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Asymptomatic liver disease in haemophiliacs

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SYNOPSIS The incidence of jaundice and of abnormal liver function tests has been assessed in 91 multitransfused patients with severe haemophilia A and B. Tests of hepatocyte function were within the normal range in the majority of patients. On the contrary, tests of biliary cell function, liver cell damage, and bromsulphthalein retention gave high rates of abnormal values, which tended to increase with age. Hepatitis B surface antigen was present in 8% and the corresponding antibody in 66% of the cases; 18% had a history of jaundice. All patients were asymptomatic and only a minority showed clinical signs of liver involvement. These data suggest that in haemophiliacs repeated and prolonged contact with the agent(s) responsible for post-transfusion hepatitis may cause chronic liver damage not associated with overt illness.

Haemophiliacs are the group of multitransfused patients exposed most frequently and for the longest period of time to the agent(s) implicated in post-transfusion hepatitis.

The rate of exposure has probably increased since the introduction in the replacement therapy of the highly purified freeze-dried concentrates of factor VIII and factor IX which carry a higher risk of contamination, having been manufactured by pools of plasma from a large number of donors.

Tests for the presence of hepatitis B surface antigen (HB_sAg) in plasma are now carried out routinely by blood bank officers or commercial manufacturers. However, the available methods for universal donor screening are unlikely to eliminate the risk of post-transfusion hepatitis because it has been clearly shown that exclusion of the HB_sAg positive samples reduces it by less than 25% (World Health Organization, 1970). The incidence of clinical illness associated with jaundice is surprisingly low in haemophiliacs (Kasper and Kipnis, 1972; Biggs, 1974; Lewis, Maxwell, and Brandon, 1974). These data, however, do not exclude the occurrence of anicteric hepatitis, which is particularly frequent in children, as well as the possibility that repeated and prolonged contact with the infective agent(s) may cause chronic

liver damage not associated with overt illness. We therefore decided to assess the prevalence of abnormal liver function tests in these patients and to correlate the findings with the presumptive number of transfusions.

Patients and Methods

Ninety-one patients (75 with haemophilia A and 16 with haemophilia B) regularly examined at the Haemophilia Centre were selected solely on the basis of their availability to take part in the study once informed consent had been obtained. At the moment of blood sampling, they had not been transfused for at least two weeks. All were severely affected (factor VIII or IX: less than 0.01 u/ml) and had been repeatedly exposed in the past to replacement therapy with cryoprecipitate, commercial freeze-dried concentrates (Kryobulin and Bebulin, Immuno, Vienna; Hemophil, Hyland, Brussels) and, in the older patients, with fresh-frozen plasma. Since a precise record of the total number of transfusions in the individual recipient was usually not available, age was thought to be a rough but reliable parameter to investigate any relationship between degree of transfusion exposure and abnormality of liver function tests. Three categories were thus arbitrarily established before starting the study—0-14, 15-30, and over 30 years. During physical examination of the patients at the Haemophilia Centre, they and

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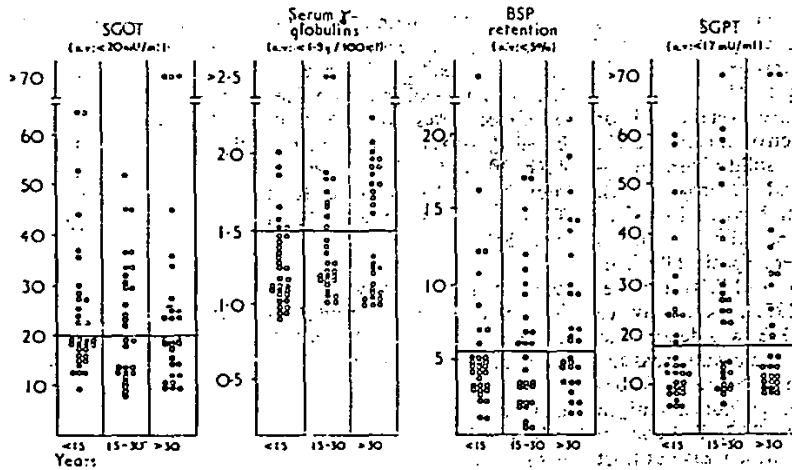


Fig 2 SGPT, SGOT, BSP retention, and γ -globulins in three age groups. The upper limit of normal range is shown by the continuous horizontal line; closed circles—patients with a history of jaundice.

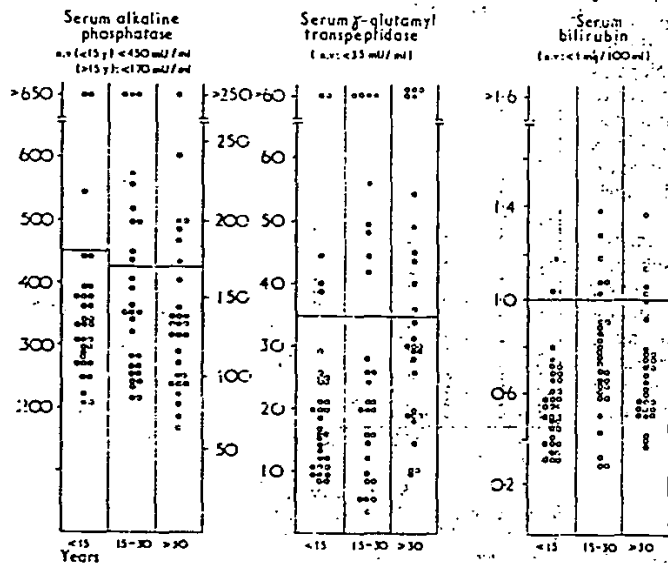


Fig 3 Tests of biliary cell function in three age groups. The upper limit of normal range is shown by the continuous horizontal line; closed circles—patients with a history of jaundice.

Age (yr)	No.	SGPT	SGOT	BSP Retention	Gamma Globulins	Serum Bilirubin	AP	γ -GT	Normotest	Serum Albumin	ChE	Serum Proteins
Total	91	45.0	45.0	40.6	34.0	12.8	23.1	27.2	0	13.1	8.7	4.4
<15	33	39.4	42.4	27.2	21.5	3.7	12.3	15.1	0	8.8	3.5	0
15-30	29	55.1	51.6	44.5	34.4	20.6	34.4	31.3	0	17.2	17.2	10.0
>30	29	41.3	41.3	51.7	48.2	17.2	24.1	37.8	0	16.6	13.7	34.0

Table III Per cent incidence of abnormal liver function tests in 91 patients with severe haemophilia

Differences between age groups have been analysed by the χ^2 test with Yates' correction. No value was significant at the 5% level

other investigators (Kasper and Kipnis, 1972; Biggs, 1974; Lewis *et al.*, 1974), a relatively low incidence of acute hepatitis, which contrasts with the observation of frequent abnormalities of liver function tests. Although anicteric hepatitis may account for a proportion of the cases without a history of jaundice, the frequent and repeated exposure of haemophiliacs to the agent involved in post-transfusion hepatitis is likely to be the most important cause of the observed abnormalities. This assumption is supported by the higher incidence of abnormal tests observed in the older patients, who have presumably been exposed to a greater number of plasma units.

The possibility that analgesic drugs may also have played a role cannot be entirely ruled out in those who have in the past made a large use of potentially hepatotoxic drugs for the relief of pain associated with bleeding episodes. However, since the introduction of early replacement therapy in the control of pain, these drugs have been practically abandoned and hence cannot be responsible for the pathological values observed in children.

The clinical and prognostic significance of the observed abnormalities is presently unknown, and the lack of liver biopsies renders the task of clarifying them rather difficult. The great majority of the patients were completely asymptomatic and free of physical signs of liver involvement. It is possible that constant exposure to the infective agent(s) induces a general immunological tolerance conditioning an attenuated pattern of chronic hepatitis (London, DiFiglia, Sutaick, and Blumberg, 1969; Grady, 1974). It also seems reasonable to suggest that antibody to hepatitis B surface antigen occurring in haemophiliacs may offer protection (Hollinger, Werch, and Melnick, 1974).

However, the evidence accumulated with the investigation of asymptomatic carriers of HB_sAg suggests that these humoral abnormalities are not entirely benign, since they may be associated with structural changes of the liver similar to those occurring in patients with chronic hepatitis (Feinman, Berris, Sinclair, Wrobel, Alter, and Holland, 1973; Simon and Patel, 1974; Woolf, Boyes, Jones, Whittaker, Tapp, MacSween, Renton, Stratton, and Dymock, 1974). In haemophiliacs, an answer to these problems can be given only by a long-term prospective evaluation of any possible relationship between the observed abnormalities and the development of overt hepatic dysfunction. We recommend, therefore, that complete liver function tests should be carried out at regular intervals for early detection of any abnormal evolution, the latter requiring the establishment of a therapeutic pro-

gramme which appears unjustified in the great majority of these patients at the present stage of our knowledge.

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