CYTOMEGALOVIRUS

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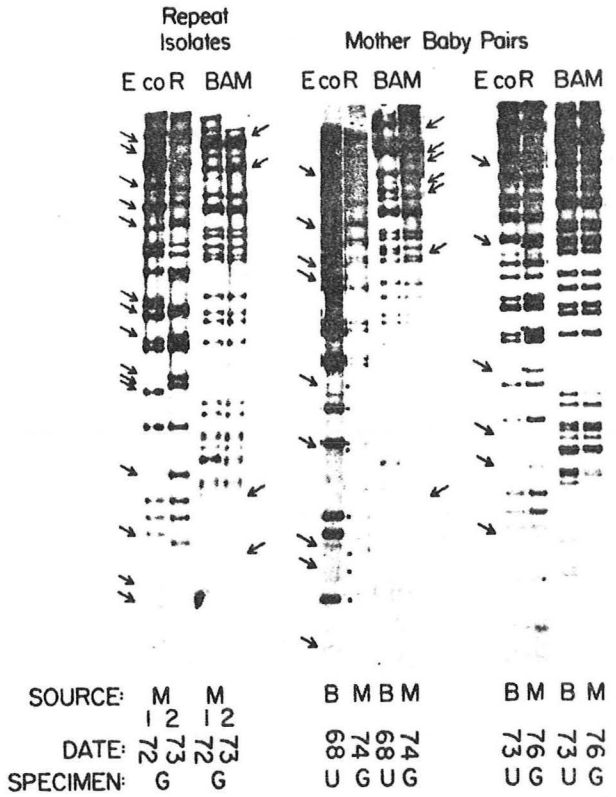
VIROLOGY

Cytomegalovirus (CMV) is a member of the herpesvirus group, which also includes herpes simplex virus types 1 and 2, Epstein-Barr virus and varicella-zoster virus. Cytomegalovirus is species specific, usually cell-associated, and has the capacity to produce cytomegaly. Cytomegalic cells are enlarged cells that have nuclei that are increased in size. There is a lesser tendency for multinuclear giant cell formation although this occurs more regularly in vitro. The cytomegalic cell has an intranuclear inclusion that on hematoxylin and eosin staining is eosinophilic and separated from a condensed nuclear membrane by a clear zone. The nucleus may be indented by an intracytoplasmic inclusion body which also has eosinophilic staining. Infection with CMV induces a receptor for the Fc fragment of human immunoglobulin G (IgG). In humans, CMV affects a variety of cellular elements, including epithelial cells, vascular endothelial cells and a variety of blood elements including polymorphonuclear leukocytes and mononuclear cells. In vitro, the virus infects only human fibroblasts easily. The characteristic cytopathic effect in these cells is associated with cytomegaly, localization to a discrete portion of the cell monolayer and the formation of a brown pigment. In tissue culture, CMV can be shown to be associated with abnormal mitotic figures.

The DNA of CMV is double stranded and has a large molecular weight (150×10^6 Daltons). It is only exceeded by vaccinia virus among animal viruses in terms of its molecular weight. The DNA of CMV consists of a long and a short segment and exists in the form of 4 isomers. At the end of the long segment, there is a long terminal repeat; at the other end of the long segment, there is an inverted long terminal repeat. The short segment is bounded by short terminal repeats. The genomic map for human cytomegalovirus is beginning to be constructed. It is known, for example, that a transforming segment exists at the first portion of the genome. This transforming segment can be isolated, cloned and transfected into animal cells and can induce transformation. The transforming segment is rich in adenine and thymidine residues and is conceived to act as an enhancer or a promotor sequence. The functions of the other regions of the genome are just beginning to become elucidated. It is estimated that CMV can code for as many as 300 proteins. The surface envelope of CMV contains a number of glycoproteins. Beneath the envelope are a series of proteins in the tegmentum. The DNA of CMV is enclosed in a capsid with an icosahedral shape and which is composed of multiple capsomeres.

It has been ascertained by DNA homology studies that all human cytomegaloviruses share at least 80% of their genomes. This has been deduced by enzymatic restriction maps of the DNA of the virus. However, it has also been determined by neutralization tests that there are at least 3 different CMV types. Specific antibody to one of these types neutralizes the homologous virus but neutralizes the other 2 heterologous types less well. It is not known at the present time whether these neutralization differences are clinically significant. It is now known that reinfection can occur with CMV. This has been shown by several different lines of evidence: 1.) Patients followed serially will occasionally excrete a new CMV type as determined by DNA restriction mapping (Figure 1). 2.) Cytomegaloviruses with different DNA restriction maps have been found at different sites in several renal transplant recipients. 3.) When a kidney from a seropositive donor is

Figure 1. Examples of genetic heterogeneity of CMV strains.



C.A. Alford, 1981

transplanted into a seropositive recipient, IgM cytolytic antibody can be detected transiently. The presence of this antibody has to date only been found in primary as opposed to reactivated infections.

In perspective, 3 features of the virology of CMV appear significant: 1.) Exact knowledge about CMV is accumulating but has not progressed as far or as rapidly as with herpes simplex virus. 2.) Cytomegalovirus possesses segment(s) which can easily transform cells in vitro. 3.) Cytomegalovirus exists at least as several different types suggesting the possibility of reinfection but the clinical significance of such an event has not been ascertained at present.

EPIDEMIOLOGY

Between 0.6 and 1.9% (1% as an average) of all newborn infants excrete CMV in the urine. Of that 1%, approximately 5% are symptomatic at birth. The majority of these symptomatic children will develop significant mental and motor retardation with sensorineural hearing deficits. Microcephaly is common in this group of infants. An additional 5% of newborns with viruria will be asymptomatic at birth but will grow up to have significant mental and

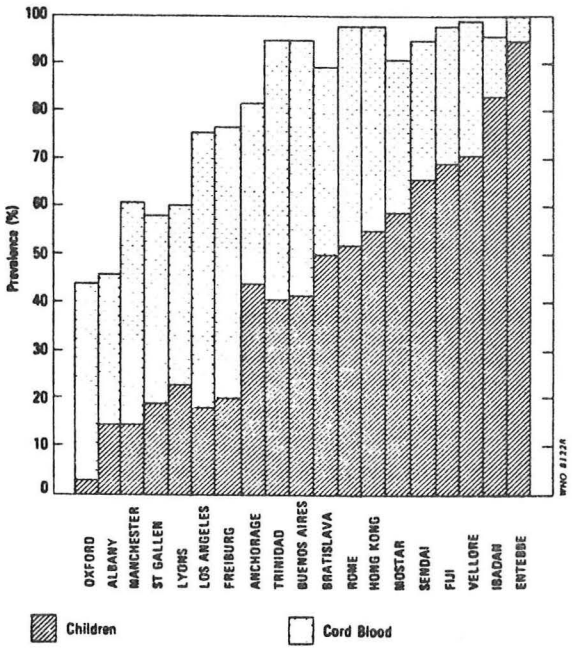
motor retardation and sensorineural hearing deficits. Thus, it is estimated that approximately 10% of infants excreting CMV at birth will eventually have some neural or hearing defect related to CMV. Prospective studies have revealed that the other 80-90% of viruric neonates will not have demonstrable difficulties. It has been determined that primary maternal infection is more serious in terms of its capacity to induce congenital deformities. In a highly immune population, approximately 2.4% of all infants will be excreting CMV, yet symptomatic disease in that population tends to be infrequent. Not all women experiencing primary infections will infect the fetus as ascertained by viruria at birth. It is estimated that only 40% of primary maternal infections are associated with congenital infection. Of all primary maternal infections, an estimated 10-15% of infants are symptomatic at birth and an additional 20% will develop sequelae related to the developing nervous system or impaired hearing. In immune mothers, the virus is reactivated and can infect the infant by transplacental passage (endometrium to placenta, viremia) but usually these infants are asymptomatic and only rarely will develop sensorineural hearing deficits or mental retardation on follow-up. Prospective studies are presently being performed around the world to determine the magnitude of abnormalities due to congenital infection with CMV and its impact on society.

In a study conducted at Parkland Memorial Hospital and Children's Medical Center 58 infants with manifest disease due to congenital CMV infection were identified during the 12 year period 1970 through 1981. Thirty of the infants were delivered at Parkland Memorial Hospital and 28 of the infants were hospitalized at Children's Medical Center or at Parkland Memorial Hospital but were born elsewhere. Each of these infants were pair matched with 2 control infants with negative urine cultures to determine the identifying features of the mothers. Over the 12 year period of the study, there was no increase in the frequency at which these infants were born which was not matched by a comparable increase in controls suggesting that the incidence of disease due to CMV in this population had not changed over the decade. The mothers of infants with congenital disease due to CMV tended to be younger and were more likely primiparous. Both of these effects (youth and parity) appeared to be independent variables. Multiparous mothers tended to differ from primiparous mothers in having a comparable age distribution to multiparous controls and to have a racial distribution which spared black persons. Three of the 58 infants with congenital disease due to CMV had an associated sexually transmitted disease: one infant had congenital syphilis, another chlamydial pneumonitis and conjunctivitis and the third had neonatal herpes simplex virus infection. Thirty infants were born at Parkland Hospital and it can be estimated a minimal risk for the occurrence in these cases is 1 per 3400 live births. Although mothers of infants with congenital disease due to CMV born at PMH had a high frequency of being unmarried at the time of delivery (60%) or of having had a sexually transmitted disease prior to delivery (24%), the differences between controls were not statistically significant. No clinical syndrome suggesting primary CMV infection could be found in these mothers. This finding is similar to other studies and it is recognized that the majority of primary infections in normal hosts at all stages of life are asymptomatic.

After birth the baby can be infected (perinatal infection). The likely sources of infection for the neonate include breast milk and cervical secretions. Although urine and saliva in the mother can be infected with

CMV, these secretions are unlikely sources of infection for the infant. It is estimated that 10% of women in a lower socioeconomic class census group will have cervical excretion of CMV at the time of delivery. Because of contact with cervical secretions, approximately 50% of exposed infants will become infected with CMV in the ensuing months. If a mother is seropositive for CMV and breast feeds for less than one month, the infant has a 40% chance of being infected with the virus. If the mother feeds the infant for longer than one month, approximately 60% of such exposed infants will become infected. An amazing potential exists for transmission of the virus vertically to the neonate (congenital or perinatal infection). In parts of the world where CMV is hyperendemic as in Nigeria or Uganda, CMV infection occurs in 95% of infants by the end of the first year of life (Figure 2).

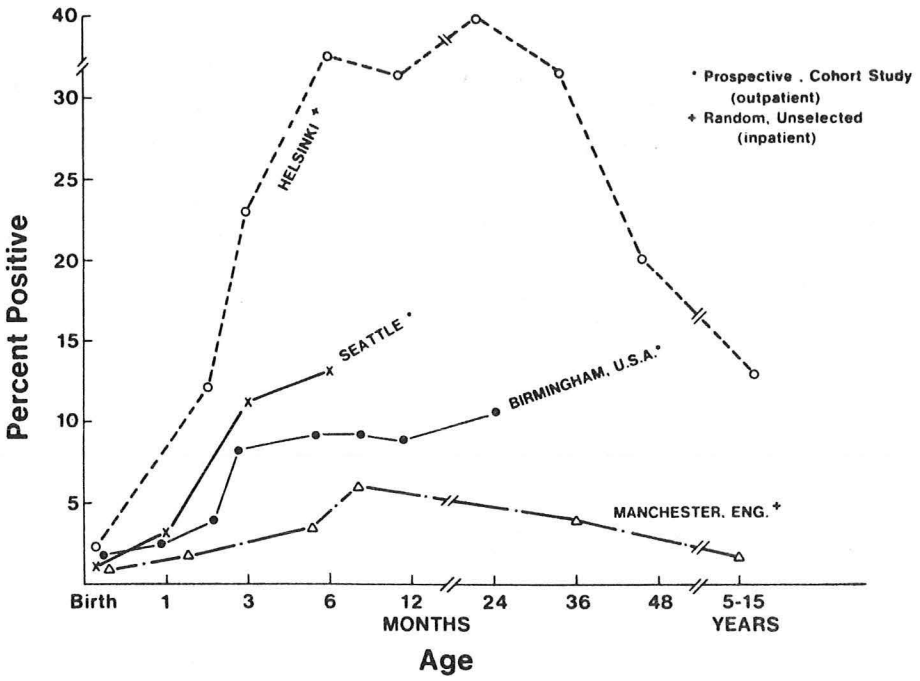
Figure 2. Cytomegalovirus complement-fixing antibody titres in serum from cord blood and from infants and children aged 4-48 months.



U. Krech, 1981

In the United States (Seattle, Washington), approximately 15% of infants in a middle class socioeconomic class population have been infected at the end of the first year of life. In developed countries like Japan and Finland, intermediate figures (40-70%) have been found, suggesting that in these countries other factors are operative, such as infant care centers (Figure 3). Cytomegalovirus acquired perinatally either from the cervix or maternal breast secretions usually results in asymptomatic infection, a benign event which serves to immunize the child. It is now recognized that CMV is a prominent cause of pneumonia occurring in the age period from one to three months. Pneumonia due to CMV can occur alone or be accompanied with agents like Pneumocystis carinii, Chlamydial trachomatis and Ureaplasma urealyticum.

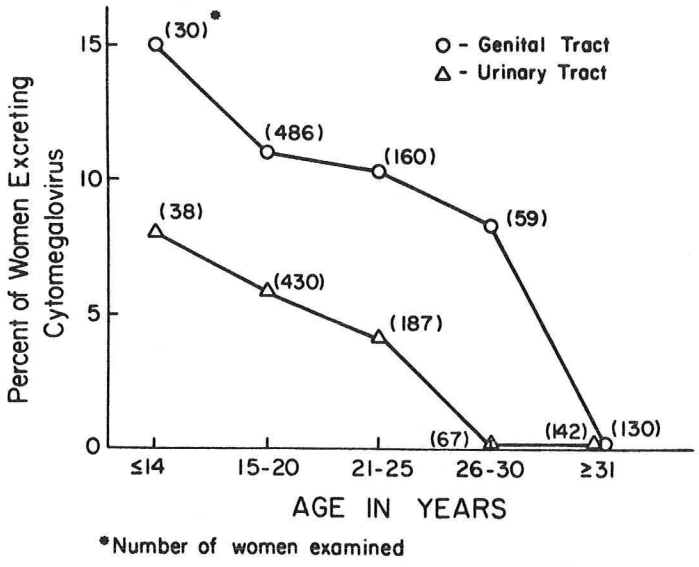
Figure 3. Prevalence of CMV excretion in infants and children.



C.A. Alford, 1981

One way in which the infant can acquire these pathogens is by contact or aspiration of infected cervical secretions. Infected younger women tend to excrete CMV in cervical secretions for long periods of time. With age cervical secretion of CMV falls so it is generally at a 0% level at 35 years of age (Figure 4). Excretion of the virus in infected infants in saliva or

Figure 4. Prevalence of CMV excretion from the genital and urinary tracts of low income females in relation to age after puberty.



C.A. Alford, 1981

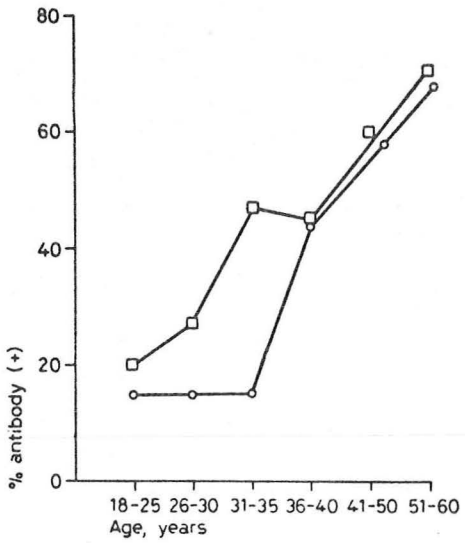
urine continues through at least a 5 year period with lesser numbers of children continuing to excrete virus at the end of 3 years.

A new source of CMV to the infant is now recognized as the Intensive Care Nursery. The infant can become infected by contact with secretions from another infected infant or more commonly can become infected by transfusion of seropositive (CMV antibody positive) blood. If an infant is seronegative (no CMV antibody) and premature and is administered seropositive blood the infection rate can be high and significant morbidity and occasionally death may occur. Infants transfused with seropositive blood can develop multiple organ system involvement due to CMV. Recently, an infant has been described at Children's Medical Center (Kevin Shannon, M.D., et al) with transfusion associated CMV disease who developed immunosuppression with reversal of his T4/T8 lymphocyte subset ratio, recurrent infections and subsequently, combined pneumonia due to CMV and Pneumocystis carinii.

After the first year of life, infants may come into contact with other infected infants. Day care centers may constitute a place where CMV infection may be very frequent. In a day care center in Birmingham Alabama caring for middle socioeconomic class infants, 100% of 2 year old infants were found to be infected as determined either by antibody levels or viral excretion. Infants were seen to mouth toys and the virus was shown to persist on the toys. Other infants would then mouth the same toy, completing a common pathway for infection. Infected infants can infect their parents by close contact. If a seronegative pregnant woman should come into contact with one of these children, it would constitute a threat to the developing fetus. After the age of 5 and through middle childhood, infection with CMV occurs but at a lower level than during the first 4 years of life. Viral excretion tends to fall off after the age of 5 years. The next period of life where CMV infection is common can be correlated with increased sexual activity. It is now recognized that CMV is frequently transmitted by sexual contact. The sexual transmission of CMV has been deduced from the following lines of evidence. 1.) Cytomegalovirus is found in cervical excretions more often in sexually promiscuous women, e.g., 20-25% of prostitutes or women with disseminated gonococcal infection. 2.) Nuns of the same age lack cervical CMV excretion. 3.) If a women is excreting CMV from her cervix, her male partner stands a 75% chance of having antibodies to CMV and approximately 20% of such partners will excrete the virus in semen. 4.) In serological surveys, an increasing prevalence of antibody to CMV occurs concomitantly with the onset of increased sexual activity (Figure 5). 5.) In homosexual men, in certain communities, CMV infection is extremely common and antibody to this virus almost universal.

Major sites of CMV transmission are gay communities. In cities like San Francisco, California and Seattle, Washington, more than 95% of gay men will have antibody to CMV (Tables 1, 2). Approximately 20% of such men will have urinary excretion of the virus and 30% will excrete the virus in semen. If multiple semen specimens are taken for analysis more than 50% of sampled gay men in San Francisco will excrete CMV. The concentration of CMV in semen, when measured, has ranged up to 10^8 ID_{50} (50% infectious dose) per ml. The duration of CMV excretion in semen in men with CMV mononucleosis can exceed 15 months. Not all gay communities in the world have such a high rate of CMV antibody prevalence or CMV excretion. It has recently been determined that in London, England, only 76% of gay men had antibodies to CMV, a figure only

Figure 5. Frequency of antibody to CMV in white females compared to white males.



R.F. Betts, 1982

Table 1

Prevalence of antibody to cytomegalovirus among homosexual and heterosexual men attending a venereal disease clinic and volunteer male blood donors.

Age (years)	No. positive/no. tested (%)		
	Heterosexual	Homosexual	Blood donors
18–29	18/38 (47.4)	70/75 (93.3)	10/28 (35.7)
≥30	20/32 (62.5)	60/64 (93.8)	34/75 (45.9)
Total	38/70 (54.3)	130/139 (93.5)	44/103 (42.7)

NOTE. Differences between homosexual men and both heterosexual men and volunteer male blood donors are statistically significant ($P < 0.005$) for each age group and for totals. Blood donors were unselected as to sexual orientation.

Table 2

Urinary excretion of cytomegalovirus in homosexual and heterosexual men attending a venereal disease clinic in San Francisco, Calif.

Age (years)	No. positive/no. cultured (%)		
	Homosexual	Hetero-sexual	*P*
18–29	14/101 (13.9)*	0/58	<0.001
≥30	0/89*	0/43	NS
Total	14/190 (7.4)	0/101	<0.005

NOTE. NS = not significant.
* $P < 0.001$.

W.L. Drew, 1981

slightly greater than heterosexual controls and that none of the gay men in this sample excreted CMV in urine. Attempts have been made in San Francisco by Drew and colleagues to determine the means of transmission of cytomegalovirus between gay men. These investigators determined that passive partners in genital-anal sexual contact had an antibody prevalence greater than 95%, whereas gay men not acting as passive partners in this form of sexual intercourse had an approximate 74% antibody prevalence. In San Francisco, of 31 gay men found initially to be seronegative, 75% seroconverted to CMV in the course of the ensuing year. There is an increasing realization of the hyperendemicity of CMV in gay populations in certain sections of the country.

Another means of contracting CMV infection is by receiving a transfusion of blood from a seropositive donor. In studies from 7 centers, it has been determined that the risk of CMV transmission by transfusing a single blood unit is 2.5% i.e., 2.5% of persons receiving a single blood unit will develop a 4-fold rise in antibody titer to CMV at the appropriate interval. In a study conducted in Kansas City, 7 men were found to be viruric. The three recipients of blood from these donors developed evidence of active CMV infection. The virus is usually thought to be present in white blood cells since freezing blood virtually eliminates CMV transmission. White blood cell concentrates can obviously be a major infecting source particulary as they cause serious and significant morbidity in bone marrow transplant patients. Cytomegalovirus has been such a problem in bone marrow transplant recipients that prophylactic or therapeutic white blood cell transfusion are no longer performed at UCLA, one of the three major centers in the country presently performing bone marrow transplantation procedures.

Organ allografts in transplantation may also harbour CMV. This extends at least to the kidney, the heart, and the marrow and to renal, cardiac and bone marrow transplantations. If a seronegative recipient receives a kidney from a seropositive donor there is an approximate 50% risk of infection. Primary infections tend are more severe than reactivated infections or infections occurring in the background of antibody. Since CMV antibody prevalence increases with age, the risk of an older donor being an infecting source rises concomitantly. Cadaveric donors are often young and have a greater chance of not being infected with CMV. Seropositive recipients who receive kidneys from seropositive donors may become suprainfected with another CMV strain; these persons will have a transient rise of IgM cytolytic antibody activity after transplantation.

Since cytomegalovirus is a herpesvirus, it can cause persisting infections and remain latent for the life time of the individual. It is known that either host vs graft or graft vs host reactions can reactivate or exacerbate CMV infections. This has been shown to be true in experimental situations in animals and is particularly clinically manifest in the bone marrow transplantation experience. Graft vs host disease is strongly correlated with the occurrence of interstitial pneumonia due to CMV. Interstitial pneumonia is the leading cause in death among bone marrow transplant recipients and the chief cause of this disease is CMV. The exact mechanism of how host vs graft or graft vs host reactions reactivates the virus or makes the viral infection worse is not known although a leading postulate is that the virus can persist in a latent form in some memory cell of the immunologic system and that viral replication ensues after intense

antigenic stimulation. The initiation of immunosuppressive therapy also serves as another mechanism for reactivating CMV.

In this regard, corticosteroid therapy, azathioprine, cyclophosphamide, and cyclosporin A can each be incriminated as specific agents inducing reactivation of the virus. In a study of patients on a Rheumatology Service at the University of Pittsburgh, patients who were placed on steroids and cytotoxic therapy seroconverted to CMV antigen commonly within three months after having been placed on these drugs. Since the organ allograft recipient may come to the transplantation process immunologically naive, may be transfused with blood from seropositive donors, may receive an organ allograft from a seropositive donor, may have significant host vs graft or graft vs host reactions and be on high dosages of immunosuppressive agents, it is not surprising that these patients represent the major disease threat posed by CMV aside from congenital infection. Cytomegalovirus now constitutes a major problem in the transplantation process, and is the major infectious disease threat in bone marrow transplantation. Cytomegalovirus accounts for 40% of the interstitial pneumonia in bone marrow transplant recipients and CMV pneumonia has a case fatality ratio of 90%.

Patients receiving combination chemotherapy for solid tumors or leukemias may also reactivate CMV. Although they may have disseminated disease due to this virus, the threat to these patients is considerably less than with transplant recipients.

Although CMV is passed between persons more easily than EBV, there appears to be relatively little risk from nosocomial acquisition in the ordinary hospital circumstance. This particularly pertains to personnel who take care of transplant recipients. The risk of nosocomial infection in personnel taking care of diseased infants needs to be determined better as well as the risk of engaging in the rehabilitation of these infants. Transmission of CMV in military recruit populations does not constitute a particular problem. Evidently close human contact with infection secretions is necessary. Most infections are asymptomatic but in view of the magnitude of viral transmission in the population at the present time, further studies of a prospective nature need to be performed on persons experiencing primary infections.

IMMUNOLOGY

The immunological aspects of CMV infections are just beginning to become understood. Humoral antibody does not prevent infection but in all probability modifies the severity of the illness which might be experienced with the infection. Since the virus is largely cell associated, mechanisms of recovery from viral infection must be mediated through the destruction of the infected cell. To some extent this involves antibody but to a greater extent, cell-mediated immunity is important, particularly natural killer (NK) cell function and HLA restricted cytotoxic T-cell activity. These latter two functions are presently thought to be essential for recovery from symptomatic infection with CMV. It is known that host vs graft or graft vs host reactions reactivate virus and accentuate infection. This presumably occurs because some immunologic memory cell has been induced to produce infectious virus from a latent state after exposure to a significant antigenic stimulus.

Cytomegalovirus is now recognized to be a potent agent inducing immunosuppression.

Following infection with CMV the following antibody types are produced: 1.) IgM antibody which can be detected in vitro either by indirect immunfluorescence or by the enzyme-linked immunosorbent assay (ELISA). A new antibody assay to detect cytolytic IgM antibody revolves about the ability of this antibody to attach to infected cells in vitro, to fix complement and subsequently lyse the cells. IgM cytolytic antibody is perhaps the first to be produced in active infections and has the capacity to destroy infected cells. 2.) IgG antibody is next formed and can be detected by complement fixation (CF), indirect immunofluorescence (IF), anticomplement immunofluorescence (ACIF) and ELISA. The neutralizing capacity of antibody can be separated from its complement fixing activity. The neutralizing activity of antibody usually implies protection and is directed against one or more of the glycoproteins of the viral envelope. Complement fixing antibody is directed against a variety of antigens of the virus, some of which need not be protective and also to some nonstructural antigens. 3.) IgA antibody can also be found both in serum and secretions during the course of infection.

During CMV mononucleosis or post-transfusion mononucleosis, a variety of auto- and heteroantibodies may be formed. Cytomegalovirus, like EBV, is presently perceived to be a polyclonal B cell activator. Rheumatoid factor, cold agglutinins, cryoglobulins, and antinuclear factor are among the antibodies that can be formed. These antibodies are infrequently seen in organ allograft recipients. In infants with congenital disease due to CMV, immune complexes are formed, can be detected in serum by various assays and may be deposited in the glomerulus.

The major host mechanism for recovery from CMV infections is cell-mediated immunity. This can be measured by lymphocytic proliferative responses to antigenic stimulation as demonstrated by tritiated thymidine incorporation into lymphocyte DNA, by the demonstration of antigen induced interferon (γ-interferon) production or by the measurement of other lymphokines. Cytomegalovirus is a relatively poor inducer of either α or β interferon. In a cell-free state, CMV is sensitive to the action of interferon but when the virus is cell-associated, it tends to be resistant. Another cell-associated immunological modality induced during CMV infections is antibody dependent cellular cytotoxicity (ADCC). In ADCC, infected cells combine with antibody and attract T lymphocytes bearing receptors for the Fc region of IgG. Cell destruction occurs after attachment of the T lymphocytes. The two most important cell-mediated immune defenses against CMV infections are NK cell activity and HLA restricted T lymphocyte cellular cytoxicity. Natural killer cell activity can be assay in vitro by incubating peripheral blood leukocytes with target cells radiolabeled with chromium. The attack is not antigen specific and the target cells may be, for example, a tumor cell to which the patient has never been exposed. Interferon enhances NK cell activity. HLA restricted T lymphocyte cellular cytotoxicity can be demonstrated by matching T lymphocytes from the patient with fibroblasts from a library of different HLA types and that also are infected with CMV. In order for cell destruction to occur, the T lymphocyte and fibroblast must be matched at an HLA A or B locus and the lymphocyte must recognize CMV antigen as foreign. HLA mismatched target cell lysis is

usually a product of the action of NK cells. In acute CMV infections, HLA restricted T lymphocyte cellular cytotoxicity generally occurs as an acute, transient phenomenon, disappearing when the infection has been controlled. In bone marrow and renal transplant recipients, successful outcome from the infection has been best correlated with NK cell activity and HLA restricted T lymphocyte cellular cytotoxicity.

Both host vs graft and graft vs host reactions have been shown to reactivate CMV infections and to accentuate their intensity. The titer of murine CMV that can be found in organs like spleen and liver has been shown to be elevated in mice given an incompatible skin graft. In a murine CMV model, latently infected B lymphocytes have been shown by Oldstone and colleagues to reactivate virus when placed on a allogeneic fibroblast monolayer but not on a syngeneic fibroblast monolayer. In bone marrow transplant recipients, the severity of CMV infections is closely correlated with graft vs host disease. Recipients of marrow transplants from syngeneic donors essentially do not develop CMV pneumonia whereas recipients of marrow transplants from allogeneic donors frequently develop severe pneumonia due to this virus (Table 3).

Table 3

Incidence of nonbacterial, nonfungal pneumonia after marrow transplantation for hematological malignancy

	Syngeneic	Allogeneic
Total pneumonia	0.17 [a]	0.48 [b]
Idiopathic	0.11	0.13
P. carinii	0.01	0.07 [b]
Cytomegalovirus	0	0.19 [b]
Other virus	0.01 [c]	0.03
Clinical	0.04	0.09

[a] Entries indicate proportion of patients with each pneumonia type.

[b] Differences between syngeneic and allogeneic transplants are statistically significant.

[c] Herpes simplex virus.

F.R. Appelbaum, 1982

Another element of the relationship of CMV to the immunological system is immunosuppression: CMV is among the foremost known viral immunosuppressing agents. It has been shown that renal transplant recipients who have fatal infections due to CMV fail to mount an antibody response. In experimental animals, antibody responses to other agents are less if the animal is infected with CMV as compared to control animals. Lymphocyte proliferative responses to CMV antigen, to other herpesvirus antigens, to

common bacterial antigens and to non-specific mitogens (PHA, PWM, Con A) may be depressed during acute CMV infection, and return after the infection has been controlled (Table 4).

Table 4

Lymphocyte reactivity (LR) to bacterial recall antigens, phytohaemagglutinin (PHA), concanavalin A (Con A) and pokeweed mitogen (PWM) in eighteen patients with acute CMV infection and in matched controls

		PHA		Con A		
Patients	Bacterial Ag	1 μl/ml	5 μl/ml	1 μg/ml	5 μg/ml	PWM
Acute (0–50 days)	1142* (0–8774)	5673† (45–38,700)	26,856 (1303–67,722)	1137* (96–8788)	2517* (0–23,337)	4828* (0–19,414)
Convalescence (50–250 days)	2375* (0–30,469)	8234 (1683–45,033)	42,266 (12,245–81,949)	2594* (380–6248)	3729* (309–14,105)	7725* (1615–22,869)
Follow-up (> 250 days)	4178‡ (766–31,957)	15,701 (3172–53,272)	37,744 (16,053–55,181)	3552 (317–25,754)	12,059 (286–45,539)	10,943† (387–25,291)
Controls	13,594 (468–53,317)	10,911 (3063–56,565)	31,967 (10,821–62,049)	9591 (970–36,016)	16,460 (2294–43,435)	15,054 (5685–50,604)

LR test results are expressed as median value and a range (in parentheses) of specific increase in d/min.
* $P < 0.01$.
† $P < 0.05$.
‡ $P < 0.02$.
All P values opposed to controls.

C.H.H. ten Napel, 1980

γ interferon responses are similarly affected (Table 5).

Interferon production in mitogen-stimulated cultures of mononuclear leukocytes from acute and convalescent cytomegaloviral (CMV) mononucleosis patients.

		Mitogen treatment†			
Group	Tests*	None	PHA	PWM	Con A
Patients					
Acute	6 (5)	<10	17 ± 13	12 ± 4‡	13 ± 7
Convalescent	6 (6)	<10	62 ± 24	70 ± 20	47 ± 23
Normal donors	21 (11)	<10	39 ± 15	53 ± 10	34 ± 16

NOTE. Patients with acute CMV mononucleosis were studied a mean of 19 days (range, 13–26 days) after the onset of illness, while convalescent patients were studied a mean of 164 days (range, 49–354 days) after the onset of illness. The patients in this table represent only a portion of the total group of acute- and convalescent-phase patients studied. PHA = phytohemagglutinin, PWM = pokeweed mitogen, and Con A = concanavalin A.

* Number of tests (number of donors).
† Mean level of interferon (units/0.2 ml) ± SE.
‡ Differs significantly from convalescent value ($P < 0.01$) and normal value ($P < 0.025$) (Student's t-test).

C.R. Rinaldo, Jr., 1980

The first function that returns is the lymphocyte proliferative response to CMV antigen. During active CMV infections, enhancement of NK cell activity by interferon is depressed. In CMV mononucleosis or post-transfusion mononucleosis, OKT8 staining cells are expanded in number with a relatively normal component of OKT4 staining lymphocytes. The T4/T8 ratio is reversed but these syndromes are usually associated with lymphocytosis and not lymphopenia. The atypical or stimulated lymphocyte in CMV mononucleosis is an OKT8 positive, Ia bearing cell. In renal transplant recipients, the T4/T8 ratio in CMV disease is also depressed but because of concomitant immunosuppression, there is lymphopenia and the T4-T8 subset abnormalities closely approximate that seen in AIDS. CMV induced immunosuppression can last for protracted periods. Since the virus in vivo infects only polymorphonuclear leukocytes, macrophages and perhaps T lymphocytes and the number of infected cells are few, the mechanism whereby such a depression of the immunologic system can be mediated would appear not to be actual infection of immunologic cells by the virus. Perhaps, circulating factors are involved but the mechanism of CMV induced immunosuppression is not presently known.

In murine CMV infections, pathogenic bacteria are poorly cleared by the reticuloendothelial system. In humans with CMV mononucleosis or post-transfusions mononucleosis, it has been determined that there is normal polymorphonuclear leukocyte function. In most series of patients who are transplanted and have disease due to CMV, there is an increase in the incidence of bacterial infections and infections with opportunistic organisms such as Pneumocystis or Nocardia (Table 6).

Table 6

Pulmonary Infections Other than Cytomegalovirus (CMV) after Cardiac Transplantation.

Group	Primary CMV Infection	Pre-Transplant CMV Infection	No CMV Infection
Early infections (no.):	12	20	8
Bacterial:			
Pneumonia	2	1	0
Abscess	4	0	0
Totals	6/12	1/20 (P<0.01*)	0/8 (P<0.025*)
Nocardia	0	1	0
Fungal	3	2	1
Total 1st 90 days	7/12†	4/20† (P = 0.03*)	1/8 (P = 0.05*)
Late infections (no.):	11‡	19‡	8
Bacterial:			
Pneumonia	3	1	1
Abscess	1	0	0
Totals	4/11	1/19 (P = 0.04*)	1/8 (NS§)
Pneumocystis	4	1 (P = 0.04*)	1 (NS§)
Fungal	1	1	0
Nocardia	0	3	0
Mycobacterial	0	1	0
Subtotal for 90 days–1 yr	7/11†	6/19† (NS§)	2/8 (NS§)
Total for 1st yr	10/12†	8/20† (P = 0.02*)	2/8 (P<0.01*)

*By Fisher's exact-probability test as compared with the primary-CMV group.
†Patients with >1 infection are only counted once.
‡1 patient in each group died before 90 days.
§Difference not significant by Fisher's exact-probability test.

K.H. Rand, 1978

Suprainfection with one of these organisms during disease due to CMV constitutes one of the major threats to the survival of allograft recipients. It has been shown that bacteria coated with antibody adhere to the Fc receptor bearing portion of CMV infected cells. What role this phenomenon plays in the increased infection problem seen during the course of CMV disease in transplant recipients remains to be determined.

In renal transplant recipients with CMV viremia, a glomerulopathy has been demonstrated by investigators at the Massachusetts General Hospital. The glomerulopathy is characterized by deposits of IgM along basement membranes and the presence of IgM complexes. This glomerulopathy has evidently been seen at other institutions. Its incidence, causation and prognosis need further independent documentation and assessment.

The complicated inter-relationships of the immunologic system and CMV infections is best exemplified in renal transplant recipients. Host vs graft reaction reactivates and exacerbates CMV infection. Viremic CMV infection may be associated with a glomerulopathy. If rejection is diagnosed, more immunosuppressive drugs and the global effect of CMV on the immunologic system pave the way for serious bacterial infections and opportunistic infections by Pneumocystis, Nocardia, Cryptococcus and other organisms. Severe disease due to these infections may lead in turn to increasing renal dysfunction.

CLINICAL MANIFESTATIONS

For the most part, CMV infections are asymptomatic. Primary infections, (negative to positive antibody titer rises) generally are considered to cause the most clinical symptomatology. Reactivated infections (antibody rise from an initial positive value) are thought to cause proportionately less clinical illness. Reinfections are now known to occur with CMV and it is possible that with further time and study, reinfection will be placed in the intermediate zone between primary and reactivated infections in terms of induction of clinical signs and symptoms.

The infant with congenital disease due to CMV has a clinical syndrome which includes a low birth weight, microcephaly, mental and motor retardation, sensorineural hearing deficits, hepatosplenomegaly, jaundice, and petechiae. The infant may also have thrombocytopenic purpura and acquired hemolytic anemia. Males have a high frequency of inguinal hernias. Infants can develop interstitial pneumonia. It has also been determined that a certain percentage of infants congenitally infected but asymptomatic at birth will go on to develop sensorineural hearing deficits, mental and motor retardation. Perinatally infected infants, acquiring the virus either from cervical secretions or maternal breast milk, infrequently may develop pneumonia between the first and third months of life. The pneumonia is probably acquired by aspiration, may have a chronic course and may be associated with infection due to Chlamydia trachomatis, Pneumocystis carinii, or Ureaplasma urealyticum.

The next clinical syndrome that can occur is CMV mononucleosis. It has been estimated that 8% of all cases of infectious mononucleosis are caused by CMV. In general and depending upon the series of patients that are analyzed,

CMV mononucleosis tends to be more typhoidal in character than pharyngeal, i.e., patients more commonly present as a fever of undetermined origin than with pharyngitis (Table 7). Patients with CMV mononucleosis, however, can

Table 7

Symptoms and Signs in Nine Patients with Spontaneous Cytomegalovirus Mononucleosis

Symptoms	Number of Patients
Malaise	9
Fever	8
Chills	6
Myalgia	6
Sore throat	5
Headache	4
Anorexia	3
Abdominal pain	2
Signs	
Pharyngeal erythema	5
Lymphadenopathy	5
Rash*	5
Splenomegaly	3
Hepatomegaly	0
Exudative pharyngitis	0

* Includes one patient whose rash was associated with ampicillin therapy.

M.C. Jordan, 1973

have pharyngitis and this can extend to exudative tonsillitis. Fever is invariable. There may be generalized lymphadenopathy and hepatosplenomegaly. Pneumonia, a diffuse maculopapular rash and myocarditis occur infrequently. The rash may be brought on by the administration of a drug like ampicillin. Myopericarditis can occur during the course of CMV mononucleosis but cardiac dilatation and congestive heart failure would be distinctly unusual. A Guillain-Barre' syndrome may be produced. Encephalitis has rarely been reported. As more cases are tested for antibodies to CMV and EBV, these agents are increasingly recognized as precipitating causes of the Guillain-Barre' syndrome. There have been instances of thromocytopenic purpura and acquired hemolytic anemia occuring during the course of CMV mononucleosis. The course is almost always benign and the disease process is usually over within a 3-4 week period of time. On occasion the clinical picture of hepatitis may outweigh the other manifestations of the disease process.

From a laboratory standpoint, the white blood count is usually elevated with an absolute and relative lymphocytosis and with the presence of atypical or stimulated lymphocytes (Tables 8, 9). Mild hepatic dysfunction is the rule. CMV is one of the organisms that can cause diffuse granulomas of the liver. The alkaline phosphotase is sometimes disporportionally elevated in respect to the SGOT but is rare that the SGOT exceeds 500 International units. Occasional patients with CMV mononucleosis can be jaundiced but this tends to be the exception rather than the rule. A variety of hetero and auto- antibodies appear in the circulation. Closely allied to CMV mononucleosis syndrome is post-transfusion mononucleosis. Following the receipt

Table 8

Laboratory Findings in Nine Patients with Spontaneous Cytomegalovirus Mononucleosis

Data*	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age, *yr*; Sex	25 F	22 F	26 F	20 F	21 F	28 F	19 F	21 F	24 F
Leukocyte count, *no./mm³*	10 900	12 800	15 100	7 500	12 100	19 100	10 600	5 500	8 000
Lymphocytes †, %	63	61	61	60	72	67	64	62	77
Atypical forms †, %	25	15	27	25	34	27	10	13	32
SGOT, *IU* (normal, 0 to 12 *IU*)	40	36	34	12	23	25	13	13	35
SGPT, *IU* (normal, 0 to 12 *IU*)	35	28	70	12	14	19	15	11	34
LDH, *mIU* (normal, <200 *mIU*)	525	—	250	—	—	390	320	—	—
Alkaline phosphatase, *Sigma units* (normal, 0.8 to 2.3 *Sigma units*)	3.2	2.3	2.2	0.7	1.5	3.3	3.1	2.0	—
Cold agglutinin titer	1:224	1:32	—	—	—	1:64	—	—	—

* Highest value recorded for each test. SGOT = Serum glutamic-oxalacetic transaminase; SGPT = Serum glutamic-pyruvic transaminase; LDH = lactic acid dehydrogenase.
† Percent of total leukocytes.

M.C. Jordan, 1973

Table 9

Clinical and laboratory data for four homosexual men with spontaneous mononucleosis due to cytomegalovirus (CMV).

Case no.	Age (years)	Duration of illness (weeks)	Temperature (C)	Splenomegaly	No. of leukocytes/mm³	Percentage of atypical lymphocytes	CMV in urine	Antibody titer* Acute-phase	Antibody titer* Convalescent-phase	Infectious mononucleosis serology	HBsAg†	Presence of antibody to *Toxoplasma gondii*	SGOT‡	LDH§
1	21	2	39.0	–	5,800	6	+	128	512	–	–	–	500	475
2	28	6	37.5	+	6,800	40	–	<8	32	–	–	–	55	332
3	20	35	39.0	–	7,500	90	+	ND	≥2,048	–‖	ND	ND	ND	ND
4	26	3	38.3	+	4,100	29	+	64	64	–	–	–	50	188

NOTE. Laboratory data are expressed as the highest value recorded for each test. Positive = +; negative = –; not done = ND.
* Expressed as the reciprocal titer of CF antibody.
† HBsAg = hepatitis B surface antigen.
‡ SGOT = serum glutamic oxaloacetic transaminase (normal value, 10–50 units/liter).
§ LDH = lactic dehydrogenase (normal value, 90–225 units/liter).
‖ Performed three times.

W.L. Drew, 1981

of transfused blood, oftentimes during cardiac surgery, the patient can develop fever, hepatosplenomegaly and hepatic dysfunction. Absolute and relative lymphocytosis with atypical lymphocytes are part of the characteristic laboratory picture. Hetero- and autoantibodies occur and acquired hemolytic anemia is not uncommon. The syndrome must be distinguished from bacterial endocarditis following cardiac surgery but its course generally is benign unless significant immunosuppression is present.

Approximately 20-30% of renal transplant recipients develop a syndrome related to CMV infection (Table 10). Primary infections are usually the most severe though on occasion reactivated infections can also cause significant morbidity. The patient develops fever, malaise, arthralgias, myalgias and

Table 10

CHARACTERISTICS OF PATIENTS AND
MANIFESTATIONS OF DISEASE DUE TO CMV

	Patients	Controls	p
LRD/CAD	5/4	5/13	NS
1^{o} CMV/2^{o} CMV or No CMV	5/4	2/16	0.02
SEX (M/F)	5/4	10/8	NS
RACE (W/B)	9/0	10/8	0.02
AGE (MEDIAN)	31	31.5	
Fever > 3 days/No fever	9/0	2/16	<0.001
SGOT ↑/Normal SGOT	7/2	2/16	0.001
WBC ↓/Normal WBC	8/1	0/18	<0.001
Cr ↑/No change in Cr	5/4	3/15	0.05
Bolus/No bolus	6/3	3/15	0.02
Assoc. inf./No infection	4/5	3/15	NS
Pneumonia/No pneumonia	4/5	1/17	0.03
+ CMV culture/ - culture	7/2	2/8	0.02

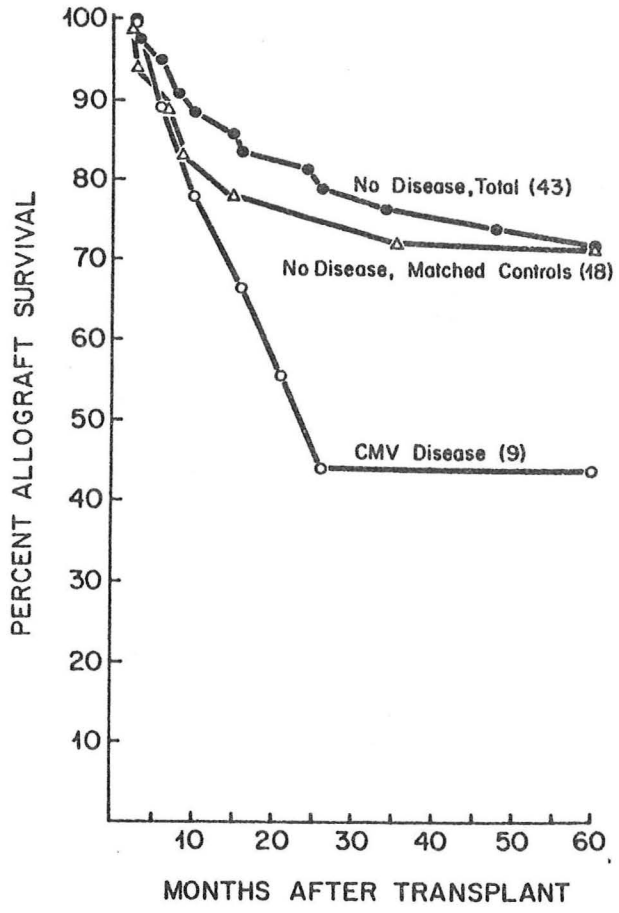
J.P. Luby, A.J. Ware, A.R. Hull, J.H. Helderman, P. Gailiunas, S. Butler, and C. Atkins,

hepatosplenomegaly, generally between the first and third month after transplantation. Pharyngitis and lymphadenopathy are not seen. Leukopenia is common and lymphocytosis or atypical lymphocytosis does not result because of immunosuppressive therapy. Neutropenia can result with the absolute neutrophil count being below 2500. Patients can develop pneumonia which is usually generalized and interstitial but on occasion can be focal and nodular. Plural effusions can occur but are infrequent. Auto and heteroantibodies are usually not observed in these patients probably because of the associated immunosuppression.

Renal allograft dysfunction occurs more commonly in patients with disease due to CMV than in closely matched chronological patient controls. The mechanism of allograft dysfunction has not been elucidated but may in part be due to a distinctive glomerulopathy that can occur in the course of CMV viremia. If glomerulopathy associated with CMV viremia is diagnosed, the therapy is reducing immunosuppression rather than increasing it as would be required for allograft rejection. The disease can be relatively long lasting but the majority of cases are generally over within a month period of time. One of the major difficulties with the syndrome is that it can only be diagnosed by laboratory means towards its clinical end. This oftentimes necessitates an extensive and expensive work-up in the hospital to exclude

other causes of fever. On occasion the disease may be protracted resulting in significant immunosuppression, T4/T8 ratio reversal and leukopenia and it is during this period that pyogenic and opportunistic infections may occur at a high frequency. Infrequently in the renal transplant recipient, CMV may cause a widespread dissemination with encephalitis, pneumonia simulating ARDS, pancreatitis, gastrointestinal tract ulcerations and associated other complications. Cytomegalovirus can induce progress retinopathy in some patients. This retinopathy has a characteristic clinical appearance and its therapy usually necessitates withdrawal of immunosuppression. It is presently debated as to whether or not CMV can cause loss of the allograft. The issue is not settled and it will be of interest to determine which comes first: allograft rejection initiating and exacerbating the CMV infection or some event like glomerulopathy inducing loss of the graft (Figure 6).

Figure 6. Percent allograft survival after transplantation (PMH)



J.P. Luby, A.J. Ware, A.R. Hull, J.H. Helderman, P. Gailiunas, S. Butler, and C. Atkins, 1983.

The most serious disease caused by CMV occurs in the bone marrow transplant recipient. By in situ hybridization, it has been found pathologically that CMV can exist in many cells such as in the salivary glands, the pancreas, hepatocytes, myocytes, etc. The basic pathogenic

process for the occurrence of such disseminated foci is probably through infection of the vascular endothelium and this has been documented. The most feared complication of CMV infection in the bone marrow transplant recipient is interstitial pneumonia. The leading cause of death in bone marrow transplantation is interstitial pneumonia and in approximately 40% of cases it is caused by CMV. The case fatality ratio for interstitial pneumonia induced by CMV is presently 90%.

The relationship between CMV and AIDS (acquired immunodeficiency syndrome) is presently undergoing investigation. Antibody to CMV is almost invariable in the gay population and in Haitians. Antibody to CMV is less common in hemophiliacs and in heterosexual drug abusers. In the latter two categories, cases of AIDS have occurred in the absence of detectable evidence of CMV infection. Since the onset of the AIDS epidemic occurred in all four groups at the same time, most investigators feel that another agent(s) is (are) responsible for the etiology of that syndrome. Cytomegalovirus, however, may play an adjunctive role particularly in gay populations and disseminated disease may complicate AIDS. Viruria due to CMV is common in the gay population in cities like Seattle, Washington and San Francisco, California. It can occur in 20% of a random sample of gay men. CMV can be found in the semen in more than 50% of such persons if multiple samples are cultured. In the study of the risk of CMV transmission by blood units, it was found that recipients of transfused blood from viruric donors sero-converted to CMV. This may indicate the possible presence of viremia in a certain number of gay men who are viruric. The common alteration in T-cell subsets observed in gay populations in New York and Los Angeles could be explained by infection with CMV (Table 11). The severe immunosuppression and

Table 11

Comparison of T-Subset Changes in Patients with AIDS (and Opportunistic Infection or Kaposi's Sarcoma) and in Healthy, Sexually Active Homosexual Men.

	Control Population *	AIDS and Opportunistic Infection	AIDS and Kaposi's Sarcoma	Healthy Homosexual Men	
				A †	B ‡
No. tested	28	20	18	8	89 (37)
Leu-3:Leu-2 ratio	1.72	0.50 §	0.58 §	1.14 §	1.24 § (0.70) §
Leu-3 (mean/mm^3)	787	307	239 §	1236	860 (718)
Leu-2 (mean/mm^3)	504	649	463	1261 ¶	776 (986) ¶

*Adult female and male heterosexuals. †Healthy male homosexuals, as described elsewhere.[5]

‡Healthy male homosexuals (average age, 27 years).[8] Figures in parentheses refer to a subset with a Leu-3:Leu-2 ratio <1.0.

§P<0.05 as compared with controls. ¶P>0.05 as compared with controls.

J.L. Fahey, 1983

the immunological abnormalities seen in AIDS are reproduced only in the transplant recipients in which immunosuppressive drugs are further operative in addition to disease due to CMV. Not all gay populations in the world are similar to those found in San Francisco. In a recent study in London, only 76% of gay men had a positive antibody titer for CMV, as opposed to 50% of

heterosexual controls, and none were viruric. A pre- AIDS syndrome with generalized lymphadenopathy has been shown to exist. CMV antibody prevalence is high in this group of persons, as is viruria and the presence of virus in semen. IgM antibody titers for CMV tend to be elevated but at a level less than in the actual AIDS cases. AIDS and pre-AIDS cases in gay men are strikingly different from heterosexual controls in terms of CMV. AIDS patients tend to have high titered antibody to EBV, a high prevalence of past infection with syphilis, and high antibody rates to hepatitis B. The issue of how much CMV contributes to the AIDS syndrome in gay men will only be determined as new agents such as human T-cell leukemia virus (HTLV) are excluded from consideration.

Kaposi's sarcoma is frequent in AIDS patients. This sarcoma is also seen in equatorial Africa where it has an bimodal age incidence: the first peak occurs in the first 10 years of life and the second peak occurs in the age group, 30-39 years of age. There is a male predominance of cases. In Zaire, Kaposi's sarcoma accounts for approximately 10% of all cancers. Kaposi's sarcoma in equatorial Africa tends to be highly malignant with a short course and rapid metastasis to visceral organs. Because of its striking geographical distribution and because of the Burkitt's lymphoma experience, investigators have studied the potential viral etiology of Kaposi's sarcoma. Giraldo was the first to culture Kaposi's sarcoma biopsies and found both CMV antigen and herpes virus-like particles. In a sample of American men with Kaposi's sarcoma, prior to the AIDS experience, 100% had antibody to CMV as opposed to an antibody prevalence that was significantly less in American melanoma patients that were age and sex matched. Cytomegalovirus antigen can be found in Kaposi's sarcoma cells by anticomplementary immunofluorescence as well as by DNA DNA-reassociation kinetics (Table 12).

Table 12

DETECTION OF CMV-RELATED ANTIGENS AND CMV-DNA IN KAPOSI'S SARCOMA BIOPSIES AND/OR TISSUE CULTURE (TC) CELLS DERIVED FROM THEM

KS code	Geographic location	Sex	Age (Years)	CMV-related antigens[1]		CMV-DNA[2]
				Cryostat sections	TC cells	Biopsies
KS- 22	Uganda	M	53	NT[3]	+	NT
KS- 32	Uganda	M	40	+	+	NT
KS- 38	Uganda	M	35	+	NT	NT
KS- 55	Senegal	M	15	+	NT	NT
KS- 71	Senagal	M	24	+	NT	NT
KS- 80	Uganda	M	34	+	NT	+
KS- 82	Uganda	M	25	NT	+	NT
KS- 93	Uganda	M	50	+	NT	NT
KS- 95	Uganda	M	60	+	NT	NT
KS-102	Uganda	M	44	NT	NT	+
KS-111	Uganda	M	34	NT	+	+

[1] 7/31 (22%) tumor biopsies and 4/12 (33%) cell lines deriving from them were positive for CMV-related antigens when tested as cryostat sections by ACIF. – [2] 3/8 (37%) tumor biopsies were positive when tested for CMV-DNA by DNA-DNA reassociation kinetics. – [3] NT, not tested.

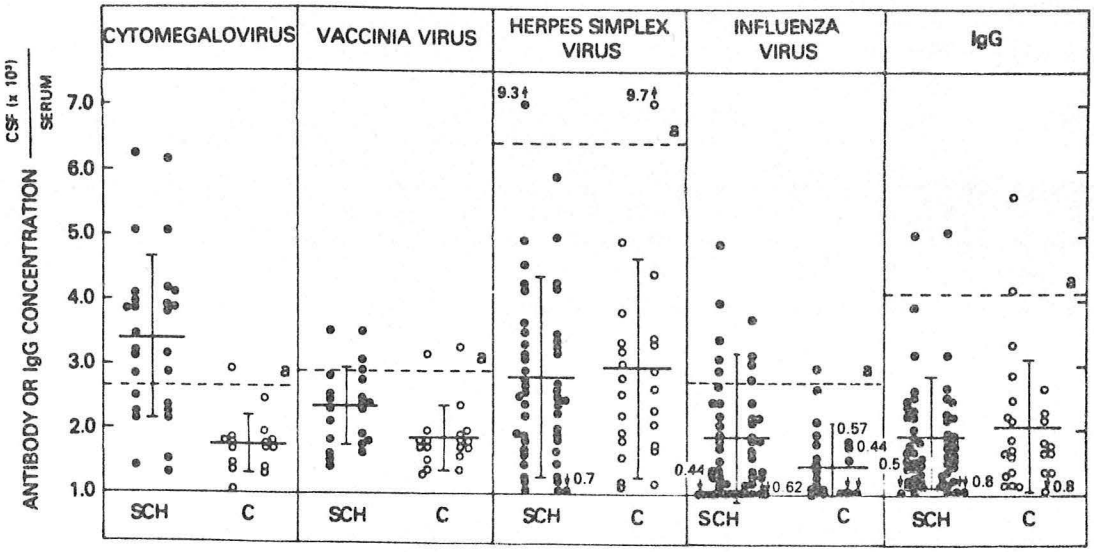
G. Giraldo, 1980

In the recent epidemic of Kaposi's sarcoma in San Francisco, CMV antigen was found in 16 of 30 sarcoma biopsies by anticomplementary immunofluorescence and only one of 22 normal skin biopsies from the same patients. Kaposi's

sarcoma accounts for 3% of all tumors occurring in the renal transplant population. Two events may be necessary for the occurrence of Kaposi's sarcoma in renal transplant requests, viz., immunosuppression and a high frequency of CMV infection. Disseminated CMV infections may occur in AIDS patients and CMV pneumonia oftentimes accompanies pneumonia due to Pneumocystis. There may be evidence of disseminated CMV infection in the brain, the gastrointestinal tract, the pancreas and other organ systems. One cannot completely sort out the contribution of CMV to AIDS, particularly in gay men, at the present time but it is conceivable that the transmission of this virus can be reduced since not all gay populations in the world have such a high prevalence of infection.

We need to determine the extent to which CMV infections are symptomatic. This will probably only be done by careful prospective study of persons undergoing CMV seroconversion such as in sexually transmitted disease clinics, in gay populations or in immunosuppressed patients. A recent interesting observation has been recorded demonstrating that antibody to CMV can be elevated in the cerebrospinal fluid of randomly selected schizophrenic patients. Comparably elevated titers as compared to controls were not seen with herpes simplex virus, vaccinia virus or influenza A virus (Figure 7).

Figure 7. Distribution of viral antibody and IgG across the blood-brain barrier in schizophrenic patients and controls.



P. Albrecht, 1980

DIAGNOSIS

In the neonate, the best way to establish the diagnosis of CMV infection is by culture of the urine or throat. In neonates with congenital disease due to CMV, urine oftentimes contains virus in high titer and the characteristic cytopathic effect can be observed within a few days. Buffy coat cultures can also be performed but it may take some time (up to one month) for the specimen to become positive. In the adult, urine, throat,

buffy coat, and semen samples can be assayed for virus. In addition, autopsy specimens can also be cultured. The cultures are usually placed on human fibroblast cells. In the past, the diagnosis of CMV infection has been made by finding characteristic cells in urinary sediment. This method is quite insensitive in comparison to culture.

Serological studies utilize CF, IF, ACIF and ELISA. The CF test should utilize a glycine extracted antigen from a strain of CMV which is known to have broad serological cross reactivity (AD 169). Complement fixation tests require that a 4-fold rise in titer be demonstrated before infection with the virus can be proven. The IF tests can be utilized to detect IgG antibody. A modification of the IF test which utilizes guinea pig complement and fluorescinated anti-guinea pig complement antibody is presently one of the most specific and sensitive ways to test for antibody to CMV (ACIF). This ACIF test eliminates the non-specific immunofluorescence that can be seen due to the occurrence of Fc receptors on CMV infected cells. A test that would detect acute infection early would be quite desirable. Several possible tests have been mentioned in this regard. One test utilizes immunofluorescence and the early antigen of CMV. This antigen appears within 72 hours of infection and occurs in spite of a block with cytosine arabinoside. Unfortunately antibody to this particular antigen can persist in infected persons for relatively long periods of time and may limit its utility in diagnosing acute infections. A immunofluorescent test to detect the presence of IgM antibody has been proposed. Unfortunately, false positive results tend to occur in this test: acute EBV and VZV infections may give rise to a false positive IF test for IgM antibody to CMV. The IgM IF test may be falsely positive in the presence of rheumatoid factor. Some investigators have felt that an ELISA test system to detect IgM antibody to CMV might be more sensitive and specific but this thesis needs to be confirmed. Cytolytic IgM antibody to CMV has been described. This test probably is the most specific for acute infection. Unfortunately, the test is presently difficult to perform.

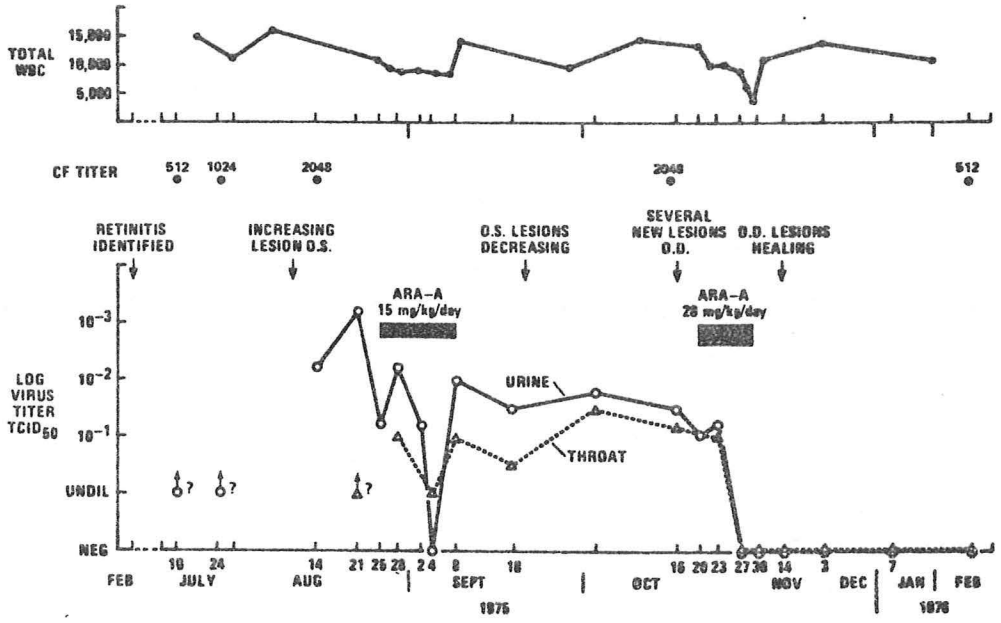
Simple isolation of a virus from a bodily secretion has to be considered in the total context of the fact that people excrete virus for long periods of time after infection. In children, viruria can last for as long as 5 years and in adults the virus can be found in semen for as long as 15 to 18 months following initial infection. Because of the availability of other tests, that can be performed more easily, the indirect hemagglutination test is infrequently utilized.

For the clinician trying to diagnose CMV disease, a urine specimen, a throat swab placed in viral transport media, a buffy coat preparation, or a sample of semen should be collected promptly and transmitted to the laboratory as rapidly as possible. If plating cannot be performed immediately, the specimens should be placed at $4^{o}C$ and should not be frozen. An acute phase serum should be drawn from the patient and an appropriate serological test performed. If tests for IgM antibody to CMV are performed, it should be recognized that false positives occur during the course of EBV and VZV infections and in the presence of rheumatoid factor. A convalescent serum sample, 2-3 weeks after the onset of illness, should subsequently be drawn and submitted to the laboratory to detect rises in antibody titer.

TREATMENT

IDUR (5-Iodo-2'-deoxyuridine) and cytosine arabinoside were used intially to treat neonates with disease without success. The virus in vitro is resistant to these drugs as well as adenine arabinoside (Ara-A) and acyclovir (ACV). Therapeutically, interferon has not been effective in interstitial pneumonia due to CMV or in neonates with congenital disease. Combinations of ACV or Ara-A with interferon have been tried to treat serious infections due to CMV with no success. Ara-A may be partially therapeutic in CMV retinopathy. Retinopathy occurs in immunosuppressed patients, characterized by white retinal patches, hemorrhages and venular sheathing. The lesions increase in size in a brush fire manner, eventually involving the macula with loss of central vision. If CMV retinopathy is progressive, the principal means of treatment at the present time is to withdraw immunosuppression. In the case of the renal transplant recipient, this may mean the loss of the kidney. This is not possible in cardiac transplant recipients and as a result, intravenous Ara-A has been tried by the group at Stanford with some success (Figure 8). Doses of Ara-A have been large

Figure 8. Ara-A therapy of CMV retinopathy.



R.B. Pollard, 1980

(15 mg/kg) and have been given over 10-14 day courses. Occasionally, the courses have been repeated. The combination of Ara-A and the reduction of immunosuppressive therapy has resulted in stopping the course of CMV retinopathy in some patients. This effect on CMV retinopathy has to be balanced with the complications of Ara-A therapy given to patients who may have reduced renal function and some degree of hepatic disease. Particularly disturbing has been the central nervous system dysfunction that has been progressive after the Ara-A therapy has been stopped. This central nervous system dysfunction is characterized by tremulousness, hallucinations, and

convulsions. The course of the neurological disease has progressed in some instances for several weeks after the cessation of Ara-A therapy. New drugs are desperately needed which have the capacity to stop CMV replication.

New drugs have recently emerged which do have an influence on CMV replication. Phosphonoformate (PFA) is actively being investigated in Sweden. Bromovinyldeoxyuridine (BVDU) is presently being investigated in Belgium. New nucleoside analogs have also emerged. These drugs have the capacity of reducing CMV plaque formation by 50% at micromolar concentrations of 0.1-0.4 per ml whereas ACV has a comparable effect at 100 mmoles. The new drugs have been given initials to simplify terminology. FIAC (5-iodo-2'-fluoroarabinosylcytosine), FMAC (5-methyl-2'-fluoroarabinosylcytosine), FIAU (5-iodo-2'-fluoroarabinosyluracil), FMAU (5-methyl-2'-fluoroarabinosyl-uracil) are the most prominent of the new compounds. In addition, another compound called 2'-NDG (2'-Nor-2-deoxyguanosine) has also been found to have significant activity against CMV. All of these drugs should have some effect on host cell DNA metabolism, so it should be expected that their side-effects would be directed toward rapidly reproducing tissues such as the bone marrow. Nevertheless, new compounds have emerged finally which have the capacity for inhibiting CMV replication at very low concentrations. It should be easy to reach these concentrations in serum and in tissue by the systemic administration of the drugs. FIAC and FIAU will be developed by Bristol Pharmaceutical Company on a license from Sloan-Kettering. 2'-NDG will be developed by Syntex.

PREVENTION

Preventing CMV infection is critical in reducing the morbidity and mortality associated with the disease process. To prevent infection more exact knowledge concerning the transmission of the virus needs to be gathered. At the present time, some practical methods for the avoidance of infection with CMV can be applied. The first of these would consist of identifying premature neonates in intensive care units who are seronegative and not transfusing them with blood from seropositive donors. In the premature infant, this type of infection has had serious complications and it would be a relatively easy goal to work for its elimination. If further evidence documents that the passive recipient in genital-anal intercourse is at high risk for getting infected with CMV as opposed to the person who does not engage in such an activity, the simple process of the active partner wearing a condom may be able to eliminate some infections.

There are now 3 major paths of action toward preventing CMV infection. The first of these is the administration of prophylactic interferon to renal allograft recipients. The second of these is the administration of immune globulin to renal and bone marrow transplant recipients. The third of these is the use of a vaccine, either a live attenuated vaccine or a subunit product. In studies at the Massachusetts General Hospital, it has been found that leukocyte interferon derived from the Finnish Blood Bank given prophylactically to renal allograft recipients decreased the incidence of viremia and demonstrable disease due to CMV in the post transplant period. Death and loss of the allograft occurred at comparable incidence figures, however, in the interferon and placebo treated groups. These studies are promising and need extension because of the potential availability of large

quantities of human interferon for use in patients through the use of recombinant DNA technology.

The second approach has been the use of immune globulin administered passively to bone marrow transplants. At least two studies have been reported. The first of these was conducted at the University of Minnesota in bone marrow transplants and studied three groups of patients. One group was given no immune globulin, the second group given low titered of immune globulin, and the third, a high titered immune globulin prophylactically. Interstitial pneumonia caused by CMV was reduced in the group given the immune globulin with the high titer of CMV antibody. At UCLA, white blood cell transfusions are no longer given either prophylactically or therapeutically because of the consequences of CMV infection. If bone marrow transplant recipients are not given white blood cell transfusions, the administration of immune globulin prophylactically does not reduce the incidence of infection in seronegative patients but does reduce the incidence of significant disease due to CMV. This includes interstitial pneumonia caused by CMV and death due to disseminated viral infection (Table 13).

Table 13

Incidence and Type of Cytomegalovirus Infection and Interstitial Pneumonia in Patients Not Receiving Leukocyte Transfusions

	Control Subjects (n = 18)	Recipients of Cytomegalovirus Immune Plasma (n = 17)	p Value*
	n		
Cytomegalovirus infection	9	7	0.73
Symptomatic†	8	1	0.03
Asymptomatic‡	1	6	
Interstitial pneumonia	9	1	0.01
Cytomegalovirus	6§	0	0.02
Respiratory syncytial virus	1	0	
Idiopathic	2	1	
Death from interstitial pneumonia	6	1	0.09
Death with cytomegalovirus	4	0	0.10

* p Values determined by Yates' corrected chi-squared test.

† Control subjects: pneumonia, six; febrile illness with seroconversion, one; and febrile illness with seroconversion and isolation of cytomegalovirus from bronchopulmonary lavage, one. Plasma recipients: fever with viremia, one.

‡ Control subjects: asymptomatic viruria, one. Plasma recipients: asymptomatic viremia, four; asymptomatic viruria, two.

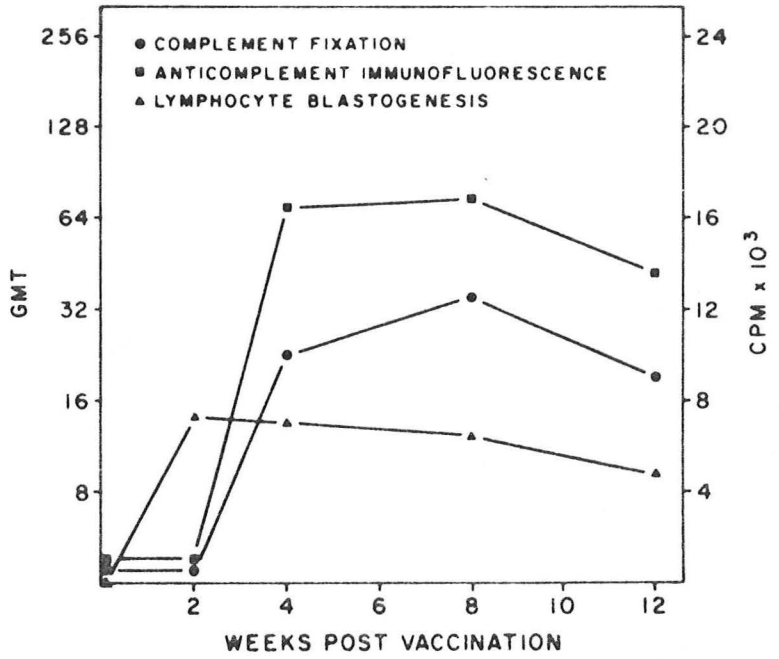
§ One control subject who did not take prophylactic trimethoprim-sulfamethoxazole had *Pneumocystis carinii* and cytomegalovirus pneumonia.

D.J. Winston, 1982

The UCLA study is of interest because in its second portion, they used a commercial immune globulin currently prepared by Cutter Laboratories. The administration of high titered immune globulin to bone marrow transplants is probably the most promising means of preventing severe disease, particularly if white blood cell transfusions are not given. Studies need to be performed with the use of interferon and/or immune globulin in renal transplant recipients.

A major focus of attention toward the prevention of CMV infection is the production of a live attenuated vaccine. An English vaccine utilizing the AD169 strain of CMV has been bipassed as a candidate and the most promising vaccine at the present time is the one developed by Dr. Plotkin and his collaborators at the University of Pennsylvania. These investigators have utilized the Towne strain of CMV, have passaged it 125 times in WI-38 human embryonic lung diploid fibroblasts and cloned the virus 3 times during its multiple passages. The virus is attenuated in that it produces no disease in volunteers when inoculated subcutaneously and live virus is not excreted after inoculation. The only side reactions have been erythema and swelling with pain at the site of the local injection. The Towne vaccine strain of virus differs from virulent virus in that it has an increased resistance to inactivation by trypsin and an increase in cell free virus after inoculation of fibroblast tissue culture. The Towne strain of vaccine virus has been given successfully to volunteer populations and has been shown to induce serum neutalizing antibody, complement fixing antibody and lymphocyte proliferative responses (Figure 9). When given to renal transplant

Figure 9. Mean antibody and blastogenic responses of 4 pediatric nurses given Towne strain CMV vaccine.



S.A. Plotkin, 1981

recipients, as expected, not as many undergo a serological response to the vaccine, and the titers are not as high as in normal subjects. In the majority, however, there is some immunological response. The Towne strain of vaccine has been given to renal transplant recipients who were seronegative prior to transplantation at two locations, the University of Pennsylvania and the University of Minnesota. Local reactions were the only major side effects.

The renal transplant group at particular risk for disease due to CMV are seronegative recipients receiving renal allografts from seropositive donors. Administration of the vaccine did not prevent infection, did not prevention symptomatic disease, but did appear to reduce the severity of that symptomatic disease. Vaccine virus was recovered from only one of 60 recipients. There is no information, at the present time, as to allograft loss in vaccine or placebo groups. Further studies are continuing at both of these institutions to test the safety and efficacy of the vaccine. The eventual major use of the vaccine is immunization of seronegative young women to prevent the disastrous consequences of congenital disease due to CMV.

A subunit vaccine being developed by several different groups. Candidate antigens consist of some combination of surface envelope glycoproteins. At the present time, there is not enough information to ascertain which of the particular antigens expressed on the cell surface are protective. An inactivated subunit vaccine would have the advantage that the DNA of the virus would not be inoculated into the vaccine recipient but the disadvantages that multiple doses might be necessary and that the protective antigens of the virus are not yet known. In the long run, it is probable that a CMV live attenuated vaccine will be produced and be available. It remains to be determined whether it can reduce the societal burden of congenital disease due to CMV or the other consequences of CMV infection in immunosuppressed patients.

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