The history of cytomegalovirus and its diseases

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Abstract Intranuclear inclusions typical of cytomegalovirus infections were first noticed in 1881 by German scientists who thought they represented protozoa. After viruses were grown in cell cultures, Weller, Smith and Rowe independently isolated and grew CMV from man and mice in 1956–1957. Antibodies in 30–100% of normal adults indicate not only a past infection, but the presence of a present latent infection. The presence of CMV DNA in tissues and most organs surveyed indicates the ubiquity of latent infection. CMV disease requires the virus and some deficiency of immunity such as occurs in the immature fetus, in AIDS, and in transplant patients on immunosuppressive drugs. Antiviral agents can inhibit CMV replication but they cannot prevent or cure latent infections. A pharmacological approach using the many leads in understanding latency is needed.

Keywords Antiviral therapy · CMV in AIDS · CMV after transplantation · Discovery of CMV · Epidemiology of CMV · Latent infection by CMV

Discovery of cytomegalovirus

Ribbert [1] wrote that in 1881, he saw large cells in sections of the kidney of a luetic stillborn and in the parotid gland of children which he was unable to interpret until he saw the report of Jesionek and Kiolemenoglou ([2], Fig. 1), who described similar cells as “protozoan like” cells in the lungs, kidneys and liver of an 8-month luetic fetus. The

eccentrically placed nuclei of these large cells contained a “central nuclear body” surrounded by clear halo. Löwenstein [3] working in Ribbert’s laboratory found such cells in the parotid glands of 4 out of 30 infants. These appear to be the first descriptions of typical cytomegalic cells with intranuclear inclusions.

Von Glahn and Pappenheimer [4] noted that Lipschuetz [5] had discovered intranuclear inclusion containing cells in lesions in man infected by herpes zoster and herpes genitalis. Thus they believed such abnormal cells were produced by viruses, and they doubted that they were related to protozoa. This was the first indication that cells with intranuclear inclusions might be related to a group of related viruses, now known as the herpesviridae.

Farber and Wolbach [6] found such inclusion bearing cells in the salivary glands of 26 out of 183 children examined after death from diverse causes. This was the first approximation of the fact that infection by cytomegalovirus is highly frequent.

By 1932, 25 cases of a rare lethal congenial infection characterized by petechiae, hepatosplenomegaly, and intracerebral calcification had been described. All of them had cells with typical intranuclear inclusions. Wyatt et al. [7] suggested the name, “generalized cytomegalic inclusion disease (CID)”, although its viral etiology was not yet known. A uniform site of involvement were cells of the renal tubules. They suggested that the disease might be diagnosed during life by searching for cells with inclusions in urinary sediments.

Following this clue, Fetterman [8] made a cytological preparation from the urine sediment of a suspected case, and made the first intravital diagnosis of CID.

Minder [9] first saw by electronmicroscopy 199 nm particles, suggestive of a virus, in the clear halo around the intranuclear inclusion of pancreatic cells in a case of CID.

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Fig. 1 *Left* Cells with intranuclear inclusions with halo thought by Jesionek and Kiolemenoglou [2] to represent parasites. *Right* CMV infected cytomegalic cell with intranuclear inclusion with halo. Note also cytoplasmic inclusion on the *left* side of the cell

Human CMV could not be cultured until human cells were routinely grown in culture. This became possible after Enders et al. [10] isolated poliovirus in human embryonic cell cultures. They received the Nobel Prize in 1954 for this achievement. Enders' and Weller's laboratories at Harvard University became a Mecca for virologists throughout the world who were eager to learn this technique. Weller was a pediatrician and parasitologist. Applying the newly discovered cell culture techniques, he was initially interested in culturing the protozoa *Toxoplasma* in human embryonic culture. *Toxoplasma gondii* causes a lethal congenital disease in neonates remarkably similar to CID clinically. From an infant suspected to have congenital toxoplasmosis, a virus later identified as cytomegalovirus was isolated in 1957 ([11], Fig. 2).

Earlier, in 1955, Margaret Smith isolated from the salivary gland of a dead patient a virus which grew only in human but not in mouse cell culture. The paper describing this finding was rejected because she was also working with the mouse salivary gland virus and the editor thought her human agent might have been a mouse contaminant. We now know that this was not correct because cytomegaloviruses are specific in their respective animal species. It was only in 1956 when she reisolated the virus and isolated the same virus from the kidney of another patient with CID that her paper was accepted [12].

Rowe et al. [13], who were interested in respiratory viruses, isolated from adenoid tissue of a subject a virus that he suspected to be varicella virus, since it had cells with intranuclear inclusions like those described by Weller

Fig. 2 Thomas H. Weller, pediatrician, parasitologist and virologist, discoverer of CMV, emeritus professor and chair, Department of Tropical Public Health, Harvard School of Public Health, Boston, MA

in 1953 in cases of varicella [14]. Rowe took his material to Weller's lab for confirmation. Weller determined that his virus was not varicella virus but that it was similar to the

virus Weller had isolated from the patient with suspected toxoplasmosis [11].

These three independently isolated agents were exchanged among the three scientists, and the similarity of agents recovered was established in advance of publication [15]. This is an excellent and commendable example of collaboration in science! Weller named the virus “cytomegalovirus”.

Weller et al. [16] tested serum from two cases of CID against 14 isolates using the complement-fixation (CF) test, including the 3 isolates mentioned above. The early 3 months serum acted in high titers against the homologous strains, but only in low titers against the heterologous strains. This was the first indication of strain differences among CMV isolates. More recently, Boppana et al. [17] studied maternal serum with preconceptual immunity against CMV before and after conception of an infant with congenital CMV infection; ten of the 16 mothers with congenitally infected children acquired new antibody specificities against glycoprotein H (gH). This protein is part of the armamentarium of neutralizing antibodies. The gene for gH is highly pleomorphic and is partially responsible for the heterogeneity of CMV isolates. This heterogeneity explains the phenomenon of superinfection of one strain upon another in a single patient. This finding also explains why immunity from infection is not absolute in CMV. It also creates a problem for the design of an effective vaccine [18]. Another source of strain variation is *in vitro* cultivation. Cha et al. [19] found that the Towne strain, which is a cell culture derived vaccine strain, lacked large segments of the genome found in recent clinical isolates not frequently passed in cell cultures.

Scope of cytomegalovirus infection and disease

The discovery of CMV in cell culture made it possible to identify and measure lytic virus in pathological materials infected by CMV using the morphological method of cytopathology.

An offshoot of the discovery of cytomegalovirus was the development of tools to study the epidemiology of past and latent infections of CMV. Rowe et al. [13] prepared a CMV antigen by sonic inactivation of the virus and used it to develop a complement fixation (CF) test. He used this test to measure the antibodies in the general population in Washington, DC [13]. The CF test became the mainstay method to study the epidemiology of CMV by measuring specific antibodies against CMV for 20 years. Later it would become apparent that the presence of circulating antibodies not only indicated past infection, but that it indicated the presence of latent infection by CMV, not apparent by cytopathology. Latent infection occurs *pari passu* with

acquired immunity and is not cured by it. At times, silent latent infection may be activated so that lytic virus is produced. In the immunologically competent subject, virus shedding is usually asymptomatic, such as shedding of CMV in urine, in saliva, in the uterine cervix, in semen and in milk. In the presence of immune deficiency, activation of latent infection may result in a gamut of symptomatic clinical diseases (see below).

Rowe et al. [13] found that in Washington, DC, subjects over 35 years old were 81% seropositive. The frequency of seropositivity increased with age. This conclusion was generally confirmed by others in other population groups throughout the world [20].

There were however important differences in different population groups. Generally, there was an inverse correlation with socio-economic conditions, the lower strata having higher frequencies. This is the case within different nations, and also among different nations. Northern European nations, North America and Australia have lower rates (40–60%) than nations in Southeastern Asia and Africa, where it is close to 100% [21].

Instead of being a rare infection as might be expected from the rarity of CID, CMV infection was found to be ubiquitous but usually asymptomatic. This was indicated by the high frequency of CMV specific antibodies in the general human population.

There are two age ranges during which there is a large amount of infection. The first is infection during the perinatal period (0–2 years). Infection during this period may be measured by seroconversion or by viruria. The sources of infection of these children are virus shed from the uterine cervix of the mother [21], virus in breast milk of the mother [22], and virus from saliva and urine [23]. CMV from the uterine cervix may infect the neonate during its passage through the birth canal. Breast milk may contain shed virus from a seropositive mother which may infect the nursing infant. There may be a community problem if breast milk is pooled as in some Scandinavian countries. CMV in urine and saliva from newly infected infants and toddlers may be the source of infections as fomites in nurseries, day care centers and large families. Perinatal infection with CMV indicated by the presence of viruria may reach as high as 56% in some studies [22].

Sexual transmission of CMV represents the second most important mode of horizontal transmission after puberty. CMV mononucleosis has been epidemiologically associated in partners of heterosexual sex [24, 25]. CMV shedding from the uterine cervix of females has been associated with number of sex partners, early age of first intercourse, and being nonwhite [26].

CMV infection is even more strongly associated with homosexual sex in the immunocompetent gay male. There is a vast difference between the frequency of seropositivity

in the gay male compared with heterosexual males of the same socio-economic stratum (94 vs 54%, [27]). CMV seropositivity or latent infection was correlated with duration of sexual activity, number of sexual partners, history of syphilis and anal intercourse [28, 29]. Interestingly, there is also evidence of continuous lytic infection activity in the immunocompetent healthy sexually active gay male. This is indicated by the high titer and long duration of circulating CMV specific IgM antibodies; the high frequency of semen shedding of CMV (35%, [30]), and the high frequency of urine shedding as detected by serial testing (30%).

Modes of infection: lytic and latent infection

Despite the tremendous surge of knowledge of the molecular biology of cytomegalovirus and anti-CMV immunology, the understanding of the mechanisms of latent infections is still incomplete [31]. This includes the nature of the latent state, how it is maintained, and the processes of its activation to a lytic infection.

In 1975, we [32] did a study about CMV seroconversion after kidney transplantation. We found that 10 out of 12 (83%) seronegative recipients who received an organ from a seropositive donor converted to seropositivity within three months after their operation. From this we deduced that the grafted kidney was the vehicle of transmission of CMV, and that it harbored latent CMV infection. Later, we and others found that this was also the case with other types of organ transplantation, such as transplantations of the heart, liver and lung (for review, see [33]). For the first time we used seropositivity as a sign of latent CMV infection besides immunity against CMV. Although we could not find any virus upon culturing kidneys from seropositive subjects, we suspected that latent CMV infection without demonstrable production of lytic viruses exists probably in all organs of the body of seropositive subjects. After allograft transplantation of any organ, the latent CMV infections in the grafted organs are activated, and the recipient becomes infected or superinfected with intact, lytic virus, which stimulates the production of antibody. This hypothesis has now been confirmed by Hendrix et al. [34]. They found that CMV DNA, demonstrated by dot blot hybridization and in situ hybridization with a probe for immediate early (IE) sequences (UL123), and by nested PCR with primers derived from immediate early gene (UL123 exon 4), was found widely distributed in organs of healthy subjects, including the liver, kidney, spleen, pancreas and smooth muscle cells in arterial walls. Significantly, immunochemical studies using monoclonal antiserum against UL123 protein were negative, suggesting that the DNA positive sites represented sites of latent infection without IE gene expression or lytic intact virus.

A predominant current theory is that latent infection is harbored in undifferentiated monocytes, by which it is extensively distributed in various organs of the body [35]. Latency represents blockage of virus production at the level of expression of IE antigen. This blockage is released after differentiation of monocytes, or when latent infection can be activated to produce lytic virus infection.

Determinants of diseases

CMV disease is produced by the action of intact lytic virus and attendant pathological reactions, including inflammation. These produce clinical signs and symptoms which together constitute a syndrome called disease. Infection may occur *de novo*, as a primary infection, or it could arise secondarily in an immune patient; that is from reactivation of a latent infection already present in the patient or by reinfection with a new strain in the patient. Primary infection occurs in seronegative subjects without prior specific immunity against CMV. Secondary infection occurs in seropositive individuals who already have some specific immunity against CMV. Primary infection occurring in the absence of specific immunity produces a more severe disease than secondary infection. Primary infection as opposed to secondary infection is the first and most important determinant of CMV disease.

The second major determinant of CMV disease is immunological deficiency. As mentioned above, even most primary infections in humans are asymptomatic. No trace of the infection is observable except seroconversion. On top of immunological incompetence, however, disease has become more common. Much CMV disease has been brought about by modern medicine, specifically the wide spread use of immunosuppressants in oncology and transplantation medicine, and the prolonged survival of the very young. Specific immunosuppressants of cellular or T cell immunity are uniformly applied after major organ transplantation to maintain the integrity of the graft. Immunity against organ graft and immune defenses against CMV and other herpesviruses are not clearly distinguishable. Patients now survive with deficiencies in immunity that underlie CMV diseases, in many cases not yet clearly elucidated, such as deficiencies related to the unborn fetus (see below).

Perhaps the best example of immunological deficiency in determining CMV disease is an experiment of nature, the newly emergent disease, AIDS, or “acquired immunological deficiency syndrome”. The deficiency is primarily that of cellular or T cell immunity. Immunological competence can be clinically quantified precisely by the peripheral blood T cell count, which normally is around $800 \mu\text{L}^{-1}$. Symptomatic CMV disease, types often rarely found in man, occurs after the immunological state is severely

compromised, or when the T cell count decreases to $100 \mu\text{L}^{-1}$ or lower.

In other cases, the nature of the immunological incompetence determining CMV disease is obscure or only unclearly understood. Extreme young age in humans is a critical determinant of CMV disease. An infant in utero is at great risk for developing CMV disease. The earliest recognized CMV disease was CID, which results from a primary infection of the mother during pregnancy, where the infant is infected congenitally through the placenta and primarily, in utero (for review of recent findings, see [36]). On the other hand, a slightly older neonate infected primarily during passage through a CMV infected uterine cervix rather than through the placenta can also become infected, but remains asymptomatic.

Categories of diseases

CMV mononucleosis

Klemola and Kaariainen [37] recognized a form of infectious mononucleosis in young adults caused by CMV on the basis of a rise in specific serology and a negative heterophile agglutinin test for EBV infection. The clinical syndrome is similar to EBV infectious mononucleosis. The patient had fever and atypical lymphocytes in the peripheral blood. Tonsillitis, pharyngitis and lymphadenopathy were less frequent than in EBV mononucleosis. It is interesting that this disease was first recognized in Finland, a well developed Northern European country, where the frequency of seropositivity is lower than in less developed countries, where most people are immune to CMV when they are adults.

Post transfusion CMV infection or disease is a special case of infection or mononucleosis transmitted by CMV in units of blood. Blood may contain leucocytes which may be the source of lytic infections, or demonstrable viremia. Infected cells were thought to be polymorphonuclear leucocytes and monocytes [38, 39]. But finding such cases of viremia in the normal adult population is extremely unusual. Despite repeated attempts, there is only one positive report in the literature [40]. It is more likely that viral transmission is effected by blood cells that contain latent, non-lytic virus which are then reactivated in the recipient.

Our studies in Pittsburgh may serve as an example of the nature of the problem of transmission by blood [41, 42]. We studied 93 seronegative children whose average age was 7.6 years. Thirteen percent seroconverted following open heart surgery after receiving an average of 3.9 units (500 ml). Each unit of blood produced a 3.3% chance of

conversion, or transmission of infection. As the seroprevalence rate in the general population in Pittsburgh is around 50%, the risk of a unit of seropositive blood is 6.6%. None of the children were ill. This degree of seroconversion, or infection, is consistent with 18 other studies in normal subjects [40].

This calculated risk and danger however underestimates the frequency of latently infected blood from donors. Yeager et al. [43] found that this is a function of the nature of recipients. She showed different risks in transfusions of neonates, many of whom were immature babies. When neonates whose mothers were seronegative were given blood from seropositive donors, 10 out of 74 (13.5%) became primarily infected, demonstrated by viruria in the recipient. Five infants died or were seriously ill (6.8%). When 90 neonates, whose mothers were seronegative were given blood from seronegative donors, none became infected and none died. This result suggested to her a new policy of prevention of CMV in neonates born of seronegative mothers by giving them only blood from seronegative donors. The infecting dose of blood was calculated to be between 50 and 100 ml.

A similar situation occurs in adults who undergo bone marrow transplantation. This procedure involves essentially destruction of host defenses before successful engraftment of the marrow transplant, at which time the patient is at high risk for serious and fatal CMV disease, especially pneumonia. One possible source of the virus is seropositive blood and blood products. Bowden et al. [44] tested the effect of providing only seronegative blood and blood products for transplant recipients who were seronegative. In 32 patients who were treated in this manner, there was one infection, while in 25 seronegative control patients who received standard blood products, there were 8 (3.1 vs 32%, $P < 0.007$). Using only seronegative blood and blood products in seronegative marrow recipients became the standard practice at the University of Washington.

Congenital CMV infection (CID)

About 1% (40,000 a year) of babies born in the United States are congenitally infected. Of these about 5% are symptomatic at birth. They may be small for their gestational age, and have petechiae, jaundice, hepatosplenomegaly, thrombocytopenia, chorioretinitis, microcephaly or hearing loss. Hearing loss may be identified only later in life [45]. The presence of periventricular calcification seen on CT scan is a typical finding in severe cases. Most of these cases are from primary infections in the mother, but congenital CMV infection has now been identified in mothers who were immune before their pregnancies. Some have developed neurosensory hearing loss [17].

CMV diseases in AIDS

Except for CID in infants, the most severe cases of CMV diseases have been found in patients with AIDS. Uncharacteristically, they have occurred, at least in adults, in seropositive or previously immune subjects. Another unusual characteristic of CMV disease in AIDS is the severe involvement of the central nervous system. This suggests that probably most body parts are potentially permissive for cytomegalovirus infection. This again reflects on the ubiquity of latent CMV infection. There is a gradient of organs and cells that become involved in disease which is a function of the severity of immunological deficiency.

CMV disease occurred in 21–44% of AIDS patients before the introduction of highly active antiretroviral therapy (HAART), usually late in their disease when the CD4 lymphocyte count was below 50 μL [46]. CMV retinitis is the most disabling and characteristic disease, as it involves loss of sight. Antiviral therapy has been most effective in this area (see “therapy”, below). Reversal of immunological deficiency and rise of CD4 counts toward normality has been an effective preventive against CMV retinitis [47].

CMV polyradiculopathy is the most frequent and characteristic involvement of the central nervous system. Patients experience weakness, loss of reflexes and sensation, usually in the legs, and loss of control bladder and anal function. The cerebrospinal fluid shows evidence of infection, pleocytosis and low sugar levels [48]. CMV mononeuritis is less common.

There are two types of CMV encephalitis. The first type is difficult to distinguish from HIV dementia. It is a diffuse, multifocal, micronodular encephalitis [49]. Both types exhibit cognitive and motor disturbances such as forgetfulness, confusion, impaired memory and unsteadiness. CMV cannot be cultured in the CSF, but CMV PCR is almost always positive. The second is a ventriculoencephalitis reminiscent of what is observed in neonatal CID [49]. Ventriculitis can be demonstrated by magnetic resonance imaging with gadolinium enhancement [50]. Patients have acute onset of apathy, disorientation, cranial nerve palsies, abnormal CSF and a rapid downhill course. Ganciclovir treatment may be partly responsive [51].

The gastrointestinal tract from the mouth, esophagus, stomach, small intestines, colon to the rectum may be involved in both AIDS and after transplantation. There may be painful erosions of the mouth, epiglottis or pharynx. Painful ulcerations of the esophagus associated with dysphagia, odynophagia and upper gastrointestinal bleeding occur. Stomach ulcers may cause bleeding, obstruction or perforation. Studies indicate 30–90% of AIDS patients develop chronic diarrhea and wasting [52]. In Africa, there is a syndrome called “slim disease”. Often it is not possible

to determine which virus, bacterium, parasites or fungus may be responsible.

CMV diseases after allograft transplantation

CMV is the single most important cause of infectious diseases after organ transplantation. It affects 75% of the organ recipients during one year after transplantation [53]. In a prospective study, Ho et al. [32] found that 80% of seronegative recipients converted to seropositivity after they received a kidney from a seropositive donor. Summarizing 16 studies of kidney transplantations, Ho [54] calculated that 52% of pretransplant seronegative recipients became primarily infected after transplantation and converted to seropositivity. Since not all donors of kidneys were seropositive, one can surmise that practically all seropositive donors had latent CMV infections that were reactivated in the recipient. Similar figures were obtained after cardiac, liver and marrow transplantations. This is evidence that probably all organs in seropositive subjects have latent CMV infection [55].

The morbidity of CMV infection was different in primary compared to secondary infections after kidney transplantation. Primary infections were 83% symptomatic; that is they at least had fever. Some had pneumonias. Secondary infections were 44% symptomatic, being usually limited to mononucleosis type of symptomology [55, 56].

Morbidity also varied depending on the type of transplantation. The most severe type of pathology was pneumonia in bone marrow transplantation, with a mortality of 84% [57]. This type of pneumonia was probably complicated by additional immunopathology unrelated to CMV, a graft versus host reaction. Pneumonia in kidney transplantation had a mortality of 48% [58]. The frequencies of CMV pneumonia after different transplantations decreased in the following order: heart-lung>heart>liver>kidney (32, 8, 3 and 2%) [59, 60]. The reason why pneumonias should occur so frequently after heart-lung and heart transplantations is obscure. In the beginning it was thought that the reason lay in the type or dose of immunosuppressants used. Indeed, before their use was moderated, it was found that antilymphocyte serums or OKT-3 serum enhanced the severity of post-transplant CMV disease [61, 62]. However when a new immunosuppressive agent was introduced in renal transplantation, such as cyclosporine or tacrolimus [63, 64], CMV disease was not enhanced. In fact all four types of transplantations cited above were performed at the University of Pittsburgh where similar prednisone-cyclosporine immunosuppressant regimes without antilymphocyte serum were used. Heart and heart-lung transplantations must have some unknown general or local immunosuppressive effect apart from the drugs used. Indeed, CMV pneumonia is such a problem after heart transplantations that

additional preventive and therapeutic measures are now routinely practiced (see below).

Antiviral therapy and prevention of CMV diseases

There are now effective drugs against lytic CMV infections [65]. Therapy does not affect the latent virus. In that respect, there is no cure for CMV disease as infection will persist in the latent state.

Ganciclovir {[9-(1,3-dihydroxy-2-propoxy)methyl]-guanine, DHPG} is an acyclovir nucleoside synthesized in 1982. It is a potent inhibitor of the reproduction of herpesviridae [66]. It has been the drug of choice against CMV for the last twenty-five years. It is usually given intravenously. An oral preparation is available in the form of the monovalyl ester of ganciclovir (valganciclovir, [65]).

If ganciclovir cannot be tolerated, or if resistance develops against it, foscarnet and cidofovir are available as intravenous drugs. Formivirsen is an FDA approved antisense compound to be used intravitreally against CMV retinitis when other agents cannot be used [65].

One of the most gratifying experiences in antiviral therapy was to observe the efficacy of ganciclovir against CMV retinitis in AIDS [67–69]. Sight was saved and the progression of the retinal lesions stopped! However it was found that when therapy was discontinued, the disease would recur. Further treatment was usually necessary, especially in the pre HAART days when no improvement of immunity could be anticipated. Prolonged use of ganciclovir often resulted in leucopenia and other hematological side effects. Other drugs had to be used. Intravitreal injections was one way to avoid toxicity of the systemic drugs. With the inception of HAART, when the CD4 count could be brought above 100 cells per μL , it was finally possible to stop antiviral drugs [47].

Ganciclovir has been used to treat other CMV diseases in AIDS and after organ transplantation in the lung, the gastrointestinal tract, and the central nervous system. Its effectiveness is related to the degree of immunodeficiency associated with the disease in question. It can vary from stabilizing the disease during therapy but without objective improvement to complete clearing of the pathology. It is least effective in treating diseases of the central nervous system, firstly, because involvement of that system does not occur unless immunity is severely deficient, as in the late stages of AIDS. Secondly, drugs may not be effective in the central nervous system because of the blood brain barrier prevents the achievement of an effective concentration of the antiviral drug [65].

There has been a great deal of research and study on the treatment and prevention of pneumonias, which is the most important disease after bone marrow and organ transplantations. Pneumonias after marrow transplantation have a

mortality of 70–85% [57]. Ganciclovir alone suppresses the virus but it does not reduce morbidity or mortality. Addition of immune globulin was found to reduce mortality to 30% [70]. This is now routine practice.

There are two methods of preventing CMV disease after major transplantations. The first is preemptive treatment of patients with ganciclovir before onset of disease. For the first few months after transplantation, patients undergo surveillance for signs of impending disease. This is indicated by three possible methods; CMV viremia, circulating CMV antigenemia or quantitative CMV PCR. In the antigenemia method CMV infection is diagnosed by the detection of CMV matrix protein pp65 in peripheral blood polymorphonuclear leukocytes. The quantity of antigen has been correlated with development of disease [71]. Qualitative and quantitative PCR assays for CMV DNA or RNA are available to diagnose or predict CMV disease in blood and in tissues [72]. The second method for preventing CMV disease is to administer ganciclovir to all patients for the period they are deemed to be at risk for disease, usually 90–100 days after transplantation [73, 74]. Both methods are effective, and are used especially in transplantations where the risk of CMV disease is high, that is after bone marrow, heart-lung, lung and heart transplantations.

Summary and conclusions

About one hundred years ago, developments in pathologic anatomy led to the recognition of the morphological cellular characteristics of infection by CMV. It took another 50 years before the virus was successfully cultured and isolated. The elucidation of its epidemiology, and its wide scope of infection followed when methods to measure intact virus and specific immunity became available.

The second half of the twentieth century was characterized by rapid advances in human technology and medicine as well as break down of social relationships that are important for the preservation of the family and individual health. These changes have had a profound effect on CMV infection and diseases. There are increasing numbers of individuals who are immunodeficient in general or specific ways and who are prone to CMV infection. The scope of CMV diseases has extended from a previously rare lethal, congenital infection to increasing numbers of patients who have undergone organ transplantation and who are immunosuppressed for the survival of their grafts. Break down of social relations contributed in the eighties to the emergence of a world wide pandemic of AIDS, a new disease of mankind that specifically destroys cellular immunity, the type of immunity responsible for holding latent CMV infection in check. CMV diseases are an integral part of clinical side of AIDS.

The understanding of the molecular and chemical events of viral reproduction has made possible the development of effective antiviral compounds. They are able to arrest viral replication and restrict some of the pathologic processes of CMV diseases. They do not have long lasting effect, however, unless immunological competence can be restored.

The basis of persistence of CMV infection is latent infection. As long as CMV infection can revert to the latent state, it is incurable. Latent CMV lurks behind appearances and acts like fifth columnists which can activate into a lytic infection and subvert the host. Our understanding of latency, limited though it is, has not been dedicated technologically to its elimination.

We need new approaches to antiviral therapy targeted against latency. Along with basic understanding of the molecular biology [31], a parallel technological, pharmacological approach is needed. One is faced with the same type of challenge in this regard as in the development of a vaccine against CMV [18].

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