Chronicle Oct6, 2008
“Surgeon changes study of brain tumours”[A-3]

Support for Cobb's hypothesis

A variety of support exists for the theory that CMv plays an active role in the development of brain tumours, details of three research papers are provided here…

- *The first uses statistical analysis to establish that gliomas display space and time clustering patterns consistent with an infectious agent.*
- *The second demonstrates that CMv can cause the growth of tumours.*
- *The third suggests that the presence of CMv within glioblastomas is of high prognostic value for patient survival, that is the higher the grade of CMv infection within a tumour the shorter the patient's survival.*

McNally et al:

Statistical evidence of space-time clustering of glioma tumours, typical of diseases caused by an infectious agent

McNally with his British and Dutch team analysed a database of adult brain tumours diagnosed in patients from the North Brabant province of the Netherlands between 1983 and 2001. They found clusters of cases of glioma tumours, which make up about half of all brain tumours, at different time intervals in different geographical locations.

This 'space-time clustering' of cases is a pattern typical of diseases caused by infections, adding weight to the theory that outbreaks of viruses are a potential contributory cause of brain tumours. Diseases caused by more constant environmental factors, such as pollution, produce clusters of cases in one place over a much longer time period.

From Dr Richard McNally, 24-01-2006. Infections could contribute to adult brain tumours. Alphagalieo. Retrieved from www.innovations-report.com/html/reports/medicine_health/report-54234.html[A-4]
European Journal of Cancer 41 (2005) 2917–2923. Space–time clustering patterns of gliomas in the Netherlands suggest an infectious aetiology. R.J.Q. McNally et al[A-5]

University of Wisconsin-Madison and Harvard Medical School:

CMv an infectious agent, shown to cause tumours

A study performed by researchers at the University of Wisconsin-Madison and Harvard Medical School found that human cytomegalovirus (HCMV) can mimic a common regulatory protein to hijack normal cell growth machinery, disrupting a cell's primary anti-cancer mechanism. Essentially the virus is able dupe it's host's cells into helping it grow and spread.

The report suggested that a viral protein, called UL97, masquerades as a normal regulatory enzyme to modify a tumor-suppressing protein in human cells. Unlike the normal enzyme, which can be switched on and off by the cell as needed, the viral stand-in lacks an off switch and evades cellular control. The findings represent a previously unknown way that viruses can cause uncontrolled cell growth and division [ie. cancer].

From University of Wisconsin-Madison (2008, May 10). Virus Mimics Human Protein To Hijack Cell Division Machinery. ScienceDaily. Retrieved from www.sciencedaily.com/releases/2008/05/080508143310.htm[A-6]
Science 320, 797 (2008). Protein by Viral Protein with Cyclin-Dependent Kinase Function. Adam J. Hume et al[A-7]

Karolinska Institute – Centre for Molecular Medicine Stockholm Sweden:

CMv is detected in glioblastomas and is of high prognostic value for patient survival

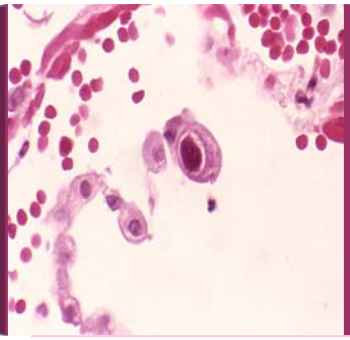
Recently the Karolinska Institute discovered that glioblastoma patients with less than 25% CMv infected tumor cells at diagnosis survived over 2 years longer than patients with 25-90% CMv infected tumor cells. At two years, approximately 60% of the patients with low-grade CMv infection in the tumor were alive, as compared with 20% of patients with high grade infection. Time to progression was 22 versus 9 months. These observations strongly suggest that CMv has a pathogenetic [*capable of producing disease*] role rather than being an epiphenomenon [*a secondary or additional symptom or complication arising from the course of disease*] in malignant glioblastoma.

From the Centre for Molecular Medicine Karolinska Institute Stockholm Sweden. Retrieved from www.cmm.ki.se/en/Research/Cardiovascular-and-Metabolic-Diseases/Cell-and-Molecular-Immunology/Cia/Our-research/CMv-infection-in-cancer/[A-8]

Quick summary: **Gliomas & CMv**

- *Glioma tumours display space-time clustering patterns typical of disease caused by an infectious agent*
- *CMv is an infectious agent*
- *CMv has been shown to cause tumour growth*
- *CMv is found in gliomas*
- *The higher the grade of CMv infection within a glioma the shorter the patient's expected survival.*

So what is CMv?



The name of the virus refers to the large epithial cells that can be seen when viewed under a microscope. In Greek 'Cyto' means cell and 'mega' means large.

Cytomegalovirus (CMv) is an extremely wide-spread, but usually harmless infection. It often presents no symptoms in otherwise healthy children and adults.

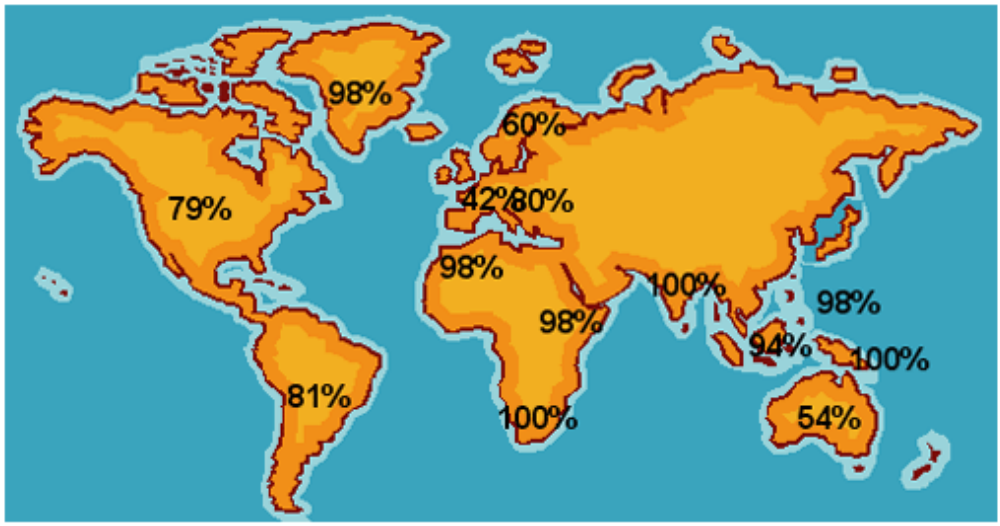
The virus is a member of the herpesvirus family and like other viruses in this family it has the ability to lie dormant within the body long after the initial mild infection.

A healthy immune system is able to hold the virus in check, however if the immune system is weakened the virus can re-activate and cause serious illness.

CMv is passed along
- at birth,
- in breast milk,
- by sexual transmission,
- via blood transfusion and organ transplant, or
- by close person to person contact that allows infected body fluids to pass to another person.

Active CMv infections are more likely to occur in young children and those with compromised immune systems such as HIV patients, transplant recipients, blood transfusion recipients and patients on chemotherapy.

Who has CMv?



There is wide variation in prevalence rates based on geography:
Africa: 82-100% | Australia/Western Europe/USA: 42-85% | South America: 81-98% *

CMv is found throughout the world in all geographic and socioeconomic groups, but in general it is more widespread in ***developing countries*** and in areas of ***lower socioeconomic conditions***.

The map shown displays the rate of CMv prevalence in different geographic areas. CMv prevalence in the high socioeconomic areas of Europe and Australia is low at 42% and 54% respectively, while the rate in some developing areas is double this reaching 100% in Papua New Guinea and India.

The majority of infections occur during childhood. A recent Australian survey showed that of those infected with CMv more than half had been infected before the age of one [refer following page].

Not surprisingly therefore children are a significant source of infection. Studies conducted at day-care centres in the United States have shown that in the first year of life, approximately 10% of children shed the virus. This figure increases significantly to approximately 80% by the time these children have reached 12-18 months of age[A-9].

As females have close contact with children they are slightly more likely to carry the virus than males.

In fact the lowest rates of CMv incidence are found amongst males of high socio-economic status. This group is also most likely to become infected later in their life.

In the United States **white non-hispanic males** have the **lowest incidence** of CMv and their **average age of infection is highest** at 29 years of age[A-16].

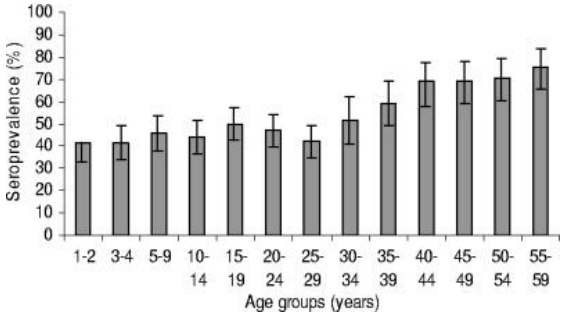
* *Prevalence map retrieved from: http://www.abbottdiagnostics.com.au/Your_Health/Infectious_Diseases/CMv/* however the year of the data was not specified

CMv in Australia

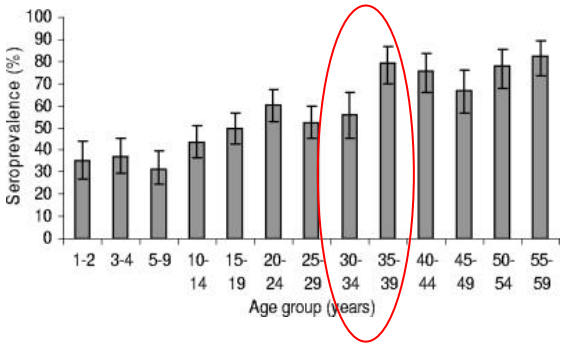
In Australia a recent (2006) national survey of CMv found that the population-weighted rate of CMv seropositivity in subjects between 1 and 59 years of age was 57%, with over half of these individuals being infected by the age of one.

Females are slightly more likely to carry the virus (54%) than males (51%) and CMv incidence rates in females increased significantly between the group aged 30 to 34 years and that aged 35 to 39 years, which may be explained by motherhood and the fact that women in these age groups have close contact with young children who act as a vehicle for transmission.

CMv in Australian Males



CMv in Australian Females



Clin Vaccine Immunol. 2006 November; 13(11): 1181–1184. National Serosurvey of Cytomegalovirus in Australia. National Centre for Immunisation Research and Surveillance. Holly Seale et al. Retrieved at www.ncbi.nlm.nih.gov/pmc/articles/PMC1656547/[A-10]

So if CMv is so common why aren't brain tumours more common?

As mentioned, Cobbs believes that the "hyper-hygienic" lifestyles of his glioma patients had possibly left their immune systems susceptible to CMv.

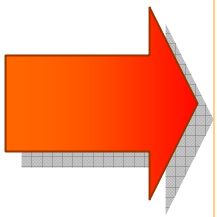
Although perhaps not consistent with Cobb's theory, our experience with Polio might shed some light on the mechanisms of CMv and how it is that many people are infected with CMv but only a small percentage go on to develop brain tumours.

Polio

Polio, or poliomyelitis, was one of the most feared and studied diseases of the first half of the 20th Century. It is caused by a virus which results in an acute infection. However, contrary to common beliefs, the virus did not typically result in paralysis. Rather, the majority of infected individuals experienced only mild respiratory or gastrointestinal symptoms, often accompanied by fever, headache, and muscle stiffness. These symptoms lasted only a few days, and many had such mild cases that they did not even realize they were ill.

It is believed that the polio virus is spread by contact with the faeces of an already infected person. Before the advent of modern sewage treatment plants and other improvements in public sanitation, virtually all individuals were exposed to the polio virus early in their lives when they were at least partially protected by maternal antibodies. Thus, they developed mild, non-paralytic infections, probably during infancy, which provided them with lifelong immunity.

However, with better sanitation, both these early infections as well as the likelihood of receiving antibody protection from their mothers decreased, resulting in greater susceptibility to paralytic polio. Thus, in the words of Smith:

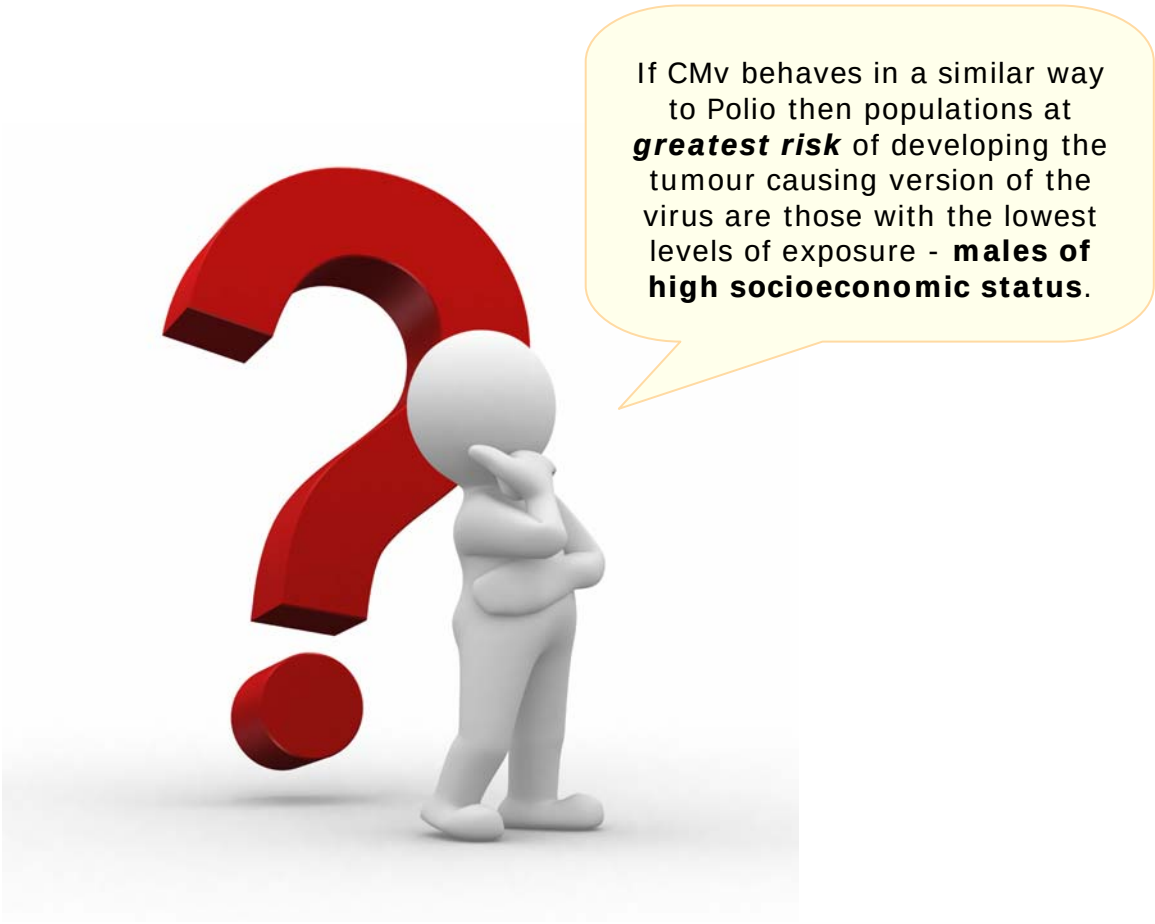


Put simply, paralytic polio was an inadvertent by-product of modern sanitary conditions. When people were no longer in contact with the open sewers and privies that had once exposed them to the polio virus in very early infancy when paralysis rarely occurs, the disease changed from an endemic condition so mild that no one knew of its existence to a seemingly new epidemic threat of mysterious origins and terrifyingly unknown scope.

From Polio's Legacy: An Oral History (Sass, 1996). Retrieved at www.cloudnet.com/%7Eedrbsass/poliodefinition.htm[A-11]

Quick summary: **CMv**

- *Active infections of CMv are more likely to occur in **children** and those with **suppressed immune systems***
- ***Males** are slightly **less likely** to carry CMv than females*
- *Populations of **higher socioeconomic status** have a **lower incidence** of the virus and generally acquire the infection later in life.*



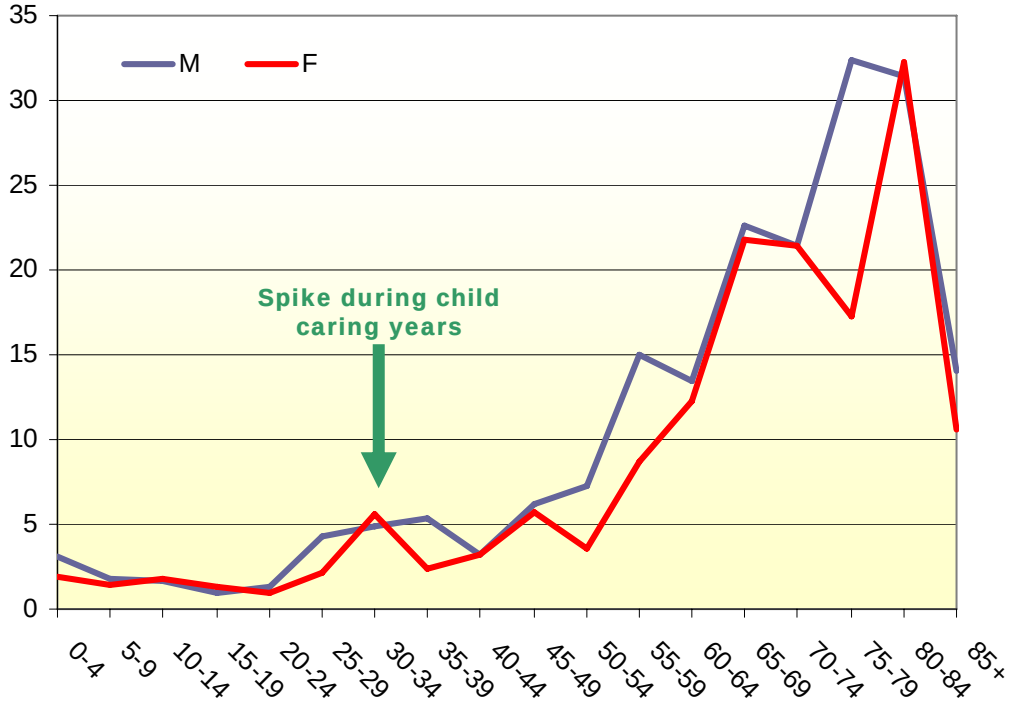
Can CMv explain some of the historical trends seen in Brain Tumour incidence?

If CMv plays an active role in the development of brain tumours can our knowledge of CMv help us explain trends in brain tumour incidence.

Please note, the following relationships have not been proven and without proper statistical analysis it is entirely possible, perhaps likely, that no real relationships exist.

CMv FACT	- - THEORY - -	BRAIN TUMOUR FACT
Males are slightly **less likely to carry CMv** than females.	*If CMv behaves in a similar way to Polio (that is, populations at greatest risk of developing the life threatening version of the virus are those with the lowest levels of exposure) then as males have a lower exposure to the virus than females they should have a greater risk of developing the tumour causing version of the disease. That is, males should have a slightly increased incidence of brain tumours than females.*	According to the 'Cancer in NSW: Incidence and Mortality Report 2006'[A-1] "After allowing for differences in age, **males were 1.3 times more likely to be diagnosed with brain cancer** than females" 
Populations **of high socio-economic status** have **a lower incidence of CMv** than those of low socio-economic status.	*Again if CMv behaves like polio then high socio-economic populations should be at greater risk of developing the tumour causing version of the disease than low socio-economic populations.*	A population based study of glioblastoma multiforme in Los Angeles County[A-12] arrived at the following conclusion: *"Older age, male gender, **higher SES** [socio-economic status] and non-latino white race **increased the risk of Glioblastoma Multiforme**."* In addition we have Cobbs observation that his patients diagnosed with malignant glioma were mostly older, well-educated and from higher socioeconomic backgrounds. 
Active infections of CMv are **more likely to occur in children** and those with suppressed immune systems	*If children are more likely to carry active CMv infections and shed the virus, there should be a spike in incidence amongst females during their child caring years when they would have close contact with children and therefore would be more likely to become infected.*	Refer graph on following page sourced from data reported in the 'Cancer in NSW: Incidence and Mortality Report 2006'[A-1] 

Brain cancer: ***Age-specific incidence rates per 100,000 population by sex, NSW, 2006***



There is a spike in the female incidence of brain tumours during their child caring years, brain cancer incidence jumps from 2.1 per 100,000 females in the 25-29 age group to 5.6 per 100,000 females in the 30-34 age group.

Increasing incidence with age

You may notice from the graph that the likelihood of developing a brain tumour increases with age. This pattern is consistent with our experience of paralytic polio. In spite of a greater number of infections in the young, the likelihood of developing the paralytic form of polio increases with age as does the extent of paralysis. In children paralysis occurs in only 1 in 1000 cases whereas in adults, paralysis occurs in 1 in 75 cases [A-13].

If CMv is the agent, what implications does this have for treatment?

Cortico-steroids: Dexamethasone

Dexamethasone is unfortunately a necessary evil for most brain tumour sufferers. It is a drug that should be taken very seriously as improper management can have fatal consequences.

Disturbingly research suggests that Dexamethasone can significantly enhance CMv replication [A-14].

This would mean that if the work of researchers at the Karolinska Institute is accurate and the higher the grade of CMv infection the shorter the patient's survival, it is possible that Dexamethasone shortens patient survival.

Anti-virals: Valcyte

Unfortunately there is currently no cure for CMv, instead anti-viral drugs such as Valcyte are generally used to slow the spread of the virus. Antiviral drugs prevent the virus from dividing and creating more of itself however like most other drugs, CMv anti-virals have side effects.

In the US and in Sweden, clinical trials using CMv anti-viral strategies to treat malignant gliomas have already begun [A-8].

Hope for the future…

Vaccines and immunotherapy are already available to treat other tumour causing viruses. For example a vaccine is now available for the Human Papilloma virus, shown to cause cervical cancer while immunotherapy techniques have been used to successfully treat tumours caused by the Epstein Barr virus[A-15]. These successes give us hope that the prevention and cure of this devastating condition is not far off.

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A-2 *Human Cytomegalovirus Infectiona and Expression in Human Malignant Gliomas by Charles Cobbs et al. Cancer Research 62, 3347-3350, June 15 2002*

A-3 *San Francisco Chronicle Oct6, 2008 "Surgeon changes study of brain tumours" by Justin Berton*

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A-14 *Enhanced Replication of Human Cytomegalovirus in Human Fibroblasts Treated with Dexamethasone by Junji Tanaka et al, Department of Virology, Cancer Research Institute, Kanazawa University, Kanazawa 920, Japan, 6-Jun-1984*

A-15 *Haque T, Wilkie GM, Jones MM, Higgins CD, Urquhart G, Wingate P, Burns D, McAulay K, Turner M, Bellamy C, Amlot PL, Kelly D, MacGilchrist A, Gandhi M, Swerdlow AJ, Crawford DH. Allogeneic cytotoxic T cell therapy for EBV positive post transplant lymphoproliferative disease: results of a phase II multicentre clinical trial. Blood 110, 1123-1131. (2007)*

A-16 *Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. Fernando AB Colugnati et al. BMC Infectious diseases 2007, 7:71*