of the effects of propranolol (5 mg. intravenously) (Table III) (Areskog and Adolfsson, 1967). Only four of the patients took part in both studies. In the propranolol study 8 of the 33 patients did not get anginal pain in spite of an E.C.G. pattern typical of coronary insufficiency, whereas in this study 3 out of 19 patients had a similar response. Thus propranolol in many cases produced a change in the usually constant time relationship between pain and E.C.G. "threshold" during work (Areskog and Hallén, 1964). This change, which implies a retardation of the appearance time of the pain compared with the appearance time of the S–T depression was seen in a few cases also after I.C.I. 50172. It is still not clear whether there is a real difference between the two drugs in this respect.

Propranolol seems to give a more rapid relief of both subjective and objective signs of coronary insufficiency *after* exercise. This might be due to its lack of intrinsic sympathomimetic activity in comparison with that of I.C.I. 50172. Since I.C.I. 50172 produces an overall improvement of the anginal pain to about the same degree as propranolol, the local anaesthetic action of the latter does not seem to be an important factor in relieving angina, as has been suggested (Levy and Richards, 1965 ; Grandjean, 1967). The improvement in the condition of the patient with coronary insufficiency and bronchial asthma is a remarkable result, and may have been, in the case of asthma, due to the intrinsic sympathomimetic activity of I.C.I. 50172. Macdonald and McNeill (1968) found a decrease in the airway resistance in 2 out of 10 patients, but an average rise of 22·6% after 15 mg. of I.C.I. 50172 intravenously. Because of its cardioselectivity this drug may be given to patients with obstructive lung disease in contradistinction to propranolol. Theoretically, owing to its intrinsic sympathomimetic activity I.C.I. 50172 might be a less dangerous drug than propranolol to give to patients with incipient cardiac insufficiency. We always recommend the combination of digitalization and beta-blockade in these cases.

The favourable effect of I.C.I. 50172 on coronary insufficiency cannot be fully explained by the reduction in heart rate, since the angina appears at a much lower heart rate after I.C.I. 50172. Dwyer *et al.* (1967) found that the effect of propranolol in angina derives mainly from suppression of contractility (left ventricular first derivative) and to a less extent from the negative chronotropic action. With the use of the formula

$$\text{ventricular work} = QR\frac{mv^2}{2}$$

where Q = stroke volume, R = the mean arterial pressure (metres H_2O), m = the mass of ejected blood, and v = velocity, I.C.I. 50172 in the dose we used decreases the work by reducing not the stroke volume (and thereby not the mass of ejected blood) but the velocity and the mean arterial pressure (Sowton *et al.*, 1968), which in turn lowers oxygen consumption. The product of mean systolic pressure times duration of systole times heart rate (tension time index)—which corresponds well to myocardial oxygen consumption—would suggest that the reduction in oxygen consumption is about 15%, by the use of our own data and those of Sowton *et al.* (1968). Since total work and especially work at the appearance of S–T depression are relatively much more increased, other factors must be concerned. The reduction of the myocardial contractility prolongs systole (Apthorp *et al.*, 1964) and reduces extravascular resistance to coronary flow, which may also improve the coronary perfusion during work (Gregg, 1964 ; Moir and DeBra, 1967). In the case of propranolol experimental data also support the possibility of improved oxygen utilization at the cellular level with reduced production of lactate (Å. Hjalmarson, personal communication ; Wolfson *et al.*, 1966). Whether these findings apply to I.C.I. 50172 is still unknown.

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Congenital Cytomegalic Inclusion Disease following Intrauterine Transfusion

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Summary: Congenital cytomegalic inclusion disease occurring in two infants who received intrauterine transfusions for severe haemolytic disease due to rhesus isoimmunization may have been transmitted in the donor blood.

Introduction

Defects of the central nervous system, including microcephaly, spasticity, and mental retardation, are the most serious manifestations of congenital cytomegalic inclusion disease, though they may not appear until the second year of life (Weller and Hanshaw, 1962; Medearis, 1964; Hanshaw, 1966). Clinical features commonly appearing in the neonatal period are hepatomegaly, splenomegaly, jaundice, and haemolytic disease. Though asymptomatic infection with cytomegalo-

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virus occurs in children and adults, it is generally associated with symptoms in neonates. The virus is transmitted from the mother during pregnancy. Furthermore, the mothers of such infants may sometimes have had a mild respiratory disease during pregnancy (Medearis, 1964 ; Hanshaw, 1966).

The infection, which may cause an infectious mononucleosis-like syndrome, has recently been described in adults following transfusions of fresh blood. In these cases the virus may have been transmitted via the blood from infected donors (Kääriäinen, Klemola, and Paloheimo, 1966). The two babies reported in this study showed evidence before birth of severe haemolytic disease due to rhesus isoimmunization and were given intrauterine transfusions. After birth unusual features were noted and cytomegalovirus was isolated from both of them. One of the babies may have been infected by donor blood received during intrauterine transfusion.

Case 1

This infant was the first living child of a rhesus-negative mother, whose first pregnancy was complicated by toxaemia and ended in the spontaneous delivery of stillborn twins at 35 weeks' gestation. In that pregnancy she developed a high anti-D titre.

During the second pregnancy two intrauterine transfusions were given because rising anti-D titres and amniotic fluid examination suggested that the foetus was likely to be severely affected. Labour was induced at 35 weeks and a normal delivery of a female infant followed. The condition of the baby at birth was good. The liver was enlarged to 3·5 cm. and the spleen to 1·5 cm. below the costal margins. The birth weight was 6 lb. 8 oz. (2,950 g.) and the head circumference 13 in. (33 cm.). The serum bilirubin rose slowly and no exchange transfusions were required, though the baby remained jaundiced for two months. On the second day of life she was purpuric and pyrexial, with signs of infection on the right side of the chest. A course of ampicillin and cloxacillin was therefore given. The next day the chest was clear and the *x*-ray picture normal. The pyrexia, however, did not settle finally until the baby was 4 weeks old. At 2 months cytomegalic inclusion cells were seen in the urine and cytomegalovirus was subsequently isolated.

The infant's first six months were uneventful, though two transfusions of packed cells were given for anaemia. Serial measurements of head circumference up until the age of 10 weeks lay along the 50th percentile. At 10 weeks, however, the skull *x*-ray film showed no evidence of intracranial calcification, and at 6 months no neurological or mental defect was present.

Bilirubin, serum enzymes, and temperature are recorded in Fig. 1. At 6 months the serum aspartate and alanine aminotransferase levels were 23 and 25 i.u./litre, respectively. On the fourth day the white blood cell count showed a mild neutrophilia (5,000/cu. mm.). At 7 weeks the platelet count was 175,000/cu. mm.

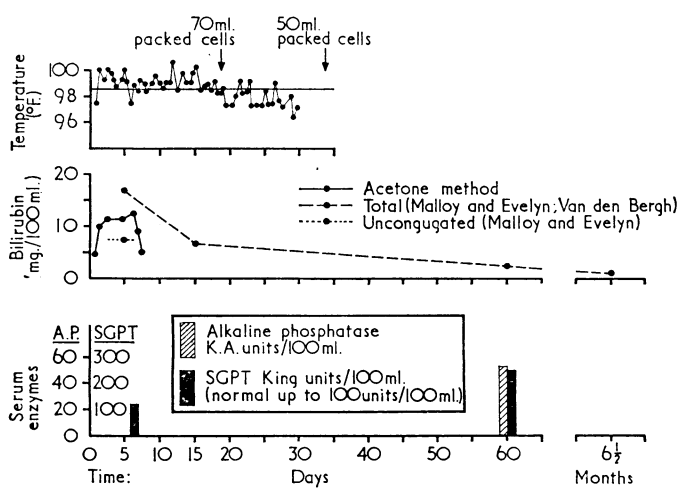

FIG. 1.—Case 1. Main events of the first few weeks, including temperature, bilirubin, and serum enzyme findings.

Case 2

This infant was the third child of a rhesus-negative mother, whose first pregnancy was complicated by a threatened miscarriage at two months' gestation. Because of a raised anti-D titre labour was induced at 39 weeks. The baby was fairly severely affected and required one exchange transfusion. Complement fixation titre to cytomegalovirus performed recently, when the child was 3 years old, was <1/8 and cytomegalovirus has not been isolated from her urine. The second child was born grossly hydropic and died soon after birth.

During the third pregnancy four intrauterine transfusions were given because examination of the amniotic fluid showed that the foetus was likely to be severely affected. The mother gave a history of " cold sores " at 25 weeks and an episode of " flu and bronchitis " a few days before the child was born.

Labour was induced at 35 weeks and a normal delivery of a boy followed. The condition of the baby at birth was good, though the liver and spleen were enlarged to 5 cm. below the costal margins. The birth weight was 4 lb. 12 oz. (2,155 g.). The head circumference at birth, however, was not recorded. The plasma bilirubin (acetone method of Mertz and West, 1956) rose rapidly and four exchange transfusions were needed during the first three days. On the fourth day the bilirubin was estimated by the method of Malloy and Evelyn, and as the jaundice was mainly due to conjugated bilirubin no further exchange transfusions were performed. The baby, however, remained jaundiced for more than two months. At 2 weeks cytomegalic inclusion cells were seen in the urine and cytomegalovirus was subsequently isolated. Complement fixation titres to cytomegalovirus at 14 weeks and 5 months were 1/64 and 1/32, respectively. When last seen, at the age of 9 months, the infant was still excreting cytomegalovirus.

On the fourteenth day of life the baby developed intestinal obstruction, which persisted on and off for four days and was treated conservatively. At 8 weeks, however, intestinal obstruction recurred and a laparotomy was performed. The gut was found to be matted together and a gangrenous loop was resected, the cause being related to the multiple intrauterine transfusions rather than to cytomegalovirus infection.

Since then the baby has made good progress. Serial measurements of head circumference in the first 10 weeks lay between the 50th and 25th percentiles, but since then the rate of increase in circumference has been slower than normal. At 5 months his weight was 11 lb. (4,990 g.). Apart from some residual reflex walking he has continued to develop normally. Skull *x*-ray examination showed no evidence of intracranial calcification.

Bilirubin and serum enzyme findings are recorded in Fig. 2. At 3 weeks there was an eosinophilia of 3,000/cu.mm. and the platelet count was 150,000/cu.mm. Subsequent white cell counts and serum proteins were both normal.

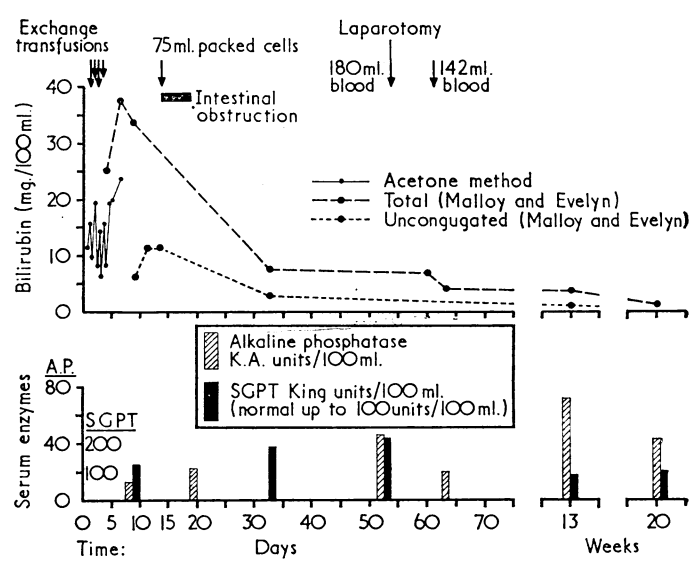

FIG. 2.—Case 2. Main events of the first few weeks, including bilirubin and serum enzyme findings.

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Results of Further Viral Studies

Complement fixation titres to cytomegalovirus were measured on serum from both mothers during and after pregnancy, and from the donors, whose blood was used for intrauterine transfusion. In Case 1 the mother's titre was <1/8 at 22 weeks' gestation and >1/128 two months after delivery. The donors had titres of 1/8 and <1/8, respectively. In Case 2 the mother's titres are shown in Fig. 3, and the donors' titres were as follows: donor I <1/8, II 1/32, III <1/8, IV 1/128.

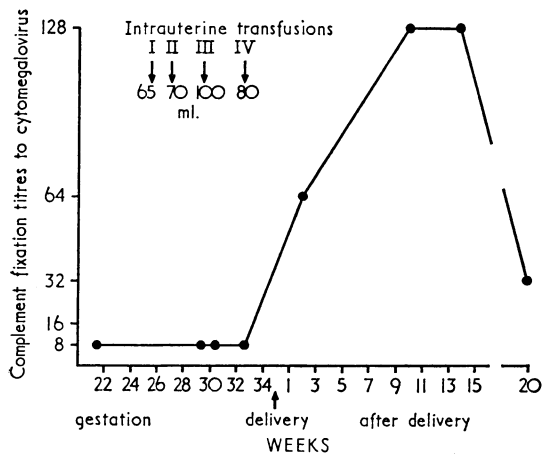

FIG. 3.—Complement fixation titres to cytomegalovirus of the mother of Case 2 during pregnancy and after delivery related to the time of the intrauterine transfusions.

Cytomegalovirus was isolated from the urine of the mother in Case 2 three months after delivery, but had disappeared two months later. Attempts were also made to isolate the virus from the throat, blood, and urine of donor IV, but without success.

Discussion

Neonatal jaundice, hepatomegaly, and splenomegaly are the usual manifestations of the severe degrees of haemolytic disease due to rhesus isoimmunization, and are also the commonest manifestations of cytomegalic inclusion disease in the first weeks of life. The two infants described had severe haemolytic disease of the newborn for which they received intrauterine transfusions. The severe jaundice, hepatomegaly, and splenomegaly were attributed initially to this condition. The unusual features, however, were the severity and persistence of the jaundice; the large amounts of conjugated bilirubin; the abnormal liver function tests, alkaline phosphatase, and serum alanine aminotransferase levels; and the prolonged pyrexia in Case 1. These findings led to further investigations which showed the presence of inclusion bodies in the urine of both infants and, subsequently, of cytomegalovirus. Recent infection with this virus was also demonstrated in both mothers. The infants had probably therefore acquired the infection in utero, and were suffering from congenital cytomegalic inclusion disease as well as from severe haemolytic disease of the newborn.

One donor in Case 1 had a low level of complement-fixing antibodies to cytomegalovirus and the second donor had none. It is unlikely therefore that in this case the infection was related to intrauterine transfusion. In Case 2, however, two of the donors had antibodies, and, since the mother's titre did not begin to rise until after the fourth intrauterine transfusion, only one donor was investigated further. Attempts to isolate the virus from him, however, were unsuccessful. His blood was collected into citric acid, trisodium citrate, and dextrose solution the day before it was used, packed immediately, and stored overnight at 4° C. The mother had had "flu and bronchitis" 12 days after the fourth intrauterine transfusion and the infant, who was born four days later, was thought to have congenital cytomegalic inclusion disease. The virus may therefore have been transmitted in the blood used for the fourth intrauterine transfusion and have been responsible for both the mother's respiratory infection and for the infant's disease.

Addendum

We have recently isolated cytomegalovirus on two occasions from the urine of a third infant, who received five exchange transfusions and one simple transfusion for severe rhesus isoimmunization. The mother's complement fixation titre to cytomegalovirus, which had remained unchanged at 1/16 from two months before delivery to six weeks after delivery, had risen to 1/128 14 weeks later. Furthermore, the infant's cord blood titre to cytomegalovirus was <1/16. Serum from five of the donors has been tested for complement-fixing antibodies. Of these four had positive results—1/32, 1/128, 1/64, and 1/16—which suggests that this infant's infection was acquired and not congenital.

Cytomegalovirus has been sought unsuccessfully in the urine of 80 other neonates. Of these 60 were "rhesus babies" and the other 20 were either rhesus-negative babies of mothers with anti-D antibodies or infants with unexplained jaundice.

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