Infectious diseases of children

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SEVENTH EDITION

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Preface

The opportunity to prepare the seventh edition of this book in its span of 22 years was a challenge that we welcomed with enthusiasm. Changes in the field of infectious diseases during these two decades have been remarkable. Continued investigative progress in basic microbiology, immunology, and pharmacology ensure a similar record of achievement in clinical developments during the next 20 years.

One of the fascinating aspects of change has been the shifting epidemiology in infectious diseases such as rubella and measles. The success of rubella vaccine in markedly reducing congenital infections and controlling the disease among younger children has been accompanied by small outbreaks among adolescents and college campus groups. Similarly clusters of cases among young adults have occurred in the residual population unprotected against measles. The challenges for prompt and accurate diagnosis have been focused on internists, family physicians, and pediatricians who provide care for teenagers. It has been more than 13 years since the use of inactivated measles vaccine was discontinued. In the meantime, a cohort of more than a half million young adults, who received this vaccine during childhood, remain susceptible with the likelihood of developing the atypical measles syndrome some time in the future.

In preparing this seventh edition we attempted to preserve the book as a handy, concise, practical reference for students, house staff, and clinicians. The scope of this edition has been expanded to include new chapters on infant botulism, osteomyelitis, otitis media, and urinary tract infections. We are grateful to Laura Gutman of Duke University for preparing the chapter on osteomyelitis and to Jerome Klein of Boston University for preparing the chapter on otitis media. In addition, significant revisions have been made in seven chapters and the entire book has been updated throughout. Collaborators, whose invaluable contributions we gratefully acknowledge, have been Anne Gershon and Robert Schacht of New York University and Catherine Wilfert of Duke University.

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Samuel L. Katz

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CHAPTER 1

Cytomegalovirus infections

When the human cytomegaloviruses (CMVs) were first reported to replicate successfully in vitro (Rowe and colleagues, 1956; Smith, 1956; Weller and colleagues, 1957), techniques became available to study the events surrounding recognized clinical infections by these agents. Most initial research focused on the known entities of salivary gland inclusion disease and generalized cytomegalic inclusion disease (CID), the congenital disseminated form of infection. Another decade passed before it was discovered that CID and other overt clinical entities were but the "tip of the proverbial iceberg," with a far greater number of inapparent infections regularly occurring in neonates as a result of vertical transmission from maternal genital shedding of CMV. Attention shifted then to the elucidation of the epidemiology, virology, and immunology of these common occult infections, which involved as many as 1% to 2% of newborns and 5% to 25% of pregnant women. Longitudinal studies are still in progress to determine the long-term effects on infant and child development of these asymptomatic perinatal infections. The most recent area of CMV morbidity to be appreciated has been its transmission or reactivation in immunosuppressed and immunocompromised patients. As with other agents whose initial association was detected with only a limited clinical syndrome, CMV has emerged as a ubiquitous virus with host interactions ranging over the full spectrum of health and illness.

ETIOLOGY

It had been suspected for many years that CID is caused by a virus. Similarities observed between cytomegalic inclusion cells and those seen in varicella (Goodpasture and Talbot, 1921) and in herpetic lesions (Von Glahn and Pappenheimer, 1925) are remarkable in the light of modern evidence classifying CMV with the herpesvirus hominis (herpes simplex) and herpesvirus varicellae group. Cole and Kuttner in 1926 established the viral cause of a related infection, salivary gland virus disease of guinea pigs. In 1930, Andrewes described inclusion bodies in tissue cultures inoculated with guinea pig virus. Further progress was delayed until the advent of the tissue culture era. Smith in 1954 was the first to carry out serial propagation of murine CMV in mouse tissue cultures.

The CMV is a DNA agent with an icosahedral capsid composed of 162 capsomeres and an inner core. The virus particles are surrounded by an envelope, and some cores contain a ringlike substructure (Fig. 1-1). The virus also contains protein and essential lipids. Human CMV appears to be one of the most heat-labile animal viruses studied to date. For example, its half-life at 37° C is approximately 55 minutes, and its Arrhenius constant is less than 55,000 calories/mole from 0° to 44° C (Krugman and Goodheart, 1964). It is grown best in human fibroblastic tissue cultures.

Neutralizing and complement-fixing antibodies are formed in infected infants and their mothers. Moreover, viral antigen may be identified in infected cells by means of fluorescence-labeled antibody (McAllister and colleagues, 1963). It has been suggested that two and possibly three or more serotypes of CMV may exist (Weller and col-

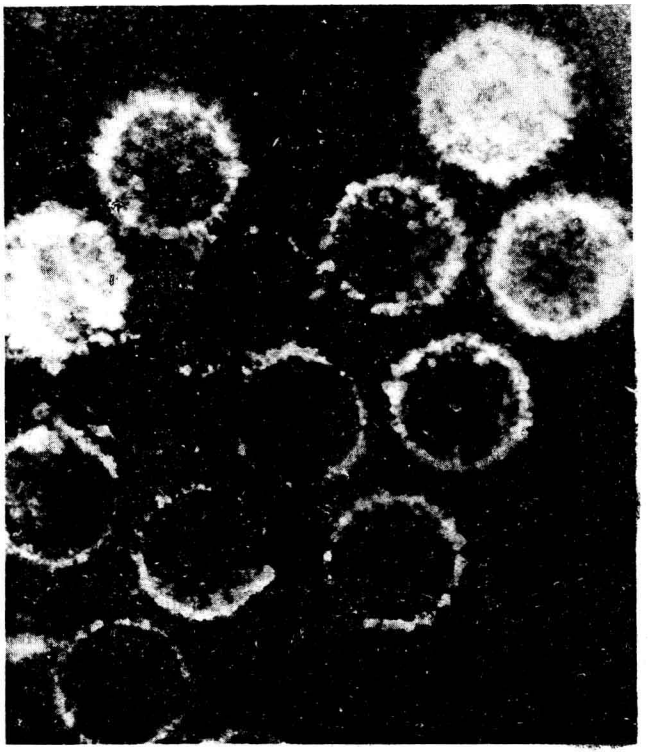

Fig. 1-1. A group of human cytomegalovirus particles showing circular and hexagonal profiles. Full and empty capsids can be observed. Capsomeres are seen to form triangular facets. (×300,000.) (Adapted from Wright, H. T., Jr., Goodheart, C. R., and Lielausis, A.: Virology 23:419, 1964.)

leagues, 1957, 1960). CMVs are related to the Epstein-Barr virus (EBV), herpesvirus varicellae, and herpesvirus types 1 and 2. Cultivation of CMV in human fibroblasts reveals characteristic cytomegaly with intranuclear inclusion bodies and paranuclear cytoplasmic "dense bodies."

PATHOGENESIS

A superb medical progress report by Weller (1971) has summarized knowledge of the natural history of CMV infection in man. The sequence of events following primary infection and subsequent reinfection or activation is shown in Fig. 1-2.

Primary infection

A susceptible (immunologically inexperienced) host may be infected during the prenatal, perinatal, or postnatal period. Prenatal, or congenital, infection is usually acquired via the transplacental route. Viremia during pregnancy may be the most common source of prenatal CMV infection. However, there are isolated reports of congenital infection resulting from intrauterine transfusion of CMV-infected blood.

Perinatal infection is probably caused by exposure to CMV-infected cervical secretions. The presence of CMV in cervical secretions was well documented by Alexander (1967) and Diosi and colleagues (1967).

Postnatal infections are most commonly acquired by contact with various secretions that are known to be infected with CMV, such as urine, semen, saliva, breast milk, and tears. The exact route of transmission is unknown; it may be the oral route, the respiratory route, or both. It has been postulated that close contact is essential for the transmission of CMV. Therefore, it is possible that CMV, like infectious mononucleosis and hepatitis B virus, may be transmitted by kissing.

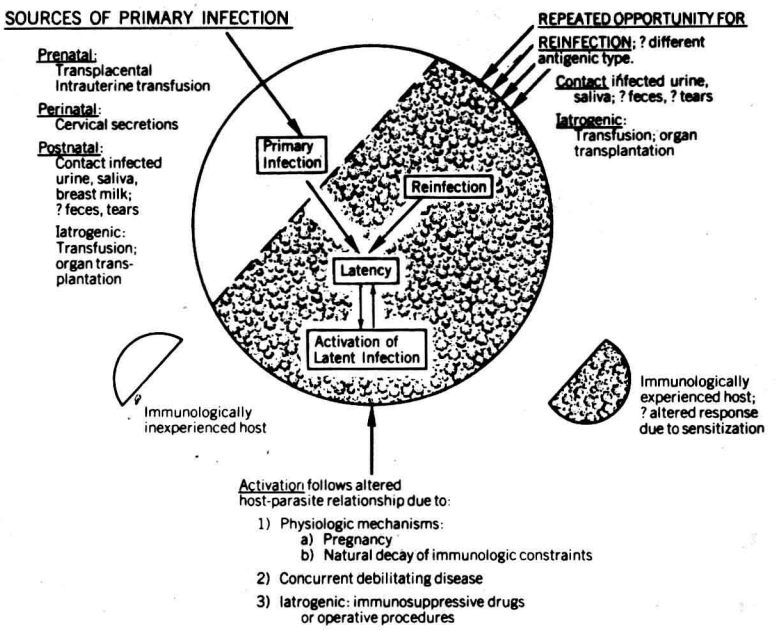

Fig. 1-2. Natural history of human cytomegalovirus infection. (From Weller, T. H.: N. Engl. J. Med. **285**:203, 1971.)

Other exogenous sources of postnatal CMV infection include transfusions with CMV-infected blood and transplantation of organs infected with the virus. These iatrogenic causes of primary CMV infection are being recognized with increasing frequency.

Reinfection or activation of CMV

The immunologically experienced host may be exposed to exogenous or endogenous sources of infection. Exogenously, reinfection may be caused by exposure to a different antigenic type of CMV or to an infectious dose of virus that causes an altered response because of sensitization of the immune host.

Activation of latent CMV infections may stem from various physiologic, pathologic, or iatrogenic mechanisms. Pregnancy or concurrent debilitating disease may be associated with an increased incidence of CMV infection. The administration of immunosuppressive drugs or surgical procedures may activate a latent infection.

Second occurrences of congenitally acquired CMV infections have been reported in a few instances and it was assumed that this is a rare happening (Stagno and colleagues, 1973). Humoral antibody in an immune mother does not prevent maternal excretion of CMV during pregnancy or curtail infant acquisition of the infection. Stagno and colleagues (1977b) found that intrauterine infection with CMV occurred in 3.4% of infants of immune (seropositive) mothers. It is not known whether these infants are at risk of developmental impairment as are those of seropositive mothers. One factor in the failure of immune mothers to restrict virus excretion and spread to their infants despite the presence of elevated antibody titers may be the specific impairment of cell-mediated immunity to CMV reported by Rola-Pleszczynski and colleagues (1977). The rates of CMV excretion in pregnant women increase in the later months.

PATHOLOGY

The histologic lesion of CID is characterized by enlarged cells that contain intranuclear and cytoplasmic inclusion bodies. The intranuclear inclusion body is approximately 9 nm in diameter, appears reddish purple after being stained with hematoxylin and eosin, and is surrounded by a halo. The para-

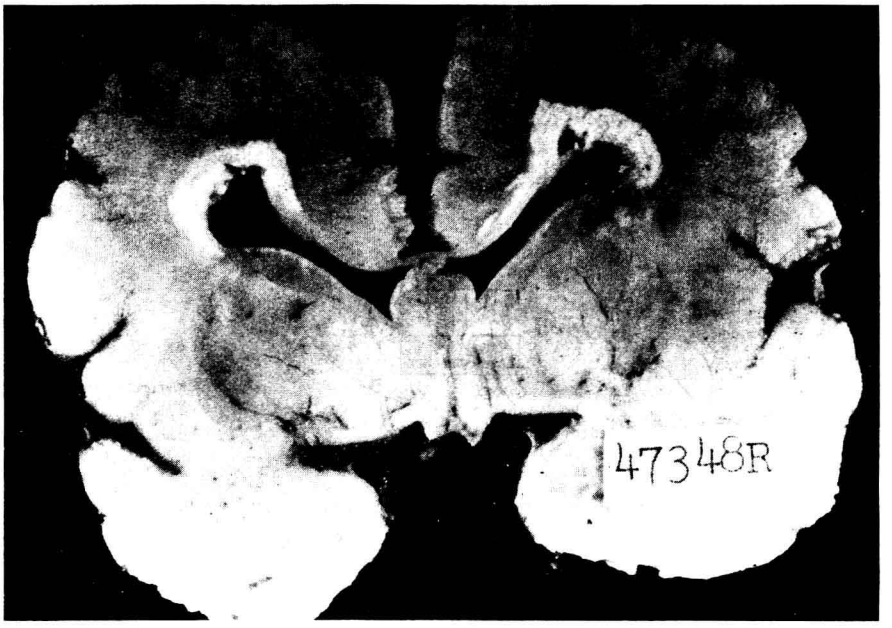

Fig. 1-3. Brain of an infant with generalized cytomegalic inclusion disease. Note extensive periventricular necrosis and calcification.

nuclear cytoplasmic inclusion, or dense, body is more granular and more basophilic in appearance.

The inclusion-bearing cells are widely disseminated. Involvement of the following organs has been seen: salivary glands, kidney, liver, lung, brain, pancreas, thyroid gland, adrenal glands, gastrointestinal tract, spleen, thymus, lymph nodes, parathyroid gland, pituitary gland, testis, epididymis, ovary, heart, eye, muscle, bone marrow, skin, and blood vessels. Involvement of the kidneys and lungs induces chronic interstitial nephritis and pneumonitis, with focal areas of infiltration of mononuclear cells in the interstitial tissue. In the liver, focal areas of necrosis may occur. The brain may show necrotizing granulomatous lesions and extensive calcifications (Fig. 1-3). The liver and spleen may have evidence of extramedullary hematopoiesis.

CLINICAL MANIFESTATIONS

The clinical manifestations of congenital and postnatal CMV infections include a broad spectrum. Both types of infection may range from an asymptomatic process associated with viruria and presence of specific antibody to a severe, widely disseminated disease involving virtually every organ in the body. The great majority of CMV infections, however, are totally inapparent.

Congenital infection

The typical clinical manifestations of severe generalized CID are listed in Fig. 1-4. This fulminating illness is characterized by jaundice, hepatosplenomegaly, and petechial rash and occurs several hours or days after birth in a newborn infant who usually is premature. Early onset of lethargy, respiratory distress, and convulsive seizures may be followed by fatal termination at any time from a few days to a few weeks later.

In infants who survive, jaundice may subside in as few as 2 weeks, or it may persist for more than 4 months. The hemorrhagic phenomena subside rapidly. The hepatosplenomegaly may increase for the first 2 to 4 months, persisting for a prolonged period thereafter. Chorioretinitis commonly occurs.

Laboratory findings usually include ane-

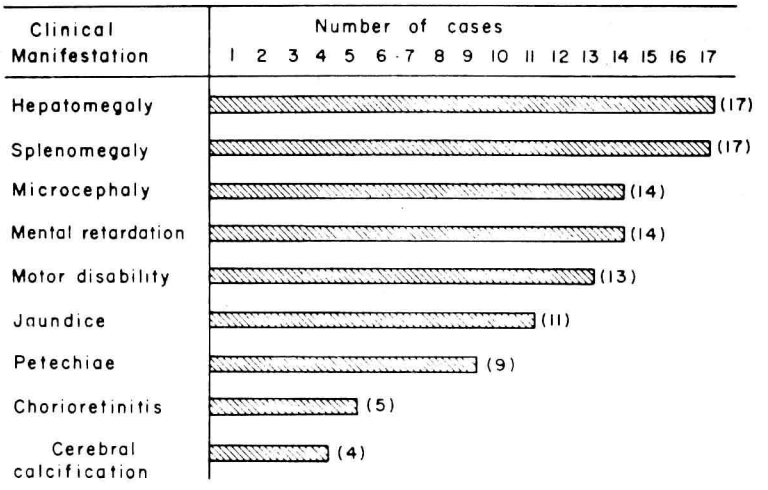

Fig. 1-4. Clinical features in 17 infants with cytomegalic inclusion disease. (From Weller, T. H., and Hanshaw, J. B.: N. Engl. J. Med. **266**:1233, 1962.)

mia and thrombocytopenia. The cerebrospinal fluid (CSF) may show pleocytosis and increased concentration of protein. Roentgenograms of the skull may reveal evidence of cerebral calcifications. Examination of a *fresh* urine specimen sometimes reveals the inclusion bodies in cells of the urinary sediment. The CMV can be isolated from urine, blood, or saliva if tissue culture facilities are available. Recovery of virus is a more sensitive technique than cytology, which on occasion may give repeatedly negative results in the face of large quantities of virus isolated from the urine.

As indicated in Fig. 1-4, many affected infants have severe neurologic sequelae. Mental retardation and motor disability are common. In many infants microcephaly either is present at birth or becomes apparent in a few months. Other manifestations of cerebral damage include spasticity, diplegia, epileptiform seizures, and blindness. Deafness has also become apparent with increasing age. An excellent review by Hanshaw (1970) includes a summary of cerebral, ocular, and extraneural abnormalities associated with congenital CMV infection of 260 infants, from birth to 12 months of age. These defects, which are as follows, occur singly or in combination. The appropriate references for these abnormalities are listed in Hanshaw's review.

Extraneural defects

Cardiovascular
- Atrial septal defect
- Congenital mitral stenosis
- Ventricular septal defect
- Tetralogy of Fallot
- Enlarged ductus
- Hyperplasia of elastica in abnormal arteries
- Accessory or semilunar fold of foramen ovale
- Anomalous venous return

Gastrointestinal
- Biliary atresia
- Esophageal atresia
- Megacolon
- Omphalocele
- Cleft palate
- Stenosis of the ileum and colon
- Intestinal perforation
- Malformed pylorus

Genitourinary
- Renomegaly
- Hypospadias

Musculoskeletal
- Flabby abdominal musculature
- Clubfeet
- Bilateral dislocation of hip
- Deformity of right ankle
- Diastesis recti
- Inguinal hernia
- Spastic diplegia and quadriplegia

Extraneural defects—cont'd
- Pulmonary
  - Lung cysts
  - Immature lungs
  - Thymic hypoplasia
- Miscellaneous
  - Small adrenal glands
  - Large adrenal glands
  - Lipoma
  - Cretinism
  - Thyroid hyperplasia
  - Angiosarcoma

Cerebral defects
- Microcephaly
- Microgyria
- Dilated ventricles
- Periventricular calcifications
- Spongiosis of brain
- Hydrocephalus
- Encephalomalacia
- Cerebral artery calcification
- Deafness
- Parietal lobe cyst
- Cerebral cortical immaturity
- Cerebellar aplasia
- Dolichocephaly

Ocular defects
- Chorioretinitis
- Anomaly of optic disc
- Microphthalmia
- Cataracts
- Retinal calcification
- Optic atrophy
- Blindness
- Anterior chamber malformation
- Pupillary membrane vestige

Again it is important to emphasize that such extensive overt disease (CID) is the exception, whereas more than 95% of congenitally infected infants are totally asymptomatic in the neonatal period (Alford and colleagues, 1975). These inapparent CMV infections have been reported in 0.5% to 2.5% of all newborns. Although infants with occult CMV infections are clinically well at birth, they do have a significant risk of later developmental handicaps. Reynolds and colleagues (1974), Hanshaw and colleagues (1976), and Stagno and colleagues (1977) have demonstrated bilateral sensorineural hearing loss ranging from moderate to profound and increased school failure rates associated with lowered IQ in 15% to 20% of congenitally infected CMV patients followed as long as 7 years.

Postnatal infection

Postnatal CMV infection in children as well as infection in adults is usually inapparent and asymptomatic. The clinical manifestations, when present, may be associated with specific involvement of the liver or lungs as well as a mononucleosislike syndrome. CMV was isolated from nine of 23 children with unexplained chronic liver disease and from the liver of a 19-year-old girl dying of chronic hepatitis (Hanshaw and colleagues, 1965). In addition, CMV infection was demonstrated in 20 children in whom liver disease was not suspected but in the majority of whom hepatomegaly and abnormal liver function were present.

Evidence of a relation between an illness resembling infectious mononucleosis and CMV has been reported by Kääriäinen and colleagues (1966a): A significant rise of complement-fixing and neutralizing antibodies to CMV was described in four adult patients and one child, all of whom had a negative heterophil agglutination test. Illness in the four adults was characterized by fever lasting 2 to 5 weeks, cough, headache or pain in the back or limbs, a large number of atypical lymphocytes, and abnormal results of liver function tests. The 22-month-old child exhibited fever; migratory polyarthritis in the knees, fingers, and toes; skin rash with small red spots; and pneumonia. The pneumonia and arthritis cleared completely, and the child was well 2 months after discharge from the hospital. None of 19 patients with heterophil-positive infectious mononucleosis showed a significant rise in titer of complement-fixing antibodies to CMV.

An illness resembling infectious mononucleosis, with fever, rubelliform rash, atypical lymphocytes, but a negative heterophil antibody test, occurred in a 28-year-old woman 3 weeks after open-heart surgery, during which she received fresh blood from 14 donors. CMV was isolated from the urine 40

days after onset of illness, and the complement-fixing antibody rose from a titer of less than 1:4 at onset to 1:512 on the fortieth day. Moreover, a significant rise in complement-fixing antibodies to CMV was demonstrated in the absence of clinical manifestations of disease in eight of 20 successive patients after open heart surgery accompanied by fresh-blood transfusion.

In summary, CMV mononucleosis is characterized by an acute onset of fever, nonspecific symptoms, and a relative and absolute lymphocytosis with many atypical lymphocytes. Fever in some cases persists for 3 weeks, and in contrast with typical infectious mononucleosis, lymphadenitis and tonsillitis are not present and results of the heterophil antibody test are normal. On the other hand, results of the liver function tests are abnormal.

CMV infection also appears to be a common complication in patients receiving kidney transplants and immunosuppressive drugs (azathioprine, prednisone, azaserine, and actinomycin D). Evidence of CID was found at autopsy in eight of 25 (32%) renal homotransplant recipients who had been given these drugs in various combinations to suppress immunologic rejection of the graft. CMV was isolated from the autopsy material of six patients. Generalized infection was present in five of the six. Large amounts of virus were found in the lungs, salivary glands, pancreas, and transplanted kidney. Pulmonary CID may have contributed to the death of two or three patients in whom cytomegalic cells with inclusion bodies were associated with interstitial pneumonia and intra-alveolar hyaline membranes. In addition, CMV was detected in the urine or oropharyngeal secretions of seven of ten adult homotransplant recipients treated with immunosuppressive drugs; no illness was associated with this infection (Kanich and Craighead, 1966).

Other immunocompromised individuals who have experienced difficulties with CMV infections include cardiac transplantation patients and bone marrow transplant recipients. In some cases, CMV has caused rejection of renal allografts. Fatal pulmonary infections caused by CMV have occurred in heart and bone marrow recipients. Ballard and colleagues (1979) have reported CMV infections in small premature infants who had received multiple blood transfusions in the first weeks of life. At about 6 weeks they developed hepatosplenomegaly, gray pallor, respiratory deterioration, lymphocytosis with atypical lymphocytes and occasional thrombocytopenia. Of 14 such infants, three died while 11 recovered spontaneously. Prospective studies indicated that these infants had acquired CMV infection in the intensive care nursery, most likely as a result of multiple blood transfusions (mean of 21 separate blood units per infant).

DIAGNOSIS

The presence of CID should be strongly considered in a newborn infant with enlargement of the liver and spleen, jaundice, petechial rash, microcephaly, thrombocytopenia, and cerebral calcification. Mental retardation and motor disability (and microcephaly) may become evident in older infants.

In older children and adults the possibility of CMV infection should be kept in mind (1) in instances of pneumonia in patients with chronic debilitating diseases such as malignant tumors and leukemia, (2) in unexplained chronic liver disease, (3) in illnesses similar to infectious mononucleosis but in which results of the heterophil antibody tests are normal that occur in patients subjected to open heart surgery and large volumes of fresh blood and in persons otherwise normal, and (4) in patients receiving kidney transplants and immunosuppressive drugs.

The diagnosis may be confirmed by one of the following procedures: (1) examination of sediment of fresh urine or gastric contents for presence of the typical inclusion bodies located in the exfoliated cells, (2) biopsy of liver for histologic evidence of typical inclusion bodies, (3) identification of virus in tissue cultures inoculated with urine or biopsy specimens, or (4) appropriate use of one of the serologic tests for the detection of CMV

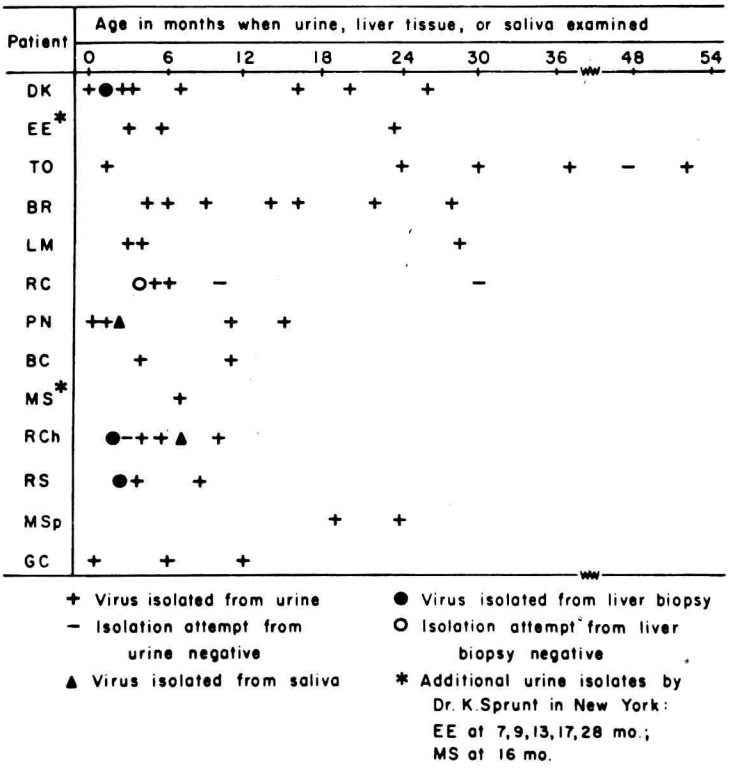

Fig. 1-5. Repeated recovery of virus from 13 infants with cytomegalic inclusion disease. (From Weller, T. A., and Hanshaw, J. B.: N. Engl. J. Med. **266**:1233, 1962.)

antibody, such as the neutralizing antibody test, complement fixation (CF) test, or indirect fluorescent antibody test. Lee and colleagues (1978) have reported the detection by electron microscopy of CMV as herpesvirus particles in urine specimens prepared for examination by the pseudoreplica technique.

As indicated in Fig. 1-5, CMV may persist in urine for prolonged periods of time—as long as 52 months. Isolation of the virus from an infant during the first weeks of life is highly significant. In the presence of the typical syndrome or its sequelae, viruria at any age is indicative of infection. The virus has been detected in a number of urine specimens that were negative for inclusion-bearing cells, which suggests that the virus assay may be the more sensitive of these two diagnostic methods (Wright, 1973).

The neutralizing antibody test, which requires the use of multiple serologic types, is too time consuming and not very practical.

The CF test measures IgG antibody almost exclusively. Therefore, the presence of CF antibody during the first 6 months of life may represent the presence of passively acquired maternal antibody. If the amount of CF antibody does not decline but persists after 6 months of age, the presence of the antibody is presumptive evidence of congenital CMV infection.

The indirect fluorescent antibody test for specific CMV macroglobulin, described by Hanshaw and colleagues (1968), has been shown to be positive in infants with symptomatic CID. The detection of specific CMV-IgM antibody in a single neonatal serum specimen provides a rapid presumptive diagnosis of prenatal infection. Horwitz and colleagues (1979) have also shown how this same test may be used to rapidly confirm CMV mononucleosis syndrome in older children and adults.

DIFFERENTIAL DIAGNOSIS

Generalized CID must be distinguished from a variety of infections and diseases that are characterized by jaundice, hepatosplenomegaly, and purpura in the neonatal period.

Congenital rubella syndrome

The consequences of fetal infection with rubella virus during the first trimester of pregnancy, which in the aggregate have been termed the *rubella syndrome*, include features also seen in infants with CID, such as hepatosplenomegaly, jaundice, petechial and purpuric rashes, thrombocytopenia, microcephaly, and mental retardation. The diagnosis of the rubella syndrome, suggested by a history of maternal infection in the first 3 to 4 months of pregnancy, may be confirmed by virologic and serologic evidence of congenital rubella infection.

Congenital toxoplasmosis

The clinical picture of congenital toxoplasmosis is remarkably similar to that of generalized CID. Both are characterized by jaundice, hepatosplenomegaly, chorioretinitis, and cerebral calcifications. Petechial and purpuric eruptions, which are common in CMV infections, are rare in toxoplasmosis. When toxoplasmosis involves the central nervous system (CNS), elevated protein levels and pleocytosis are often detected in CSF, findings much less frequently associated with CMV infections. The precise diagnosis may be established by serologic evidence of congenital toxoplasmosis or virologic and serologic evidence of CMV infection.

Erythroblastosis fetalis

The jaundice, purpura, and lethargy in an infant with this disease are associated with a positive Coombs' test. The serum glutamic oxaloacetic transaminase (SGOT) activity, which is increased in CMV hepatitis, is within normal limits in erythroblastosis fetalis.

Disseminated herpes simplex infection

Although cerebral calcification has generally not been observed in this disease, a few cases have been reported with late appearance of calcium deposition. Skin lesions, which may be found in up to 50% of herpes simplex patients, are rare in CMV infections. Isolation of the virus and serologic studies are required to confirm a diagnosis of herpes simplex virus infection.

Sepsis of the newborn

This disease is frequently characterized by lethargy, jaundice, and hepatomegaly. A blood culture usually reveals the causative organism.

Congenital syphilis

The unusual case of congenital syphilis can be differentiated from CMV infection by serologic tests and roentgenographic evidence of syphilitic osteitis.

EPIDEMIOLOGIC FACTORS

CMV infections are worldwide in distribution. Cases have been reported in North America, South America, Europe, and Asia. Virologic and serologic studies have contributed to knowledge of the epidemiology of CMV infection. Surveys of unselected newborn infants in the United States and England have revealed a 1% to 2% incidence of viruria. In addition, surveys of virus shedding in pregnant women from various countries have revealed incidences ranging from 1.9% to 5.6%. It is likely, therefore, that more than 30,000 infants with CMV infection are born each year in the United States. These findings suggest that congenital CMV infection is probably the most common fetal infection of man.

The incidence of CMV infection is related to age, geographic location, and economic status. Serologic evidence of CMV infection increases with advancing age, reaching levels of 80% in various parts of the world. In general, infection is acquired at an earlier age by children who live under crowded, unhygienic conditions that are prevalent in slum areas, institutions for mentally retarded children, and certain day-care centers.

The contribution of iatrogenic CID in the spread of infection is well recognized. Patients receiving immunosuppressive drugs