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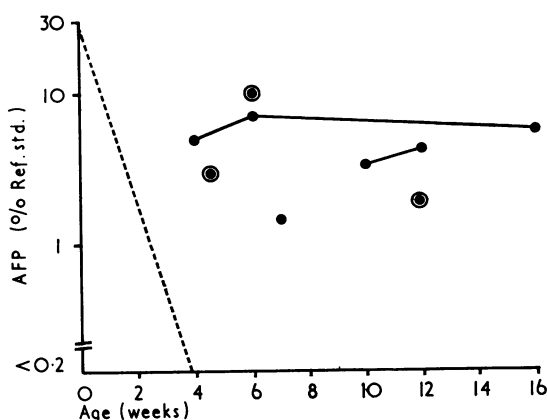


FIG.—Serum levels of  $\alpha$ -fetoprotein in 6 AFP-positive patients with neonatal hepatitis.  $\odot$  patients positive for HAA as well as AFP. The interrupted line shows the normal decay curve of AFP in the blood.

## Hepatitis antigen and $\alpha$ -fetoprotein in neonatal hepatitis

Of various embryonic proteins,  $\alpha$ -fetoprotein (AFP) has evoked considerable interest through its association with primary hepatocellular and embryonal carcinomas (Abelev, 1968). Recently, we reported the presence of AFP in 45% of patients with Indian childhood cirrhosis (Nayak *et al.*, 1972). In primary hepatoma (Vogel *et al.*, 1970), as well as in Indian childhood cirrhosis (Chandra, 1970; Chandra *et al.*, 1972), hepatitis-associated antigen (HAA) was detected in a significantly higher proportion of cases than controls, and it has been postulated that viral hepatitis may predate the development of carcinoma/cirrhosis. In both diseases there is a significant positive correlation between detection of HAA and AFP. We have looked for the presence of AFP and HAA in 24 patients with neonatal hepatitis.

### Observations

The diagnosis of neonatal hepatitis was made in 24 infants on the basis of jaundice, hepatomegaly, three- to sixfold rise in serum transaminases, and constitutional symptoms. In 5 patients, a needle biopsy of the liver (*ante mortem* in 4, *post mortem* in 1) showed varying degrees of parenchymal cell damage, cholestasis, and inflammatory cell reaction. In 2 specimens giant cell transformation was also seen. There were 15 boys and 9 girls. The age at the time of first examination ranged from 4 to 16 weeks.

HAA was detected by counterimmunoelectrophoresis (Gocke and Howe, 1970) using antiserum from a multi-transfused patient with thalassaemia who had anti-HAA antibody giving a reaction of identity with reference antisera (kindly supplied by Drs. A. M. Prince, B. S. Blumberg, and Girish Vyas). HAA was found in samples from 3 (12.5%) out of 24 patients, sampled at

the age of 4½, 6, and 12 weeks. Two (8%) out of 24 mothers showed hepatitis antigen in their sera; both had HAA-positive infants with hepatitis. One of the mothers had had hepatitis during the 7th month of pregnancy, and the other was an asymptomatic carrier.

AFP was detected by counterimmunoelectrophoresis using antiserum raised in rabbit which gave a reaction of identity with reference antiserum (kindly supplied by Dr. M. J. Simon). 6 (25%) of 24 patients were positive. Their ages were 4, 4½, 6, 7, 10, and 12 weeks. Samples positive for AFP were quantitated by the single radial immunodiffusion method as modified by Alpert, Monroe, and Schur (1970), and the results were expressed as percentages of reference serum pool obtained from 3 abortuses 20 to 24 weeks old (Fig.).

All the 24 healthy infants matched for age and sex, and their mothers, were negative for HAA as well as for AFP. The frequency occurrence of HAA in the healthy population in New Delhi is 0.7% (Chandra *et al.*, 1972).

All 3 HAA-positive infants with hepatitis were from the group of 6 showing AFP in their serum. It was not possible to distinguish AFP-positive cases or HAA-positive cases from the others by any clinical or biochemical feature.

### Discussion

The aetiology of neonatal hepatitis is debatable. A possibility is that it is the result of an infection, most probably viral, occurring in a susceptible fetus. Aterman (1963) suggested a causal relation between viral hepatitis in the mother and neonatal hepatitis. There are very few studies on the detection of HAA in infants with liver disease. HAA was found in a significant number of patients with Indian childhood cirrhosis and their mothers (Chandra, 1970; Chandra *et al.*, 1972). Wright

*et al.* (1970) reported HAA-positive acute viral hepatitis going on to cirrhosis in an infant whose mother had had antigen-positive hepatitis in the last few days of pregnancy. Krech and Sonnabend (1970) found HAA in 6% of 169 babies with liver disease. Cossart, Hargreaves, and March (1972) found possible transmission of HAA from mother to infant in 2 out of 5 instances where antigen positive hepatitis had occurred during pregnancy. In all the reported cases, cord blood did not contain HAA but the antigen was detected a few days to a few weeks after birth. Though transplacental transmission is not excluded, acquisition of the virus through the alimentary route by swallowing contaminated maternal serum or amniotic fluid, or through subsequent postnatal contact with the mother, is clearly possible.

AFP is present in the serum of the human fetus and the newborn with peak synthetic activity around 16 to 20 weeks of gestation. It has a half-life of 3 to 4 days. Its biological function is not known. After birth, the fall in AFP concentration is exponential, and by Ouchterlony's double diffusion method, AFP is not detectable beyond 3 weeks of age in healthy subjects. Its presence characterizes an early stage of liver cell differentiation and it disappears at a time when ultrastructural, chemical, and enzymatic changes in the fetal hepatocyte, presumably indicating maturity, are taking place (Dallner, Siekevitz, and Palade, 1966). The presence of AFP beyond the immediate neonatal period arouses strong suspicion of embryonal carcinoma, primary hepatoma, and Indian childhood cirrhosis, and is believed to be the result of disrupted repressor mechanisms. In hepatic cell carcinoma, there is some correlation between AFP and HAA detection. Our data show that AFP may persist or reappear in detectable amounts in a significant number of patients with neonatal hepatitis. Masopust *et al.* (1968) reported the presence of AFP in a few infants with 'hepatopathies' but no details were given and quantitation was not attempted. In normal infants beyond 2 weeks of age, Kang *et al.* (1972) could not detect AFP. The protein was, however, found in 4 cases of neonatal hepatitis and 8 cases of congenital biliary atresia, and it was suggested that quantitative estimation of AFP might help differentiate the two conditions.

The association of significant detection rate of AFP and HAA in neonatal hepatitis, Indian childhood cirrhosis, and primary hepatoma is intriguing. In neonatal hepatitis, such an association might indicate constitutional immaturity of the fetal hepatocyte making it more vulnerable to damage by

noxious agents including viruses (HAA and others). Alternatively, hepatitis as well as continued or renewed synthesis of AFP may both be the result of intrauterine viral infection. A long-term follow-up of such infants is indicated to find out if there is a causal link between neonatal hepatitis and cirrhosis/hepatoma.

### Summary

Twenty-four infants with neonatal hepatitis were tested for the presence of hepatitis antigen and  $\alpha$ -fetoprotein by counterimmunoelectrophoresis. 3 infants showed the presence of HAA and 6 AFP. All 3 HAA-positive infants were positive for AFP as well. 2 out of 24 mothers showed the presence of HAA; both had HAA-positive infants with hepatitis.

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