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Cytomegalic Inclusion Disease*

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Cytomegalovirus infection causes, in contrast to other viral infections, characteristic and specific long-lasting cellular changes (Brzosko and Michałowski, 1956; Medearis, 1957; Nelson and Wyatt, 1959; Seifert and Oehme, 1957). For this reason, histopathological diagnostic investigation is of considerable value (Bardier, Bouissou, Régnier, Martinez, Bézy, and Laplanche, 1964; Fetterman, 1952; Seifert, 1961). The group of cytomegaloviruses is widely disseminated in Europe, as well as in both Americas and Asia (Brzosko, 1959; Weller and Hanshaw, 1962; Wyatt, Saxton, Lee, and Pinkerton, 1950). Fatal cases of generalized cytomegalic inclusion disease have been reported in 1-2% of routine paediatric necropsies, and localized salivary gland infection in 10–32% of unselected paediatric necropsies (Seifert and Oehme, 1957; Weller and Hanshaw, 1962; Wyatt *et al.*, 1950). In Great Britain (Crome and France, 1959; Symmers, 1960), the condition seems to be much less common. However, the actual incidence in all countries is probably higher than that reported, since many cases, both fatal and non-fatal, remain undiagnosed. This conclusion was reached following the introduction of methods for isolation of cytomegalovirus and the development of serological procedure (Benyesh-Melnick, Dessy, and Fernbach, 1964; Carlström, 1965; Hanshaw, Betts, Gilbert, and Boynton, 1965; Stern and Elek, 1965).

It has usually been thought that this condition in infants is always congenital, but the results of the virological and serological studies of Rowe and coworkers from Washington (Rowe, Hartley, Cramblett, and Mastrota, 1958) suggest that the infection also often occurs after birth.

Over a five-year period we have observed 20 cases of generalized cytomegalic inclusion disease, which amounts to 5% of all necropsies and 6·4% of necropsies in infants under 1 year of age, and all these children died between the second and the sixth month of life. Since newborn babies are very seldom admitted to our hospital, we were not able to observe early deaths of newborns, which might have been caused by cytomegalic inclusion disease.

The following criteria for differentiating the congenital and postnatal forms of the condition in infants are suggested (Table I).

Of the 20 cases, 9 were included in the first group (Table II), and 5 in the second (Table III). 6 could not be classified with certainty because the data were incomplete. However, taking into account the available information and, particularly the histological findings, it is probable that 4 of these 6 patients were examples of neonatal infection, and that the 2 others were postnatal (Table IV).

The percentage of cytomegalic inclusion disease in our total necropsy material (5%) is rather high.

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TABLE I

Differentiating Criteria

	Congenital Neonatal Form	Post-neonatal Form
Age	Under 3 months	Over 3 months
Clinical manifestations	(a) Characteristic severe form including jaundice, hepatosplenomegaly, and thrombocytopenic purpura, or first manifestations connected with infection observed during first 4 weeks of life	(a) Presence of another severe primary illness, e.g. fibrocystic disease of pancreas or Werdnig-Hoffman syndrome
	(b) Presence of cerebral manifestations	(b) Lack of cerebral manifestations
Necropsy findings	(a) Interstitial inflammation present in several viscera, cytomegalic cells, degenerating or containing intranuclear as well as cytoplasmic inclusion	(a) Lack of interstitial inflammation, cytomegalic cells well preserved, containing mainly intranuclear inclusions
	(b) Salivary glands not involved or involved with same intensity as other glands	(b) Most intense changes in salivary glands

TABLE II

Congenital Form

Case No.	Sex and Birth-weight (g.)	Age (mth.)	Clinical Onset	Hepatomegaly	Splenomegaly	Petechiae	Jaundice	Cerebral Signs	Main Clinical Manifestations	Site of Cytomegalic Inclusions	Cause of Death
1	F 1950	3	Birth	+	+	+	+	+	Sepsis, encephalo-pathy	Lungs, liver, kidneys, oesophagus, pancreas, brain	Cytomegalic inclusion disease
2	M ?	2	2 wk.	+	+	−	−	−	Protracted pneumonia, enterocolitis	Lungs, kidneys, heart	Ulcerative enterocolitis with peritonitis (*Esch. coli* B_4O_{111})
3	M 3020	2	Birth	+	+	−	−	+	Encephalopathy, pneumonia	Lungs, liver, heart	Pneumonia with pleuritis
4	M 2890	3	4 wk.	+	+	−	+	−	Jaundice, abscesses of skin	Lungs, liver	Staphylococcal sepsis
5	M 2900	2	Birth	+	+	+	+	−	Sepsis	Lungs, kidneys, brain, spleen	Cytomegalic inclusion disease
6	M 2400	4	Birth	+	+	+	+	+	Sepsis, encephalo-pathy	Salivary glands, lungs, liver, kidneys, brain, heart	Staphylococcal sepsis
7	M 2000	2	1 mth.	+	+	−	−	−	Acute enterocolitis, anaemia	Salivary glands, lungs, liver	Enterocolitis (*Esch. coli* B_4O_{111})
8	M 2150	2	1 mth.	+	+	+	−	+	Sepsis, dermatitis	Salivary glands, lungs, liver, kidneys, pancreas, brain, pituitary gland, intestines	Cytomegalic inclusion disease
9	F 2850	2½	Birth	−	−	−	−	+	Encephalopathy, chorio-retinitis	Lungs, liver, pancreas brain	Pneumonia with pleuritis

The question immediately follows: is infection by cytomegalovirus in infants really more common in Poland than in other countries? The data from other Polish hospitals, where the percentage of diagnosed cases is much lower, raise some doubt on this question. However, a more probable explanation may be differences in necropsy procedure. In our hospital, for instance, in each case almost all viscera, and very frequently many sections of each organ, are examined microscopically.

TABLE III

Postnatal Form

Case No.	Sex and Birth-weight (g.)	Age (mth.)	Hepatomegaly	Splenomegaly	Petechiae	Jaundice	Cerebral Signs	Main Clinical Signs	Site of Cytomegalic Inclusions	Cause of Death
10	M 3760	6	−	−	−	−	−	Fibrocystic disease of pancreas	Salivary glands, lungs, pancreas, kidneys	Fibrocystic disease of pancreas, bilateral pneumonia, pneumothorax
11	M 2980	3	+	+	−	−	−	Protracted pneumonia, pertussis	Salivary glands, lungs, pancreas	Fibrocystic disease of pancreas, bilateral pneumonia
12	F ?	4	−	−	−	−	−	Pneumonia with abscesses and purulent pleuritis	Lungs	Staphylococcal sepsis
13	F 1900	5½	+	+	−	−	−	Congenital malformation of heart, pneumonia	Salivary glands, lungs, pancreas, kidneys	Congenital malformation of heart, pneumonia
14	M 2550	5½	+	+	−	−	−	Werdnig-Hoffman disease, pneumonia	Salivary glands, lungs	Bilateral pneumonia

TABLE IV

Doubtful Form of Cytomegalic Inclusion Disease (15-18 probably congenital; 19 and 20 probably postnatal)

Case No.	Sex and Birth-weight (g.)	Age (mth.)	Clinical Onset (mth.)	Hepatomegaly	Splenomegaly	Petechiae	Jaundice	Cerebral Signs	Main Clinical Signs	Site of Cytomegalic Inclusions	Cause of Death
15	F 2330	2	1	+	–	–	–	–	Pneumonia	Lungs, liver, kidneys	Fibrocystic disease of pancreas
16	M 3250	2	1	+	+	–	–	–	Pneumonia, pertussis	Salivary glands, lungs, liver, pancreas, kidney, adrenals, intestines	Massive pneumonia
17	M 2600	4	3	+	–	–	+	–	Purulent pleuritis	Lungs, liver, pancreas, kidneys	Purulent pleuritis
18	M 2400	3	2	+	+	–	–	–	Interstitial pneumonia	Salivary glands, lung, liver	Pneumocystic pneumonia
19	M 3240	3	2	+	+	–	–	–	Bronchitis, anaemia	Salivary glands, lungs, pancreas, kidneys	Fibrocystic disease of pancreas, staphylococcal sepsis
20	M 4050	3½	2	+	+	–	–	–	Enterocolitis sepsis	Lungs, liver, pancreas, kidneys, adrenals, heart	Sepsis (*Klebs., Esch. coli*, B_4O_{111})

Large numbers of cytomegalic cells were seldom observed (Fig. 1), most often the cells were single and scattered. They were readily and most frequently found in the lungs (Fig. 2 and 3), less commonly in other viscera (Table V). In the kidneys a large number of cytomegalic cells was

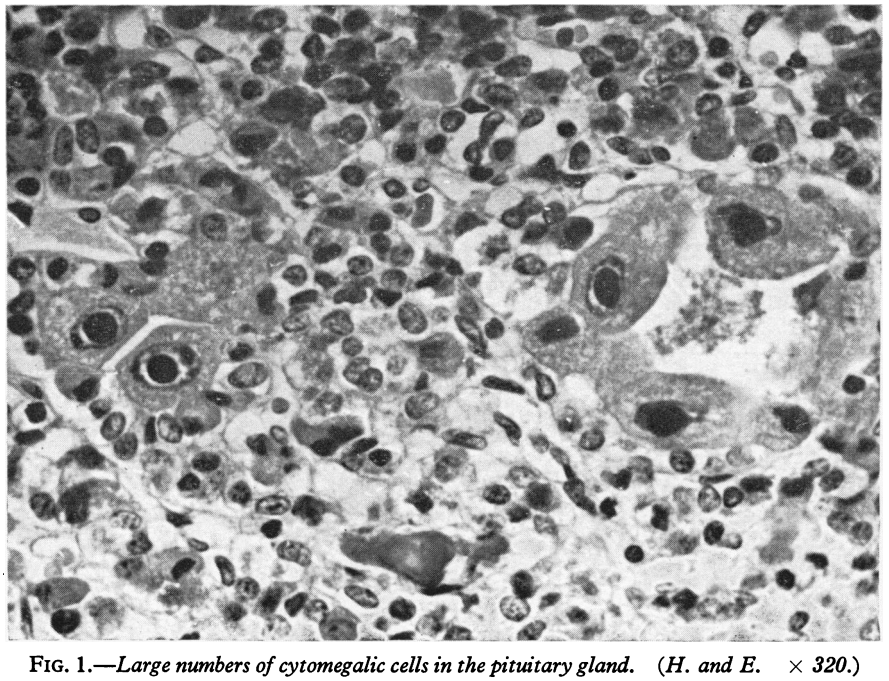

FIG. 1.—*Large numbers of cytomegalic cells in the pituitary gland.* (*H. and E.* × *320.*)

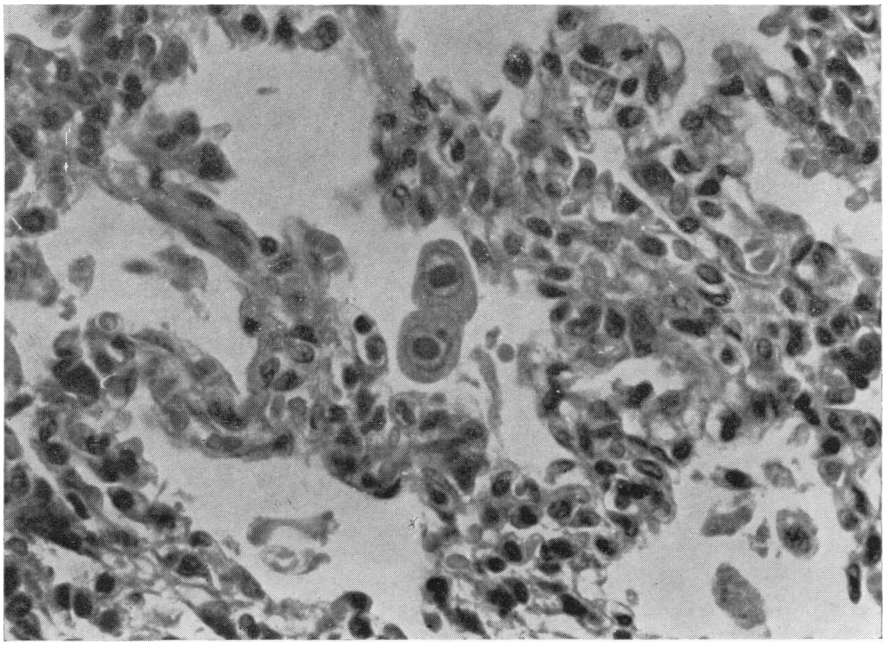

FIG. 2.—*Cytomegalic cells in alveolar space. Note slight inflammatory infiltration of alveolar septa. (H. and E. × 320.)*

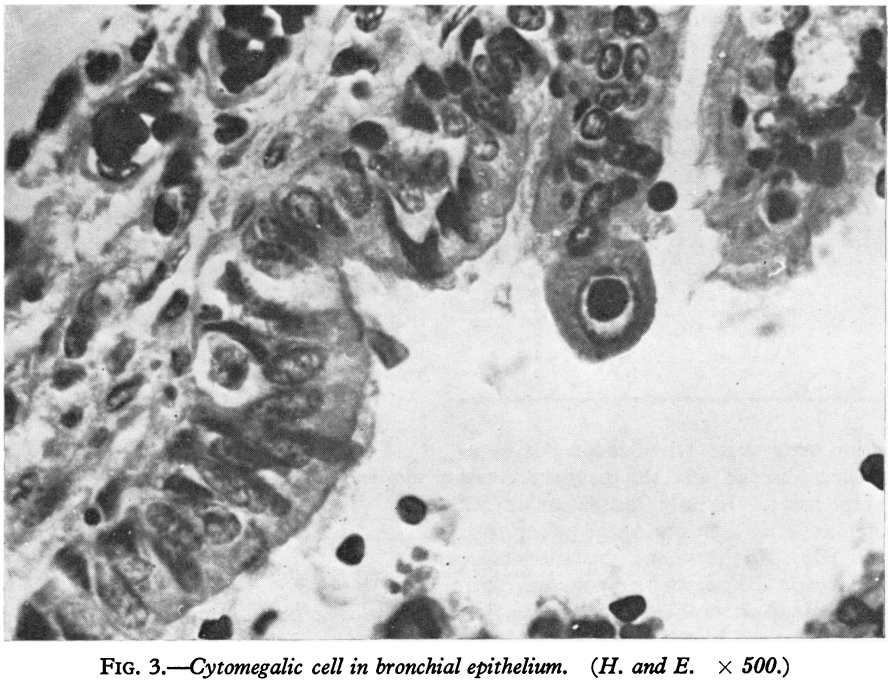

FIG. 3.—*Cytomegalic cell in bronchial epithelium. (H. and E. × 500.)*

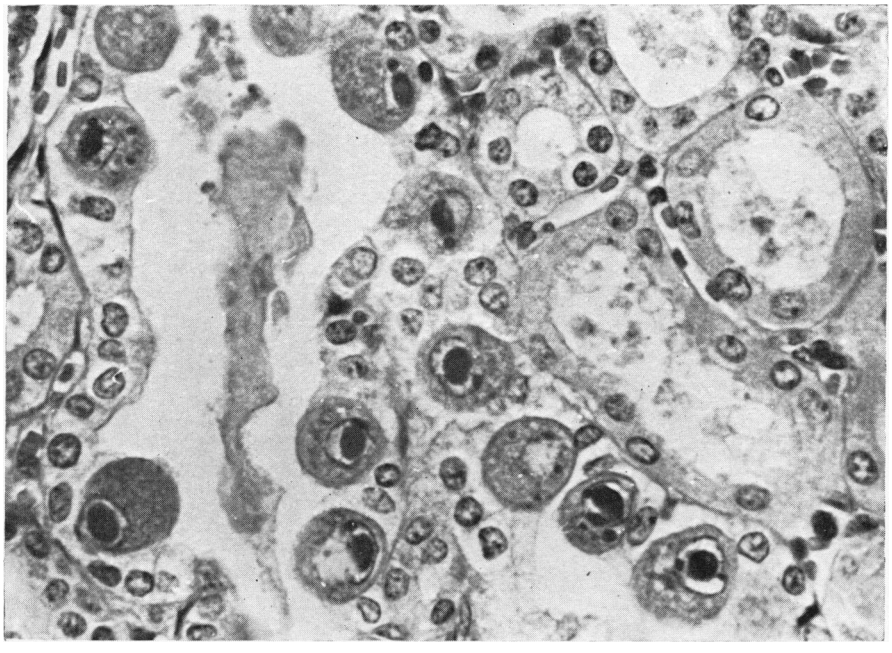

FIG. 4.—*Widespread cytomegalic transformation of renal tubular epithelium.* (*H. and E.* × *320.*)

noticed only once (Fig. 4). Usually the cells were single, often limited to vascular endothelium, and in such cases the likelihood of finding cytomegalic cells in urine seems rather small.

TABLE V

Site of Cytomegalic Inclusions

Site	Number of Cases
Lungs	20
Kidneys	12
Liver	11
Salivary gland	10
Pancreas	8
Brain	6
Heart	4
Intestine	3
Adrenals	2
Spleen	1
Hypophysis	1

The question may arise whether or not cytomegalic inclusion disease was the primary cause of death in these cases. In only 3 cases considered to be neonatal were no changes found other than those of cytomegaly. In the other 17 instances there were 4 of fibrocystic disease of the pancreas with bacterial pneumonia, 4 of staphylococcal sepsis, 3 of acute enterocolitis caused by *Esch. coli* B_4O_{111}, 1 of pneumocystic pneumonia, and 5 of massive pneumonia, 2 with exudative pleurisy (Table VI).

In view of the rather high frequency with which the cytomegalovirus can be isolated from the urine in apparently healthy children, it is possible that during a symptomless 'localized' salivary gland infection, single cytomegalic cells may be formed in other organs. The presence of these cells may be associated with persistent viruria and viraemia. In such an event, the great effort involved in the search for cytomegalic cells in various organs does not seem to have any clinical significance. One can expect, however, that in infants under 6 months of age, combined virological and histopathological investigations of a series of cases may furnish some information of considerable clinical and diagnostic value.

TABLE VI

Cause of Death

Condition	Number of Cases
Cytomegalovirus infection only	3
Cytomegalovirus + fibrocystic disease of pancreas and bacterial pneumonia	4
Cytomegalovirus + staphylococcal sepsis	4
Cytomegalovirus + acute enterocolitis caused by *Esch. coli* B_4O_{111}	3
Cytomegalovirus + pneumocystic pneumonia	1
Cytomegalovirus + massive pneumonia	5

Summary

Reported and discussed are 20 cases of generalized cytomegalic inclusion disease in infants 2-6 months of age.

Criteria for differentiating the neonatal and postnatal form of the condition are suggested on the basis of clinical manifestations and necropsy findings.

Generalized cytomegalic inclusion disease was found in 5% of unselected necropsies from the laboratory of morbid anatomy of a Warsaw Children's Hospital. This apparently high figure is probably related to the rather detailed microscopical examination undertaken, since the cytomegalic cells in the investigated organs were most frequently single. Moreover, in 17 of the 20 cases other changes were found, which might have been the cause of death.

The problem is discussed, whether during a symptomless, so-called localized, salivary gland infection, single cytomegalic cells may perhaps be formed in other organs, and be associated with persistent viruria.

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References

Bardier, A., Bouissou, H., Régnier, C., Martinez, J., Bézy, P., and Laplanche, Mlle. (1964). Maladie des inclusions cytomégaliques. Étudie anatomique et ultramicroscopique. *Arch. franç. Pédiat.*, **21**, 375.

Benyesh-Melnick, M., Dessy, S. I., and Fernbach, D. J. (1964). Cytomegaloviruria in children with acute leukemia and in other children. *Proc. Soc. exp. Biol. (N.Y.)*, **117**, 624.

Brzosko, W. J. (1959). Cytomegalic inclusion disease. *Rozpr. Wydz. Nauk med. pol. Akad. Nauk*, **4**, 121.

——, and Michałowski, A. (1956). Case of generalized cytomegalic inclusion disease. *Pediat. pol.*, **31**, 1363.

Carlström, G. (1965). Virologic studies on cytomegalic inclusion disease. *Acta paediat. (Uppsala)*, **54**, 17.

Crome, L., and France, N. E. (1959). Microgyria and cytomegalic inclusion disease in infancy. *J. clin. Path.*, **12**, 427.

Fetterman, G. H. (1952). A new laboratory aid in the clinical diagnosis of inclusion disease of infancy. *Amer. J. clin. Path.*, **22**, 424.

Hanshaw, J. B., Betts, R. F., Gilbert, S., and Boynton, R. C. (1965). Acquired cytomegalovirus infection. Association with hepatomegaly and abnormal liver function tests. *New Engl. J. Med.*, **272**, 602.

Medearis, D. N., Jr. (1957). Cytomegalic inclusion disease. *Pediatrics*, **19**, 467.

Nelson, J. S., and Wyatt, J. P. (1959). Salivary gland virus disease. *Medicine (Baltimore)*, **38**, 223.

Rowe, W. P., Hartley, J. W., Cramblett, H. G., and Mastrota, M. (1958). Detection of human salivary gland virus in the mouth and urine of children. *Amer. J. Hyg.*, **67**, 57.

Seifert, G. (1961). Die morphologische Diagnose der Zytomegalie (Pathohistologie, Zytologie, Gewebekultur, Elektronenmikroskopie). *Munch. med. Wschr.*, **103**, 139.

——, and Oehme, J. (1957). *Pathologie und Klinik der Cytomegalie.* G. Thieme, Leipzig.

Stern, H., and Elek, S. D. (1965). The incidence of infection with cytomegalovirus in a normal population. A serological study in Greater London. *J. Hyg.*, **63**, 79.

Symmers, W. St. C. (1960). Generalized cytomegalic inclusion—body disease associated with pneumocystis pneumonia in adults. A report of three cases, with Wegener's granulomatosis, thrombotic purpura, and Hodgkin's disease as predisposing conditions. *J. clin. Path.*, **13**, 1.

Weller, T. H., and Hanshaw, J. B. (1962). Virologic and clinical observations on cytomegalic inclusion disease. *New Engl. J. Med.*, **266**, 1233.

Wyatt, J. P., Saxton, J., Lee, R. S., and Pinkerton, H. (1950). Generalized cytomegalic inclusion disease. *J. Pediat.*, **36**, 271.