Cytomegalovirus: Clinical Observation of Newborn and Infantile Excreters

By

KATALIN SZÉKELY, B. KÖVÉR and V. ZOLNAI

Department of Paediatrics, University Medical School, Debrecen

(Received March 11, 1965)

The detection of German measles embryopathy revealed the great significance of intrauterine viral infections. However, the diagnosis of such conditions often meets with considerable difficulties. German measles and other infections occurring during the first 3 months of pregnancy are valuable data in the diagnosis of embryopathy. History offers no such aid in a number of other infections, such as toxoplasmosis, and even less concerning the cytomegalovirus which usually evokes no clinical symptoms in adults so that only the presence of antibodies points to a past infection. It is due to the lack of data in the history and the aspecificity of symptoms displayed by the affected babies that cytomegalic inclusion disease, although described as far back as 1881, has received scanty attention until recent times. The disease has come into the foreground of interest in the last 15 years and especially since the discovery of the human cytomegalovirus [1, 3, 6, 7, 11, 12, 14, 15a, 16, 17, 18, 19, 20, 21, 22, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41]. In Hungary, HARASZTI [8, 8a] found cytomegalic inclusion bodies at necropsy in 22 out of 100 infants and MIKLÓS [25] in 23 out of 150 newborns.

We have isolated cytomegalovirus in 8 cases. Five of the babies have been under our observation since birth; their cases will be reported in some detail. Three other infants had positive urines at the age of $4^1/_2$, 6 and 10 months, respectively; two of these were treated for interstitial pneumonia and one for bronchopneumonia, otitis, and hepatosplenomegaly.

CASE REPORTS

Case No. 1. J. B., male, born on June 5, 1964, with a weight of 1700 g, was referred to our department on account of episodes of asphyxia at the age of 3 days. The baby was jaundiced; the abdomen and the lower limbs were covered with petechiae and roseolar eruptions, there was a blood-stained discharge from the navel; the scrotum was oedematous. Bradycardia was marked, liver and spleen were moderately enlarged; there was kyphoscoliosis. Moro's reflex was weak.

The patient had repeated apnoeic episodes with cyanosis. Feeding met with difficulties, swallowing and pharyngeal reflex were uncertain. At feeding, cyanotic attacks occurred. RBC, 5.200.000; reticulocytes, 2.1 per cent; erythroblasts, 5 per cent; thrombocytes, 31.000; urine bili-

rubin, +++; blood group, AB; Rh+; Coombs' test, negative. Haemoculture negative. At the age of 5 days, cytomegalovirus was isolated from the urine. Steroid treatment was prescribed with doses of 12.5 mg daily for 6 weeks.

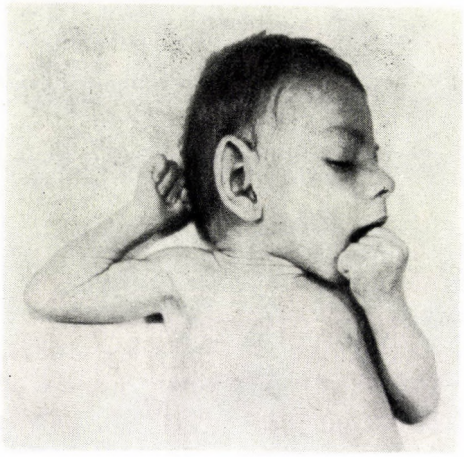

FIG. 1. Case No. 1. Microcephalia; malformed skull; hypertonicity of muscles

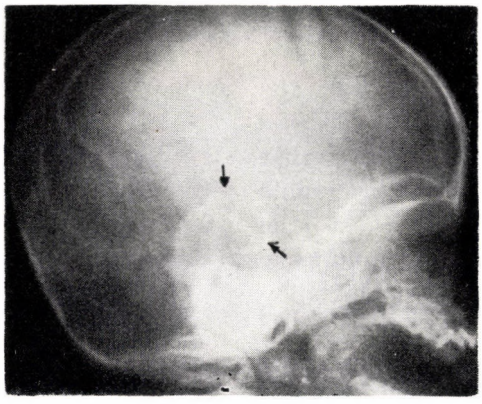

FIG. 2. Case No. 1. Suprasellar circular calcification in brain

After a standstill of 1 1/2 months body weight began to rise. The anterior fontanel was almost completely closed at the age of 2 months. The baby had a squint, an empty look, nystagmus was often noted. Repeated ophthalmologic examination revealed atrophy of the optic nerve with choroiditis on the left side. Acoustic stimuli elicited a startle reaction. The right face was paretic. The infant made sometimes large amplitude athetotic movements with the arms. Muscular tonicity was constantly increasing.

At the age of 6 months, body weight was 3500 g, length 53 cm, head circumference 35 cm, that of the chest 35 cm. At that time, the baby took the bottle well, but apnoea, bradycardia and cyanosis often occurred so that feeding by means of a gastric tube was preferred.

X-rays of the spinal column showed marked scoliosis; the other regions were normal, but for a well outlined suprasellar circular calcification. This could be followed well since the age of 3 weeks.

At 9 months, body weight was 4400 g, length 59 cm, head circumference 37 cm. Though treated with antispasmodics, the baby had practically incessant convulsions; it was incapable of sitting and holding his head while in a prone position (Figs 1, 2).

Case No. 2. A. R., male, delivered December 5, 1964, by Caesarean section on account of threatening intrauterine asphyxia. The cord was twisted around the neck. The infant weighed 2100 g; it was cyanotic, feebly whimpering, apathic and refused to feed. Scrotum and symphysis were oedematous; liver and spleen were of normal size. No jaundice was present in spite of 0—B incompatibility and a maternal anti-B titre of 1 : 1024. Moro's reflex was positive. The palate exhibited petechiae, the skin was covered with macular exanthems. X-rays of the chest and skull showed no abnormality. The urine at the age of 5 days was positive for cytomegalovirus. After the first days muscular tonicity increased especially in the lower extremities.

At one month of age the baby still refused to eat and had to be fed through a gastric tube. Body weight had reached 2500 g by that time. After the 2nd month hypertonicity, a chronic systolic murmur and bilateral inguinal hernia developed. The ears were situated low, the ear lobes displayed a minor anomaly. The baby was presumably blind, the optic disks were sharp-edged and decoloured. Body weight at 3 months was 3200 g, length 53 cm, head circumference 36 cm.

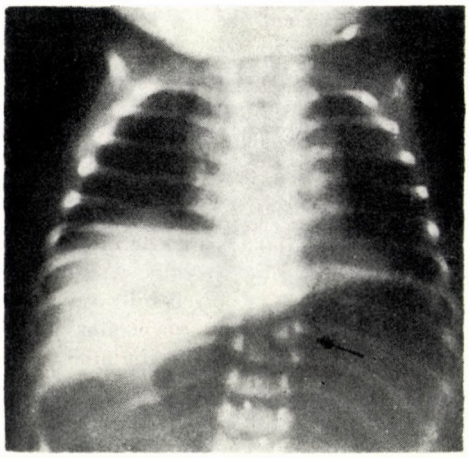

FIG. 3. Case No. 3. Hemivertebra formation

Case No. 3. Gy. Sz., male, born on June 16, 1964, with a weight of 2200 g, was referred to our department with oedema and jaundice at the age of 4 days. The patient was sluggish, short-necked, with slightly mongoloid eyes. Abdomen and lower limbs were markedly oedematous, the liver was considerably enlarged. RBC, 5.200.000; haemoglobin: 22 g per 100 ml; no erythroblasts; reticulocytes, 2.5 per cent; serum bilirubin: 13.5 mg per 100 ml. The mother's blood was 0 Rh negative, the father's A Rh positive, the child's A Rh positive. Coombs' test was negative, there was no spherocytosis. Jaundice and

oedema disappeared in a few days, but the baby refused to take the breast and had to be fed by tube until the age of 4 weeks. At 7 weeks the baby was discharged with a tentative diagnosis of kernicterus and mongolism.

After repeated episodes of *E. coli* dyspepsia and otitis the patient was re-admitted at the age of 6 months. He was recalcitrant to feeding, and lagged in weight and mental development. The skull was malformed, microcephalic, the fontanel was nearly closed, muscle tonicity was normal. Ophthalmologic examination revealed bilateral optic atrophy. X-rays of the skull were normal; ossification centres were retarded, hemivertebra formation was found at $T_9 - T_{10}$. At the age of 6 months, cytomegalovirus was repeatedly isolated from the urine.

Case No. 4. S. Sz., a premature male baby of 1400 g was admitted soon after birth with cyanosis and marked oedema of the lower extremities. The urine yielded cytomegalovirus on the 2nd day. The baby was jaundiced from the 3rd day of life, lay with the head thrown back, muscular tonicity was moderately increased, serum bilirubin rose to a peak of 14 mg per 100 ml. Jaundice lasted a month, during which development was lagging. There were periodic attacks of dyspnoea. The baby had to be fed through a gastric tube for a long time. At the age of 2 months the faeces were occasionally blood-stained but negative bacteriologically. Thereafter development was satisfactory, at the age of $3\,^1/_2$ months body weight was 3100 g. There were no signs of disease, X-rays of the skull and other parts were normal.

Case No. 5. J. R., a premature male infant of 1500 g body weight, had displayed no symptoms in the first postnatal days, but developed apnoea, aphagia and blood-stained stools by the 7th day. The condition deteriorated suddenly at the age of 6 weeks; heart action was labile, the abdomen was distended, the liver considerably enlarged. The baby was transferred to the contagious ward with the suspicion of interstitial pneumonia. The symptoms included circulatory disturbance, tachycardia, repolarization disturbance, anaemia, oedema, pyuria. At four months the infant weighed 2900 g, ocular fundi were normal, cytomegalovirus was isolated from the urine, X-rays showed no intracranial calcification.

Isolation of Virus and Serological Studies

Isolation and passage of virus was made according to Medearis [20, 21] in human embryonic fibroblast cultures. Monkey kidney and HeLa cells were not susceptible to the isolated virus. The strains were sensitive to ether. Fibroblast cultures grown on cover slips showed, after staining with haematoxylin-eosin, characteristic nuclear inclusions of type A. The isolated strains revealed specific focal fluorescence. Neutralization tests (against cytomegalovirus strains at a titre of 1 : 256 with specific immune sera showing active complement fixation) revealed a 91 to 96 per cent focal reduction as compared to controls treated with normal bovine serum.

Serological analyses were performed in Cases 1 and 4. Serum from Case 1 obtained at 18 days and $1\,^1/_2$ months contained complement-fixing antibodies; their titre (1 : 32) remained constant. The maternal serum contained complement-fixing antibodies of the same titre. The mother had not been ill during pregnancy. — The serum of Case 4 showed no complement-fixing activity.

Seventy-five samples of 49 children were used for viral isolation; 60 results were evaluable: 12 urine samples collected from 8 babies were found positive for cytomegalovirus [5].

Discussion

Since cytomegaloviruria was demonstrated on the 2nd and 5th postnatal days in three babies (Cases 1,

2, 4), in their cases infection was undoubtedly of intrauterine origin. Neonatal symptoms and the developmental anomaly of the vertebral column pointed likewise to intrauterine infection in Case 3, where the virus was isolated at the age of 6 months only. It may still have been of intrauterine origin, since surviving infants often remain virus carriers and excreters for many months [41]. Of course, the possibility of postnatal infection was likewise admissible in which case the malformation and the viruria were independent phenomena. In Case 5, the apnoea, melaena and dysphagia appearing at the age of 7 days may have been due to prenatal and postnatal infection alike; virus was revealed in the urine at 6 weeks only.

The fact that all five among the eight virus-excreting babies were prematures is not surprising, since, according to literature, about half of the patients suffering from cytomegalic inclusion disease are born before term [32]. Intrauterine infection and premature delivery are presumably in causal connection.

The pathogenicity of cytomegalovirus is highly probable. MEDEARIS, who suggested this in 1957 [20] on the evidence of numerous subsequent investigations affirmed in 1963 that there existed a correlation between cytomegalic inclusion disease and infection with human cytomegalovirus [21]. A full proof in this respect is almost impossible, owing to the strict species specificity of the virus, among others.

If clinical symptoms raise the suspicion of cytomegalic inclusion disease, the diagnosis may be confirmed by a demonstration of the virus [10, 14]. Giant cells with nuclear inclusions characteristic of cytomegalovirus have been found in urine and saliva, less frequently in gastric juice, aqueous humour and the cerebrospinal fluid. The absence of inclusions does not yet exclude the possibility of the disease [12, 40]. The number of diagnostically instructive cells is, according to NAIB [29], low even in positive cases with extensive lesion of the urinary tract so that exfoliative cytological studies have to be supplemented by viral isolation and possibly by biopsy. MEDEARIS [20, 21] studied the urine of 6 patients with cytomegalic inclusion disease for the comparison of the two methods; of 18 identical preparations 17 were positive virologically and only 4 cytologically. The superiority of viral isolation to exfoliative cytological analysis of the urine was confirmed by CRAMBLETT's comments on the communication of WELLER et al. [40] as also by the reports of STERN [35], MCALLISTER et al. [18] and MOLZ [28] whose exfoliative cytological studies of the urine yielded negative results in verified cases of cytomegalic inclusion disease. The paper of MOLZ [28] is accompanied by instructive illustrations which reveal why exfoliative cytology gives unreliable results. Affected cells in the proximal convoluted tubules are at different stages of development, so that typical cells are seen side by side with deteriorating ones containing

cytoplasmic inclusions. Detached, the necrotized cells gradually fill the tubules in the form of cytologically no longer evaluable amorphous detritus and are then excreted with the urine. MIKLÓS [25], for instance, failed to demonstrate the presence of cytomegalic cells in the urine in 24 cases, but active cytomegalovirus could be isolated from the detritus formed by the decomposing cells.

Cytomegaloviruria, especially if occurring in newborn infants, is a proof of the inclusion disease. The pathogens have never been demonstrated in healthy neonates and asymptomatic infection has not been registered in the neonatal period [12]. The correct diagnosis in the first week of life must be ensured by viral isolation [15a]; later, passage of virus in urine should only be considered characteristic in the presence of typical signs of the disease, since in older children and adults viruria may occur without cytomegalic inclusion disease. HANSHAW and SIMON [7] examined 309 older children and found viruria in 18; of these 17 exhibited also signs of some hepatic disturbance. They regard the urinary passage of virus as indicative of clinical disease and do not consider the virus an ubiquitous infectious agent. The urinary sediment and saliva of our Case 1 was repeatedly studied for cytomegalic cells, with negative results. In view of this failure and because literary evidence showed the method of viral isolation more reliable than that of exfoliative cytology, we dispensed with the search for inclusion bodies in the further course of investigations.

No biopsies were made in this study. The unreliability of liver biopsy has been shown by MOLZ [28] who observed extensive characteristic histological lesions in several organs but found only sporadic giant cells in the liver.

As to the serological tests, their diagnostic value is limited. Although the complement-fixation test is sensitive and specific [21], its positive result does not necessarily mean infection in the case of newborns. Complement-fixing antibodies occur in blood at an equal rate (71 per cent) in virologically negative newborns and adults; their incidence corresponds to the passive transfer of maternal antibodies. GÖNCZÖL et al. [5] found the cord blood positive in 47 per cent, a figure comparable to that found in adults over 30 years of age, whereas the blood of children aged 2 to 24 months was positive in 18 per cent of the examined cases. It has been mentioned that a positive result of the complement-fixation test does not necessarily mean infection in the case of newborn babies; on the other hand, a negative result does not exclude it. Serum, negative at and after birth, may gradually turn positive, and complement-fixing antibodies can be demonstrated with homologous antigen in the second year of life. The neutralization test carried out with homologous strains is an excellent serological method, which, however, cannot be used in the case of prematures, considering the repeated massive withdrawals of blood, time factor,

etc. Viruria of the newborn must, therefore, be accepted as a sign of cytomegalic inclusion disease.

As long as the diagnosis of cytomegalic inclusion disease was based exclusively on morphological evidence, it was known only as a local disease of the salivary glands, especially the parotid, or, else, in its generalized form. If the disease is generalized, cells containing characteristic nuclear inclusions are present not only in the salivary glands but also in other (mainly epithelial) organs. Cerebral lesions (necrosis, calcification, haemorrhage, inflammation) are due either directly to the infection or to the disturbance of early embryonic development. With the progress of cytological and virological examinations, it is now possible to diagnose the disease not only *post mortem* as before, but also in its milder forms *in vivo*.

Seifert and Oehme [31], relying on clinical manifestations, set up three categories: cytomegalic inclusion disease of the newborn, of the infant and that of the child. The disease of newborn babies shows much similarity to the acute haemolytic disease accompanied by jaundic hepatosplenomegaly, erythroblastaemia and the purpuric or other forms of dermal haemorrhage. About half of these infants are prematures.

Cytomegalic inclusion disease in young infants affects particular organs and is, accordingly, known in its (i) pulmonary, (ii) hepatosplenomegalic, (iii) cerebral, (iv) gastro-intestinal, (v) renal and (vi) mixed forms.

Cytomegalic inclusion disease in children and (very exceptionally) adult persons is presumably a pathogenetically insignificant infection accompanying some grave primary disease.

This grouping is, however, still a morphological one. The clinical pattern, as seen in the living infant, is far from uniform; it varies from viraemia through haemorrhages, thrombopenia, jaundice and hepatosplenomegaly to the sequelae of encephalitis, somatic and mental retardation, microcephaly, hydrocephaly, convulsions and blindness.

Not only a clinical picture suggesting haemolytic disease of the newborn accompanied by purpura and exanthems need point to cytomegalic inclusion disease in newborn prematures. The possibility of inclusion disease should be considered also if bilirubinaemia, oedema, neurological symptoms, respiratory distress, dysphagia, apathy are observed, in brief, symptoms that might point to intracranial haemorrhage.

Differential diagnosis of cytomegalic inclusion disease should embrace practically the entire range of infantile pathology, since all disorders manifesting themselves with early grave jaundice, anaemia, erythroblastosis, thrombopenia, haemorrhages, hepatosplenomegaly, nervous symptoms, intracranial calcification, respiratory distress and developmental anomalies or combinations thereof must be taken into consideration.

Cytomegalic inclusion disease may resemble and has to be differentiated

from other diseases associated with acute haemolysis, such as Rh or AB0 incompatibility, congenital syphilis and toxoplasmosis, listeriosis, herpes simplex, staphylococcal or meningococcal sepsis, connatal tuberculosis, infection with *E. coli*. Coxsackie virus, further congenital haemolytic jaundice, congenital leucaemia, hereditary nonspherocytic haemolytic anaemia, maternal idiopathic thrombopenia, atresia of the biliary tract, galactosaemia, traumatic cerebral haemorrhage, hyperbilirubinaemia of variable aetiology, developmental anomalies due to drugs, other viral embryopathies, storage diseases, etc.

Symptoms common to the cytomegalic inclusion disease and toxoplasmosis may persist in the further course of the patient's life, e.g. micro- or hydrocephaly and intracranial calcifications; since, in contradiction to earlier views, choroidoretinitis may occur in connection with the inclusion disease, the complete toxoplasmosis triad may be of cytomegalic origin. Calcifications due to toxoplasmic encephalitis appear mostly in small scattered foci, whereas paraventricular lineal calcification is characteristic of cytomegalic inclusion disease. However, radiographic evidence does not suffice, and the diagnosis of toxoplasmosis has to be ensured serologically. In addition, inclusion disease and toxoplasmosis may occur simultaneously in the same patient [9, 38].

Previously, the generalized form of inclusion disease was regarded as fatal, having always been diagnosed *post mortem* only. Recent literature contains numerous reports to the contrary [3, 11, 19, 21, 40, 41]. Although most surviving patients are gravely damaged, cases with slight sequelae and even some of complete recovery are known.

So far, no specific therapy of the disease is known. Cortisone has been found useful in several instances [1, 17]; its administration has the purpose to subdue inflammation and to reduce the predisposition to haemolytic anaemia and thrombopenia. The results are, however, far from convincing and application of the drug may involve certain risks [25, 28]. Two of the patients in this study received cortisone: Case No. 1 who had thrombopenia, and Case No. 5 who developed myocarditis of probably viral origin. Exchange transfusions [16] did not seem justified in our cases. All premature babies at our department are given gamma globulin; it might be of use in inclusion disease, too. Essentially, the present treatment of cytomegalic inclusion disease is merely palliative.

Gönczöl et al. [5] have studied by means of complement-fixation tests the incidence of cytomegalovirus infection in the Debrecen area. Eighteen per cent in the age group 2 to 24 months, 27 per cent in the group 4 to 14 years, 35 per cent in the group 14 to 30 years and 51 per cent of the persons older than 30 years yielded a positive result. The infection rate of 51 per cent compared favourably with one of 71 per cent in Vienna and 81 per cent in the U.S.A. [36, 40, 41]. This notwithstanding, the incidence of cy-

tomegalic inclusion disease seems to be high among the infants in the same area. To have diagnosed 8 cases within 6 months justifies the inference that the cytomegalovirus may play an important role in premature delivery, neonatal hyperbilirubinaemia and possibly also in developmental anomalies. It should, however, be remembered that our material originated from the premature wards, and that retrospective considerations usually tend to distort the actual importance of a condition.

Summary

Cytomegalovirus has been isolated from the urine of 8 infants. Observations of 5 patients followed up since the neonatal period, are reported. The various clinical manifestations of cytomegalic inclusion disease, its differential diagnosis and treatment are discussed. Attention is called to the pathological significance of cytomegaloviral infection of the newborn.

References

1. Birdsong, McL., Smith, D. E., Mitchell, F. N., Corey, J. H.: Generalized cytomegalic inclusion disease in newborn infants. J. Amer. med. Ass. **162,** 1305 (1956)
2. Essbach, H.: Paidopathologie. Thieme, Leipzig 1961
3. Fried, R. I., Winograd, H. L.: Maladie des inclusions cytomégaliques. (Un cas survivant au delà des premiers mois.) Pédiatrie **15,** 161 (1960)
4. Gonda, Gy.: Cytomegaliás zárványtest megbetegedés klinikuma és pathologiája. Gyermekgyógyászat **7,** 107 (1956)
5. Gönczöl, É., Váczi, L., Géder, L., Lehel, F.: Studies on cytomegalovirus. Acta microbiol. Acad. Sci. hung. In press
6. Hanshaw, J. B., Weller, T. H.: Urinary excretion of cytomegalovirus by children with generalized neoplastic disease. J. Pediat. **58,** 305 (1961)
7. Hanshaw, J. B., Simon, G.: Cytomegaloviruses in the urine of children with hepatomegaly and abnormal liver function tests. Amer. J. Dis. Child. **104,** 555 (1962)
8. Haraszti, A.: Cytomegalia infantum. Acta morph. Acad. Sci. hung. **6,** 241 (1955)

8a. Haraszti, A.: Csecsemők cytomegalia betegsége. Gyermekgyógyászat **6,** 232 (1955)

9. Haymaker, W., Girdany, B. R., Stephens, J., Lillie, R. D., Fetterman, G. H.: Cerebral involvement with advanced periventricular calcification in generalized cytomegalic inclusion disease in the newborn. J. Neuropath. exp. Neurol. **13,** 562 (1954)
10. Hooft, C., Delbeke, M. J.: Contribution à l'étude de la maladie des inclusions cytomégaliques. Arch. franç. Pédiat. **17,** 914 (1960)
11. Hurez, A., Lanvin, M., Debray, H., David, C., Le Braz, A., Hallé, B.: Forme néonatale de la maladie des inclusions cytomégaliques. Arch. franç. Pédiat. **18,** 501 (1961)
12. Katz, S. L., Kibrich, S.: Nonbacterial infections of the newborn. Ped. Clin. North Amer. **8,** 493 (1961)
13. Keresztury, S., Wöckel, F.: Meeting of the Hungarian Association of Pathologists, Budapest 1963
14. Keuth, U.: Zur intra vitam-Diagnose der generalisierten Zytomegalie. Mschr. Kinderheilk. **106,** 272 (1958)
15. Kőszegi, B., Piukovich, I.: Zytomegalie infantum und Herz-Entwicklungsanomalie. Zbl. allg. Path. **94,** 124 (1955)

15a. Krugman, S., Ward, R.: Infectious diseases of children. Mosby, St. Louis 1964

16. Lelong, M., Lepage, Fr., Le Tan Vinh, Tournier, P., Chany, Ch.: Le virus de la maladie des inclusions cytomégaliques. Arch. franç. Pédiat. **17,** 437 (1960)
17. Margileth, A. M.: The diagnosis and treatment of generalized cytomegalic inclusion disease of the new-born. Pediatrics **15,** 270 (1955)

18. McAllister, R. M., Wright, H. T., Tasem, W. M.: Cytomegalic inclusion disease in newborn twins. J. Pediat. **64,** 278 (1964)
19. McElfresh, A. E., Arey, J. B.: Generalized cytomegalic inclusion disease. J. Pediat. **51,** 146 (1957)
20. Medearis, D. N.: Cytomegalic inclusion disease. Pediatrics **19,** 467 (1957)
21. Medearis, D. N.: Observations concerning human cytomegalovirus infection and disease. Bull. Johns Hopkins Hosp. **114,** 181 (1963)
22. Mercer, R. D., Luse, S., Guyton, D. H.: Clinical diagnosis of generalised cytomegalic inclusion disease. Pediatrics **11,** 502 (1953)
23. Miklós, Gy.: Cytomegalia betegség és előfordulása koraszülöttek interstitialis plasmasejtes pneumoniájával együtt. Orv. Hetil. **101,** 1549 (1960)
24. Miklós, Gy.: Adatok a csecsemőkori pancreatitisek pathologiájához. Gyermekgyógyászat **13,** 262 (1962)
25. Miklós, Gy.: A cytomegaliás zárványtest betegségről 24 eset alapján. Gyermekgyógyászat **14,** 353 (1963)
26. Miklós, Gy., Orbán, T.: Szemészeti elváltozások cytomegalia zárványtest betegségben. Szemészet **101,** 90 (1964)
27. Mégevand, A.: Embriopathie cérébrale dans un case de maladie généralisée des inclusions cytomégaliques. Ann. paediat. (Basel) **201,** 410 (1964)
28. Molz, G.: Zur Speicheldrüsenviruskrankheit. Cytomegalie bei Neugeborenen. Helv. paediat. Acta **19,** 597 (1964)
29. Naib, Z. M.: Cytologic diagnosis of cytomegalic inclusion-body disease. Amer. J. Dis. Child. **105,** 153 (1963)
30. Oehme, J.: Klinik und Bedeutung der Cytomegalie. Münch. med. Wschr. **103,** 143 (1961)
31. Seifert, G., Oehme, J.: Pathologie und Klinik der Cytomegalie. Thieme, Leipzig 1957
32. Seifert, G., Oehme, J.: Die Bedeutung der Zytomegalie für Pathologie und Klinik. Dtsch. med. Wschr. **82,** 1759 (1957)
33. Seifert, G.: Die Speicheldrüsenviruskrankheit Zytomegalie. Med. Klin. **54,** 1734 (1959)
34. Silverman, W. A.: Cytomegalic inclusion disease. Pediatrics **21,** 682 (1958)
35. Stern, H.: Isolation of cytomegalovirus in an infant with an angiosarcoma. Arch. Dis. Child. **38,** 626 (1963)
36. Thalhammer, O., Rowe, W. P.: Gibt es im Raum von Wien Cytomegalie? Wien. klin. Wschr. **72,** 621 (1960)
37. Thalhammer, O., Zweymüller, E.: Angeborene Cytomegalie. Wien. klin. Wschr. **73,** 762 (1961)
38. Versé, H.: Zur Differentialdiagnose zwischen konnataler Toxoplasmose und generalisierter Zytomegalie. Mschr. Kinderheilk. **110,** 51 (1962)
39. Vortelj, V., Plachij, V.: Вортель, В. В. Плахий: Теперализованная цитомегалия и её значение в клинике детского возраста. Педиатрия **11,** 73 (1959)
40. Weller, Th. H., Hanshaw, J. B., Scott, D. E.: Virologic and clinical investigations on cytomegalic inclusion disease. Amer. J. Dis. Child. **100,** 469 (1960)
41. Weller, Th. H., Hanshaw, J. B.: Virologic and clinical observations on cytomegalic inclusion disease. New Engl. J. Med. **266,** 1233 (1962)

Dr. K. Székely
Gyermekklinika
Debrecen, Hungary