two hospitals from which our series was assembled. These derive from a random sample of 315 unaffected births over the 25-year period. As shown in the table, this sample shows no evidence of a downward shift in the maternal-age distribution of births in the hospital. Indeed, the slight changes in these means parallel quite closely the changes in the observed values for the affected individuals.

These data effectively rule out as an explanation of this epidemic any phenomenon that would be expected to follow a cohort pattern. The lack of a cohort pattern is consistent with explanations in terms of changes in factors operative in early pregnancy—such as would seem more consonant with existing knowledge of the causes of congenital malformations—although the specific change associated with this particular episode is still unknown.

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HOSPITAL REFERRALS

SIR,—I was interested in Dr. John Fry's view on the changing pattern of hospital referrals based on his practice records in Beckenham (July 17, p. 148). Although he does not refer to the increasing use of health centres, is it not possible that a balance will eventually accrue between those actually referred to hospital outpatients and those dealt with either by the general practitioner in the health centre or by hospital consultants actually having sessional facilities at such centres ?

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AUSTRALIA ANTIGEN, CORONAVIRUS, AND REVERSE TRANSCRIPTASE IN VIRAL HEPATITIS

SIR,—The discovery of a reverse transcriptase in Australia antigen by Hirschman and his colleagues [1] strongly suggests that the antigen is associated with an R.N.A. virus [2]; and this idea is corroborated by the finding of small amounts of R.N.A. in the same antigen.[3]

All this is in keeping with our previous studies of the acute-hepatitis liver with the electron microscope,[4,5] revealing the simultaneous presence of Australia antigen and coronaviruses, and showing how the particles of Australia antigen, present in the cytoplasm, fell together to form coronavirus membranes. From this we deduced [5] that the Australia antigen might contain an R.N.A.-polymerase capable of forming the adult virus (coronavirus). Also Zuckerman et al.,[6] Holmes et al.,[7] and Wright et al.[8] found both the Australia antigen and coronaviruses in the blood of patients with acute or chronic hepatitis.

We have tried to cultivate bits of hepatitis liver containing both the Australia antigen and the coronavirus on KB cells,[5] and we have seen that the KB cells developed clusters of particles in their cytoplasm, suggesting the early stages of Australia-antigen formation; on the other hand, we have not seen any evidence of coronavirus in these cells. Perhaps the coronavirus, or adult form of the virus, occurs only exceptionally or is very short-lived.

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APLASTIC ANÆMIA AND INFECTIOUS HEPATITIS

SIR,—I would like to report another case of aplastic anæmia associated with infectious hepatitis. A woman aged 21 was attending Queen Victoria Memorial Hospital and was at 20 weeks gestation in her first pregnancy in June, 1966, when she had mild infectious hepatitis. At that time her hæmoglobin was 9·9 g. per 100 ml. and a blood-film showed well hæmoglobinised red blood-cells with some variation in size and some polychromasia. Leucocytes and platelets appeared normal. For 2 weeks she was admitted to Fairfield Hospital for Communicable Diseases. Recovery was apparently complete, and a healthy live female baby was delivered normally at 39 weeks gestation. Membranes had ruptured 1 week before delivery, and because of this she had received penicillin 1 megaunit every 6 hours and sulphadimidine 1 g. every 6 hours for 5 days. During the pregnancy she received ferrous sulphate and for 2 weeks in the first trimester had taken meclozine 25 mg. twice daily for morning sickness.

In November, 1967, she was readmitted to Fairfield Hospital with a 2-week history of malaise, anorexia, fever, pale stools, and increasing jaundice. Her liver was enlarged 3 fingersbreadth and tender. Serum bilirubin was 14·4 mg. per 100 ml.; glutamic-oxaloacetic transaminase (G.O.T.) 1075 Sigma-Frankel (S.F.) units per ml., and alkaline phosphatase 18 King-Armstrong (K.A.) units per 100 ml. Prothrombin activity was 66% of normal. Hæmoglobin was 11 g. per 100 ml., red blood-cells were mildly hypochromic with some anistocytosis and some target cells. Leucocyte-count was 4500 per c.mm. She was treated with prednisolone 60 mg. daily reducing to 15 mg. daily over 2 weeks. Discharged at this stage, she felt well, her liver was no longer tender or palpable; serum bilirubin was 2·2 mg. per 100 ml. and G.O.T. 60 S.F. units per ml.

2 days later she had an exceptionally heavy menstrual period, but otherwise remained well for the next 3 weeks. Then she noticed bruising on her legs which gradually became generalised. Five days later she developed painful blue nodules on her hands, lips, and mouth, had a severe epistaxis, and was again admitted to Queen Victoria Memorial Hospital. At this time she was pale, febrile, and had numerous purpuric areas in her skin and a number of mixed infective-purpuric lesions on hands, lips, and mouth. Liver and spleen were impalpable. Initial blood findings were: hæmoglobin 8·6 g. per 100 ml.; white blood-cells 1000 per c.mm. (neutrophils 9%, eosinophils 1%, lymphocytes 90%); platelets 46,000 per c.mm.; reticulocytes less than 1%; blood-film showed marked anisocytosis. The bone-marrow was markedly hypocellular and consistent with marrow aplasia. Serum bilirubin 0·7 mg. per 100 ml., G.O.T. 67 S.F. units per ml., alkaline phosphatase 9 K.A. units per 100 ml. Culture of the lesions on her hands and mouth grew *Staphylococcus aureus*.

Over the next 2 months she was treated with fresh blood and platelet transfusions, corticosteroids, antibiotics, and oxymetholone. In spite of this she eventually died of a gram-negative septicæmia and associated hæmorrhagic state. At necropsy the liver was enlarged (2948 g.) with a brownish-grey, slightly granular cut surface. Histological examination showed patchy liver-cell necrosis with replacement by fibrous tissue and increased connective tissue and cellular infiltration of portal tracts, and was consistent