observed, and was often best supplied when the decision to increase the dose was left to the patient: this must, however, depend on an assessment of each individual's personality. Antibiotics given early during infections of the upper respiratory tract also appeared to reduce the risk of serious relapse.

We reiterate the view that long-term steroid therapy is a valuable form of treatment, but it must be used circumspectly, with adequate supervision and full collaboration between the hospital consultant and the family physician. Though steroids often enable patients to lead a more active and useful life, attacks of severe asthma may still occur, and need urgent and thorough treatment.

Summary

One hundred and seventy patients treated with long-term steroids have been followed for up to 13 years. There was no evidence that steroid therapy lost its effect with the progress of time. Side-effects were not significantly related to length of treatment but to the average dose of steroid used. Treatment with steroids, though reducing the number of attacks of status asthmaticus, in no way alters the need for urgent treatment if these develop. Severe attacks of asthma are particularly apt to follow "weaning" from long-term treatment, and in such cases steroid therapy should at once be resumed.

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Isolation of Cytomegalovirus and Clinical Manifestations of Infection at Different Ages

H. STERN,* M.B., PH.D., M.C.PATH.

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Cytomegalovirus was long regarded as a rare cause of disease, affecting mainly newborn babies. It is in fact an important pathogen. Infection is common in both children and adults (Rowe *et al.*, 1956 ; Stern and Elek, 1965 ; Carlström, 1965). Young children excrete the virus for long periods, and often show evidence of liver damage (Rowe *et al.*, 1958 ; Hanshaw *et al.*, 1965), while adults may develop an atypical, Paul-Bunnell-negative form of infectious mononucleosis (Klemola and Kääriäinen, 1965 ; Anderson and Stern, 1966 ; Klemola *et al.*, 1967a). This latter syndrome, which also occurs as a common complication of operations requiring large transfusions of fresh blood (Kääriäinen *et al.*, 1966a), can present with hepatitis and jaundice (Lamb and Stern, 1966 ; Toghill *et al.*, 1967) or with polyneuritis or pericarditis (Klemola *et al.*, 1967b ; Ironside and Tobin, 1967 ; Räsänen and Saikku, 1967). The neonatal disease is neither rare nor invariably fatal, but survivors are usually mentally retarded and microcephalic (Weller and Hanshaw, 1962 ; Medearis, 1964). Finally, cytomegalovirus infection is a serious and fatal hazard of the intensive immunosuppressive therapy of leukaemia and Hodgkin's disease and of renal homotransplantation (Hill *et al.*, 1964 ; Rifkind, 1965 ; Bodey *et al.*, 1965 ; Cangir and Sullivan, 1966).

The present paper reports an epidemiological study of cytomegalovirus infection in London, with an assessment of its clinical significance. Two associated studies are also described of cytomegalovirus infection in unexplained neonatal hepatitis and liver disease in children, and in Paul–Bunnell-negative glandular fever.

* Reader in Virology, St. George's Hospital Medical School, London S.W.1

Virological Methods

Urine and throat washings were collected into virus transport medium and inoculated within two hours into diploid human embryonic fibroblasts. Cytomegalovirus complement-fixing antibodies were estimated by the microtitre technique, using cell-associated antigen prepared from the Rawles strain of virus. The virus isolation and serological techniques have been described in previous papers (Stern *et al.*, 1963 ; Stern and Elek, 1965).

Prevalence of Cytomegalovirus Excretion in London

Urine was collected routinely from babies on the first or second day after birth, in the maternity units of St. George's Hospital and the Hillingdon Hospital. Urine and a throat washing or swab were taken from unselected admissions to the acute medical, surgical, and paediatric wards of St. George's

TABLE I.—*Excretion of Cytomegalovirus in Unselected Neonates and Hospital Admissions in London*

Age Groups	No. Positive / No. Tested	% Positive
Neonates	3/118	2·5
2–5 months	3/32	9
6 months–4 years	10/104	10
5–9 years	1/101	1
10–14 „	0/72	—
15–24 „	0/102	—
25–34 „	0/100	—
35–59 „	0/100	—
60+ „	0/100	—

Hospital on the day of admission or the day after, as well as from 99 healthy nurses and laboratory personnel aged 15–35.

Three out of 118 neonates were found to be excreting virus (Table I): 106 were apparently healthy newborn babies, and virus was isolated from two of them; 12 were aged 2–6 weeks, having been admitted because of minor respiratory or gastro-intestinal upsets, and one was excreting virus. The incidence of excretion increased to 10% in children aged 2–5 months and 6 months to 4 years, but among the older age groups there was only one excreter, aged 6 years. In every case virus was isolated from both urine and throat.

Associated Neonatal Illnesses

All 118 neonates were apparently healthy at birth. The 115 non-excreters subsequently made normal progress, though one of them developed mild transient jaundice when 7 days old. The three babies excreting cytomegalovirus had none of the classical symptoms commonly associated with neonatal cytomegalic inclusion disease, but two of them are mentally retarded and the other has shown abnormal liver-function tests.

Case 1.—This child, the first of healthy parents, was born at full term after an uneventful pregnancy. Her birth weight was 5 lb. 15 oz. (2,695 g.), head circumference 12.6 in. (32 cm.). Virus was isolated from urine on the day of birth. No abnormality was noted at birth, but some hours later a few purpuric spots appeared on the face and head. These had gone after a few days, and there were no other clinical abnormalities. Blood picture, including platelet counts, and skull *x*-ray films were normal. Liver-function tests showed only a mildly increased alkaline phosphatase level of 22 King–Armstrong (K.A.) units. Cytomegalovirus complement-fixing antibody titre was 128 in both baby and mother. The infant gained weight only slowly, and at 3 months was obviously severely mentally retarded and microcephalic. Liver-function tests were now clearly abnormal; alkaline phosphatase 28 K.A. units, thymol turbidity 2.4 units, serum aspartate aminotransferase (S.G.O.T.) 44 units, serum alanine aminotransferase (S.G.P.T.) 122 units. Virus was still being excreted at 18 months of age despite a serum antibody titre of 32.

Case 2.—This child was born at full term, weight 8 lb. 13 oz. (3,995 g.), head circumference 13.5 in. (34 cm.). Though virus was isolated from urine on the day of birth he appeared to be perfectly healthy. There were no clinical or haematological abnormalities and a skull *x*-ray film was normal. Cytomegalovirus antibody titre was 16. Liver-function tests at 8 weeks were abnormal; alkaline phosphatase 28 K.A. units, S.G.P.T. 68 units. At 6 months physical and mental progress was unimpaired, despite continuing viruria. There was no hepatomegaly, but the alkaline phosphatase was still raised at 28 K.A. units. Head circumference was 18.3 in. (47 cm.), inside the 97th percentile.

Case 3.—This infant's birth history was uneventful, but he was admitted at 3 weeks because of feeding difficulties and failure to gain weight. Cytomegalovirus was first isolated at that time. No clinical abnormalities were found, and chest and skull *x*-ray films, liver-function tests, and numerous biochemical and bacteriological investigations were all normal. Cytomegalovirus antibody titre was 16, his mother's 32. At 3 months of age he was found to have marked generalized muscular hypotonia and flabbiness. This persisted, with delay in the various stages of motor progress. At 22 months he could not stand unaided, and there was obvious delay in his mental development.

Associated Illnesses in Older Children

The 136 children aged 2 months to 4 years were admitted to hospital for a variety of illnesses (Table II). The virus excreters among them and also the 6-year-old excreter are described in Table III. All 14 had an uneventful neonatal history. Cases 5, 8, 9, 12, and 14–17 had minor illnesses from which they recovered in a few days, while Cases 7 and 10 were admitted for investigation of hydrocephalus and for treatment of the most recent of a series of urinary coliform infections. These 10 patients had no other significant clinical abnormalities, but Cases 14 and 17 did have abnormal liver-function tests (alkaline phosphatase 36 and 48 K.A. units, S.G.P.T. 48 and 25 units respectively). Four children (Cases 4, 6, 11, and 13) had protracted respiratory illnesses, which are described below. They showed no serological evidence of current infection with *Mycoplasma pneumoniae* or with influenza, parainfluenza, respiratory syncytial virus, or adenovirus.

TABLE II.—*Cytomegalovirus Excretion in Young Children Newly Admitted to Hospital*

Clinical Diagnosis	Incidence of Virus Excretion	
	2–5 Months	6 Months–4 Years
Upper respiratory illness	1/5	1/14
Bronchitis and pneumonia	1/6	1/7
Pertussis and croup	0/1	3/4
Otitis media	0/1	1/3
Urogenital infections	0/1	0/7
Skin diseases	0/1	0/3
Operations and injuries	0/2	2/10
Psychiatric and social conditions	0/4	0/6
Congenital heart disease	0/3	0/3
Other congenital defects	—	2/12
Mental deficiency and epilepsy	0/1	0/3
Miscellaneous conditions	1/7	0/32
Total No. of cases	3/32	10/104

TABLE III.—*Clinical Features of Children Excreting Cytomegalovirus*

Case No.	Age	Clinical Diagnosis	Hepatomegaly (H) and/or Splenomegaly (S)	Liver-function Tests
4	2 months	Pharyngitis	H–S	Abnormal
5	3 „	Chicken-pox	—	N.D.
6	5 „	Bronchitis	H–S	„
7	7 „	Hydrocephalus	—	„
8	10 „	Coryza	—	„
9	10 „	Croup	—	„
10	10 „	Caecal agenesis	—	Normal
11	18 „	Pertussis	—	Abnormal
12	2 years	Otitis media	—	N.D.
13	2 „	Pneumonia	S	Normal
14	3 „	Croup	—	Abnormal
15	4 „	Squint operation	—	N.D.
16	4 „	„ „	—	„
17	6 „	Otitis media	—	Abnormal

N.D. = Not done.

Case 4.—A 2-month-old infant had a 24-hour history of abdominal colic, diarrhoea, and vomiting. She had a congested throat and scattered rales in the chest, and the spleen tip was palpable. *Streptococcus pyogenes* was isolated from the throat, as well as cytomegalovirus from throat and urine. The chest *x*-ray picture was normal and liver-function tests showed only an increased alkaline phosphatase level, 34 K.A. units. Despite penicillin she continued unwell with persistent coughing and periodic attacks of colic, and was readmitted at 4 months old with a febrile exacerbation of symptoms. The liver was now palpable three fingerbreadths below the costal margin and the spleen was easily felt. Chest *x*-ray picture and intravenous pyelogram were normal, and bacteriological investigations proved negative. The alkaline phosphatase was still raised at 39 K.A. units. She remained unwell with febrile episodes and coughing for a further two months before starting to improve, but by 9 months of age was fit. The hepatosplenomegaly was gone, though the viruria persisted.

Case 6.—An infant with thalassaemia major was admitted to hospital at 2 months of age because of a febrile respiratory illness associated with spasmodic coughing attacks. The blood picture was typical of the underlying disease and the spleen was very large, but the liver was barely palpable. He improved on tetracycline, but the cough persisted. Virus was first isolated on his readmission at 5 months for recurrence of fever with bronchitis and noisy paroxysmal coughing. Chest and skull *x*-ray films were normal and the blood picture was unchanged, but the liver was now enlarged to five fingerbreadths below the costal margin. Despite further treatment with tetracycline and blood transfusions the symptoms did not finally clear until another three months. The hepatosplenomegaly persisted, and at 21 months he was still excreting virus.

Case 11.—An 18-month-old boy was admitted with two weeks' history of "whooping-cough"—namely, paroxysmal coughing which was followed often by vomiting and once by small haemo-

ptysis. There were no clinical abnormalities, but a chest *x*-ray film showed consolidation of the left lower lobe. The white cell count was 10,500/cu. mm., with neutrophils 8%, lymphocytes 86%, monocytes 4%, eosinophils and basophils 2%; there were some atypical mononuclears in the blood film. *Bordetella pertussis* could not be isolated from the throat, but cytomegalovirus was present in throat and urine and the cytomegalovirus antibody titre was 32. The lung changes resolved after five days, but he was readmitted two weeks later with exacerbated symptoms and widespread crepitations in the chest. The white cell count was 9,100/cu. mm., with neutrophils 4%, lymphocytes 88%, monocytes 8%, and numerous atypical mononuclears in the film. The Paul–Bunnell reaction was negative, and liver-function tests were abnormal; alkaline phosphatase 40 K.A. units, S.G.P.T. 50 units. The cytomegalovirus antibody titre had increased to 128. Symptoms slowly abated, and he was well one month later.

Case 13.—A 2-year-old child had six weeks' history of a persistent cold with spasmodic dry coughing, complicated by two bouts of generalized convulsions. She was febrile and there was some reddening of the throat and right eardrum, and the spleen tip was palpable. A chest *x*-ray film showed consolidation of the right lower lobe. Cytomegalovirus was isolated from throat and urine, but no bacterial pathogens. Blood picture and liver-function tests were normal and a tuberculin test was negative. Cytomegalovirus antibody titre was 128. The symptoms cleared slowly during two to three weeks, but viruria was still present four weeks later.

Cytomegalovirus Excretion in Cases of Neonatal Hepatitis and Liver Disease in Children

Because of the known propensity of cytomegalovirus to cause liver damage a study was made of newborn babies and older children with unexplained liver disease in order to assess the importance of this infection in causing such disease. During two years, 1965–7, 50 newborn infants and 24 children aged 3 months to 10 years from various hospitals in London were examined.

Forty-five of the neonates presented with jaundice; 17 of them also had hepatomegaly or hepatosplenomegaly and five had petechial skin rashes. Two others presented with generalized purpura and hepatosplenomegaly, and three had only unexplained hepatosplenomegaly. Blood group incompatibility was excluded in all of them. Virus was isolated from five cases—cytomegalovirus from two, rubella virus from two, and herpes simplex virus from one. Both cytomegalovirus excreters presented at birth as classical cases of neonatal cytomegalic inclusion disease, and died at 6 and 7 weeks old respectively. The rubella virus excreters were examples of the congenital rubella syndrome. One case was fatal, with obstructive jaundice, hepatosplenomegaly, giant-cell hepatitis, and microcephaly (Stern and Williams, 1966); the other had jaundice, cataracts, congenital heart disease, and microcephaly and so far has survived. The herpes virus excreter developed irritability and jitteriness soon after birth, and on the second day became deeply jaundiced. The liver was slightly enlarged. There was no hypoglycaemia, and the jaundice cleared over three to four weeks. Virus was isolated from the baby's urine at 19 days of age. The mother gave no history of current or past herpetic illness, and her herpes complement-fixing antibody titre was 128. At 6 weeks old the baby had completely recovered. She was no longer excreting virus, and her herpes antibody titre was 64.

Of the 24 older children 11 were aged 3–6 months. Six of these presented with jaundice and nine had hepatomegaly or hepatosplenomegaly. Ten were 6 months to 4 years old, of whom four had jaundice and eight had hepatosplenomegaly. Three were aged 5–9 years, two with jaundice and all three with hepatomegaly or hepatosplenomegaly. Cytomegalovirus was isolated from two children aged 5 and 8 years; the other 22 were neither excreting virus nor had cytomegalovirus complement-fixing antibodies.

Case 18.—A 5-year-old boy arrived from Singapore only four days before his admission to hospital. He had developed a febrile illness nine days previously, followed within 48 hours by jaundice. He was still deeply jaundiced, and the liver was enlarged two fingerbreadths below the costal margin. Liver function was abnormal; serum bilirubin 1.2 mg./100 ml., alkaline phosphatase 259 i.u., thymol turbidity 20 units, S.G.P.T. 23 units. Blood cultures were sterile, and no bacterial pathogens were isolated from throat, urine, or faeces. *Leptospira icterohaemorrhagiae* and *L. canicola* agglutinin titres were <10. Cytomegalovirus antibody titre 18 days after onset of illness was 32. Symptoms subsided slowly, and three months later liver-function tests were normal. Virus was isolated from urine at that time, and the cytomegalovirus antibody titre was 32.

Case 19.—An 8-year-old boy had eight days' history of fever and transient macular rash, unresponsive to penicillin. Liver and spleen were both enlarged three fingerbreadths below the costal margins. The white cell count was 3,000/cu. mm., with a normal differential and film, but the platelet count was only 33,000/cu. mm. Liver-function tests showed alkaline phosphatase 15.2 K.A. units, thymol turbidity 8 units, S.G.P.T. 10 units, and serum proteins 6.6 g./100 ml. with increased gammaglobulins. Bone-marrow biopsy four weeks after onset of illness showed "marked decrease in megakaryocyte numbers and maturation arrest of the granulocyte series resembling that caused by drugs or infection." No bacterial pathogens were isolated from throat, urine, or faeces, salmonella and brucella agglutinin titres were <10, toxoplasma dye test was negative, and the Paul–Bunnell reaction was persistently negative. Cytomegalovirus was isolated from urine and throat five weeks after onset of illness, when the antibody titre was 128. He gradually improved without treatment, and after six weeks was well. The liver was not enlarged and only the spleen tip was palpable. Platelet counts and liver-function tests were normal. Virus was reisolated six months later. At that time his 6-year-old brother had a transient febrile illness and was also found to be excreting cytomegalovirus.

Cytomegalovirus Excretion in Cases of Atypical Infectious Mononucleosis

An investigation was made of 19 children and 70 adults with a clinical diagnosis of Paul–Bunnell-negative glandular fever. The children were aged 5 to 15 years and all had unexplained cervical or generalized lymphadenopathy; two also had exudative tonsillitis, seven had splenomegaly or hepatosplenomegaly, and two had a transient maculopapular rash. However, only 11 of them had a glandular-fever-like blood picture—namely, a lymphocytosis with abnormal mononuclears. Cytomegalovirus was isolated from only one child (Case 20). The other children neither excreted virus nor showed rising titres of antibody during their illnesses; three had antibody in the acute serum, but there was no subsequent increase in titre.

Case 20.—A 6-year-old boy had a five-month history of recurrent sore throat. His tonsils were hypertrophic but not inflamed, and there were hard rubbery glands on both sides of the neck. The white cell count was 8,000/cu. mm., with neutrophils 31%, lymphocytes 61%, monocytes 8%, and a normal blood film. Cytomegalovirus antibody titre was 32. During the next three to four months his general condition remained good but he was "chesty" with croupy cough and bronchitis; he developed slightly enlarged glands in the groins, and the tip of the spleen was palpable. Chest *x*-ray examination was negative, and there was no serological evidence of infection with toxoplasma, *M. pneumoniae*, or respiratory viruses. The Paul–Bunnell test was persistently negative. The glands then gradually regressed, and six months after his original admission he was clinically fit; he has remained so during the subsequent 12 months. Nevertheless, throughout the entire observation period of about 18 months he has shown evidence of mild liver damage. The alkaline phosphatase has fluctuated between 17 and 22.5 K.A. units and the S.G.P.T. between 33 and 50 units, and the serum bilirubin on two occasions was 1.1 and 1.2 mg./100 ml. He excreted cytomegalovirus until five months after his first hospital visit, but no isolations could be made subsequently.

The 70 older patients included 43 aged 15–29 years and 27 aged 30–60. All had febrile illnesses with a typical blood

picture, a lymphocytosis with 12–60% abnormal mononuclears in the blood film, and the Paul–Bunnell was persistently negative. Of the 43 younger adults 33 had generalized lymphadenopathy and 18 of these had exudative tonsillitis. However, none of them was excreting cytomegalovirus or showing a rising titre of antibody. On the other hand, 22 of the 27 older patients had no lymphadenopathy or tonsillitis and nine of these developed rising titres of antibody; cytomegalovirus was also isolated from the throat and urine of six of them. Two of the nine positive cases presented with jaundice (Lamb and Stern, 1966; Toghill *et al.*, 1967). None of the five older adults who had generalized or cervical adenopathy with or without exudative tonsillitis had evidence of active cytomegalovirus infection, though one did develop a significantly high titre of toxoplasma complement-fixing antibody.

Discussion

When the epidemiology of cytomegalovirus infection is examined from the point of view of virus excretion a very different picture emerges from that obtained by antibody studies. A previous serological investigation in London showed that primary infection occurred predominantly in older children and young adults (Stern and Elek, 1965). Paradoxically, in the present study virus was isolated only from children of 6 years and under. This agrees with observations that infection in early life causes a chronic disease associated with cytomegalic cell formation in the salivary glands and kidneys and prolonged virus excretion in the throat and urine (Baar, 1955; Seifert and Oehme, 1957; Rowe *et al.*, 1958; Weller and Hanshaw, 1962). On the other hand, primary infection in older age groups seems to be mostly subclinical and of brief duration, occurring without or with only transient virus excretion. However, when adults develop disease they also excrete virus for prolonged periods. This is the case in cytomegalovirus mononucleosis (Lamb and Stern, 1966; Kääriäinen *et al.*, 1966b), and in persons with underlying immunological defects (Jacox *et al.*, 1964) or undergoing immunosuppressive therapy (Duvall *et al.*, 1966; Kanich and Craighead, 1966).

Thus, outside early childhood, isolation of cytomegalovirus has diagnostic significance. By contrast, the high incidence and prolonged duration of virus excretion in children under 5 or 6 years of age makes it difficult to assess its importance in relation to any particular illness with which the child presents. Nevertheless, there is already good evidence that infection in small children causes liver damage, resulting in hepatomegaly, splenomegaly, spider angiomata, and abnormal liver-function tests (Rowe *et al.*, 1958; Hanshaw *et al.*, 1965), and the present survey suggests that respiratory illness also occurs. Table II shows that 7 of the 13 excreters aged 2 months to 4 years (54%) were admitted to hospital with respiratory illnesses, as compared with 30 out of 123 non-excreters (24%). The numbers are small but appear to be significant ($P=0.05$). Four of the seven children had fever and bronchitis or pneumonia with a paroxysmal type of cough, and the symptoms tended to persist for as long as two to six months. Hanshaw (1966b) has also reported persistent "viral pneumonitis" resembling whooping-cough in infants excreting cytomegalovirus. This may therefore be one of the primary clinical manifestations of cytomegalovirus infection in childhood. Whether respiratory symptoms accompany primary infection in older age groups is unknown. It is commonly assumed that these infections are usually subclinical, but this may not be so. A history of episodes of pneumonia or influenza-like illness has been obtained from women who have given birth to infants with cytomegalic inclusion disease (Weller and Hanshaw, 1962; Medearis, 1964), and pneumonia is the commonest clinical manifestation of cytomegalovirus infection complicating immunosuppressive therapy (Wong and Warner, 1962; Hill *et al.*, 1964; Rifkind, 1965; Kanich and Craighead, 1966; Cangir *et al.*, 1967).

Only 3 of the 14 children excreting virus in the present report (Table III) had an enlarged liver or spleen, but out of six examined for liver function four gave abnormal results. Apart from this survey we have collected a further 13 children aged 3 months to 6 years, all excreting virus and on whom liver-function tests were done. Of the overall total of 19 children 12 had abnormal liver-function tests; this compares with only 2 out of 20 unselected controls of the same ages who were neither excreting virus nor possessed antibody (unpublished). While many children infected with cytomegalovirus thus show evidence of liver dysfunction, the importance of the virus as a cause of liver disease in general has yet to be assessed. Hanshaw *et al.* (1965) isolated the virus from 9 out of 23 young children (39%) with unexplained chronic liver disease, as compared with 1% of control children.

We detected virus excretion in only 2 out of 24 such children, but, obviously, further larger series must be examined. Cases 19 and 20 are probably typical examples of the sort of mild undefined ill-health associated with evidence of liver dysfunction caused by cytomegalovirus (Stern and Tucker, 1965). Though Case 20 still showed disturbed liver function after 18 months, the majority of infections in early childhood seem to be benign and to result in complete recovery, despite long-continuing virus excretion. This is so even when infection occurs in the early post-neonatal period. In the present study 9% of infants aged 2–5 months were excreting virus, and one to two years later had shown no evidence of physical or mental retardation. It is therefore necessary to revise currently held views that such early infection is always serious and often fatal (Nelson and Wyatt, 1959; Hanshaw, 1966b). Of course infection in debilitated infants can result in disseminated and fatal disease (Smith and Vellios, 1950; Wyatt *et al.*, 1950; Medearis, 1957).

The isolation of cytomegalovirus from 3% of apparently healthy newborn babies was not entirely unexpected, since 50% or more of young women are without antibodies (Stern and Elek, 1965) and as many as 6% acquire them during pregnancy (Sever *et al.*, 1963). However, intrauterine infection obviously does not always produce the classical neonatal disease. Thus Case 2 was outwardly a healthy baby who showed only some mild disturbance of liver function, and who has made normal physical and mental progress. We previously reported a similar case (Stern and Tucker, 1965). On the other hand, Case 1 became microcephalic and severely retarded mentally, and Case 3 has shown delayed physical and mental development. Therefore "inapparent" congenital infection can also cause the same kind of selective severe brain damage as the classical neonatal disease, and may indeed prove to be an unexpectedly important cause of mental retardation, particularly of the microcephalic type (Stern, 1965; Hanshaw, 1966a; Stern and Elek, unpublished). The classical form of neonatal cytomegalic inclusion disease is also commoner than is generally realized. Previous reports have stressed its rarity in Britain, but these have relied on fatal cases and on histological methods which are much less sensitive than virus isolation (Crome and France, 1959; Symmers, 1960). We have diagnosed 11 cases in the past three and a half years, including the two infants in the series of 50 cases of unexplained neonatal hepatitis. This latter syndrome is common and of diverse origin, and can be caused by rubella, herpes simplex, and cytomegalovirus, as well as by toxoplasmosis, syphilis, bacterial sepsis, biliary atresia, and blood group incompatibility.

Cytomegalovirus mononucleosis has a precise clinical picture—namely, fever of three to six weeks' duration associated with a glandular-fever-like blood picture and abnormal liver-function tests, but without exudative tonsillitis or significant lymphadenopathy. This syndrome may be more common after the age of 30. In the present investigation the majority of younger patients with Paul–Bunnell-negative infectious mononucleosis had either the glandular or anginose type of illness, and none showed evidence of active cytomegalovirus infection. On the

other hand, 22 out of 27 patients over 30 years old had the more typical picture, and nine of them developed rising titres of antibody. In most of the other reported cases of cytomegalovirus mononucleosis the patients have also been over 30 years old (Klemola and Kääriäinen, 1965; Klemola *et al.*, 1967a). When the disease occurs as a complication of open-heart operations it may be as common in younger persons (Reyman, 1966; Riemenschneider and Moss, 1966; Kääriäinen *et al.*, 1966a), but direct intravenous infection may be a potentiating factor here. A glandular-fever-like blood picture is sometimes also seen in children undergoing cytomegalovirus infection (Case 11, and Klemola *et al.*, 1966), but most of them do not show this blood picture.

Summary

In an epidemiological study of unselected hospital admissions and healthy adults in London 10% of children between 2 months and 5 years old were found to be excreting cytomegalovirus in the throat and urine, but only one excreter, aged 6 years, was detected among 575 older children and adults.

In early childhood the infection is invariably chronic with prolonged virus excretion. These children often show evidence of liver damage, from which they usually recover, and many of them also undergo protracted respiratory illnesses with bronchitis and pneumonia which can resemble whooping-cough. In older age groups infection, though common, is probably subclinical in most cases, but a few adults develop cytomegalovirus mononucleosis. This seems to be more common over 30 years of age.

Three out of 118 apparently healthy newborn babies were also found to be excreting cytomegalovirus. One showed evidence of mild liver dysfunction, from which he recovered. The other two were mentally retarded and one of them became microcephalic.

In a separate study of 50 cases of unexplained neonatal hepatitis cytomegalovirus was isolated from two cases, rubella virus from two cases, and herpes simplex virus from one case.

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