

personnel strive to provide a service which benefits patients. The frequency of unnecessary requests is poor recognition of their efforts and wastes money.

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#### NON-A, NON-B HEPATITIS AFTER INTRAVENOUS GAMMAGLOBULIN

SIR,—In 1984 we reported on twelve hypogammaglobulinaemic patients with non-A, non-B hepatitis (NANBH) after treatment with a new intravenous gammaglobulin preparation.<sup>1</sup> Although most of the patients had no symptoms of liver disease one year after the onset, we wondered if they might ultimately acquire a disease more aggressive than factor VIII transmitted hepatitis in immunocompetent haemophilic patients.<sup>2</sup>

Serum alanine aminotransferase (ALT) levels were recently measured at least twice in the surviving patients. Five still have very high ALT levels (mean 270, range 76-711 IU/l). One of these feels lethargic and ill, has a large tender liver, and has early changes of cirrhosis on liver biopsy, and another has a progressive demyelinating disease of the spinal cord and cannot walk. Four patients, two with ALT activities of 40-50 IU/l and two with activities of <40 IU/l, are symptomless, apart from their tendency to bronchitis. About half the patients in the study have continued on a different intravenous gammaglobulin preparation (usually 'Sandoglobulin') for the past two years, but there is no evidence that this has influenced the progression of the liver disease.

One patient died from overwhelming infection due to bone-marrow aplasia within a year of hepatitis developing. At the time he had grossly abnormal liver function tests and there were signs of early cirrhosis at necropsy. Two other patients have deteriorated clinically; one is on peritoneal dialysis for chronic renal failure due to rapid progression of previously mild renal disease. The other acquired a pancreatic abscess with ascending cholangitis one year ago, but now has cirrhosis with liver failure; this is unlikely to be due to the cholangitis alone.

In summary, at least half the patients have evidence of progressive liver disease, with cirrhotic changes in three. Bone-marrow aplasia is a very rare complication of primary hypogammaglobulinaemia, and we have never seen demyelination of the spinal cord in over two hundred patients with this condition.<sup>3</sup> One must ask whether these complications resulted from transmission of other viruses in the gammaglobulin. Alternatively superinfection with the NANB may have precipitated increased replication of another in-situ virus that has spread to the central nervous system and bone marrow.

NANBH is clearly a serious complication in patients with hypogammaglobulinaemia, and every effort should be made to prevent further outbreaks. Since there is still no specific marker for the infection, individual plasma donations, which are pooled before gammaglobulin is extracted, should be screened and discarded if the ALT level is raised.

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SIR,—Cohn ethanol fractionation has been generally considered to provide a safe immunoglobulin devoid of infectivity for hepatitis. However, occasional outbreaks of hepatitis B have occurred, and have been too frequent to be dismissed as due to unsatisfactory manufacturing. It was only after the World Health Organisation in 1977 recommended that every unit be screened for HBsAg before pooling that such outbreaks ceased. Even so the presence of HBsAg in commercial gammaglobulin cannot be equated with infectivity.

We have shown<sup>1</sup> that during Cohn ethanol fractionation of plasma containing hepatitis B virus the bulk of non-infectious 22 nm HB particles end up in fraction IV and V while 42 nm infectious HB virions follow the pathway to fraction III. The finding of HBsAg in fraction II by a very sensitive radioimmunoassay suggests the presence of some potentially infectious particles, although the possibility of false-positive results leaves this issue unresolved.<sup>2</sup> One possibility is that immune complexes containing virions may result in infection after gammaglobulin.<sup>3,4</sup> Either way, Cohn ethanol processing, by itself, simply reduces infectivity but does not suppress it. Anti-HBs plays a crucial part and needs to be present in sufficient excess to neutralise the HB virions which may still be present.

As with hepatitis B, the risk of transmission of NANBH by immunoglobulins was at first overlooked in the belief that Cohn ethanol fractionation inactivated NANBH agents. An outbreak of NANBH after administration of Rho(D) immunoglobulins was reported in 1981,<sup>5</sup> but it is only with the use of high-dose IVIG that we have seen epidemiological evidence that challenges the view that Cohn fractionation inactivates NANBH viruses regardless of the infectivity titre present in the starting pool. NANB infectivity titres rarely exceed 10<sup>3</sup> infectious doses/ml. Exceptionally, units may have 10<sup>6</sup>/ml and these could account for infectious lots. Since doses of IVIG given intravenously are 5-20 times higher than those given intramuscularly, the infectivity level may be reached more easily. In extraordinary circumstances, as in the Rho(D) example, intramuscular gammaglobulins may even be infectious.

If the NANB agent(s) is a retrovirus<sup>6</sup> rather than being related to HBV,<sup>7</sup> it will probably, like LAV/HTLV-III, be resistant to heat and alcohol, so that more hepatitis cases after IVIG will be reported. Experience will show whether certain industrial Cohn fractionation procedures provide additional safety.

The issues discussed here should provide a new impetus for prospective follow-up studies of IVIG recipients, better selection of donors, additional inactivation steps, and the development of specific tests for NANBH. For the moment, transaminase screening of all donors (together with screening for anti-HBc and anti-HTLV-III) may be the most immediately effective measures to exclude contaminated units.

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SIR,—A year ago<sup>1</sup> we reported that, after infusion with a new intravenous immunoglobulin (IVIG) preparation, seven out of sixteen patients with primary immunodeficiency diseases had raised aminotransferase levels, compatible with non-A, non-B hepatitis (NANBH). Because this report, and others, has generated continued discussion, we wish to provide follow-up information.

Of the sixteen patients exposed in 1982-83 to the suspect lots of IVIG, two had symptoms of liver disease. One had had raised transaminase levels for at least 8 years and was found, on serial liver biopsy between 1981 and 1984, to have lymphocytic infiltrates which progressed to micronodular cirrhosis. The other was symptomless until 1984, when jaundice and ascites developed. He had a history of nodular lymphoid hyperplasia of the small bowel,

sarcoidosis, and moderate hepatomegaly: aminotransferase levels had been normal or slightly raised between 1975 and 1978. In 1984 this patient died of coronary artery disease and necropsy revealed severe postnecrotic cirrhosis and chronic active hepatitis.<sup>1</sup> The other five patients with raised aminotransferase levels after exposure to the suspect immunoglobulin are still symptomless but continue to have fluctuating abnormal alanine aminotransferase (ALT) values (44–382, 69–660, 150–348, 42–67, and 43–421 U/l during the past year) while receiving monthly infusions of another intravenous immunoglobulin preparation.

Of the nine exposed patients who were unaffected at first, two have shown a slow, steady increase in ALT (35–66 and 53–126 U/l) but all nine have no symptoms.

The aminotransferase pattern is consistent with NANBH, but it is difficult to make this diagnosis in an immunodeficient patient given exogenous antibodies. We have recently tested frozen samples from six patients with raised aminotransferases for IgM antibodies to hepatitis B, cytomegalovirus, and Epstein-Barr virus. None were found; however, the patients' serum IgM levels were generally low and their ability to make IgM antibody is defective, making it difficult to interpret these serological tests. Liver biopsy in symptomless patients is not justified.

The two suspect lots of IVIG were produced from a single batch of fraction II paste in a pilot plant rather than a production facility. Lots produced subsequently by the same manufacturing procedure in the more controlled environment of a production facility have been given to at least six hundred patients worldwide, including twenty-three with primary immunodeficiency diseases without any reports of increased aminotransferase levels.

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#### LIVER DISEASE IN HAEMOPHILIA

SIR,—Progressive liver disease in patients with haemophilia<sup>1–3</sup> is assumed to result from replacement therapy with coagulation factor concentrates. Like Hay et al,<sup>1</sup> we think that progressive liver disease is an understated problem. Hay et al found by biopsy, progressive liver disease in 38% of patients with haemophilia (chronic active hepatitis 26%, cirrhosis 12%). These figures are close to ours. Between 1972 and 1985 we did 52 biopsies on 45 patients and found signs of subsided hepatitis in 24%, chronic persistent hepatitis in 27%, and progressive liver disease in 29% (16% chronic active hepatitis, 13% cirrhosis). The multicentre study by Aledort et al,<sup>4</sup> to which we contributed biopsy material, came to a similar conclusion about the frequency of cirrhosis.

Age may play a part<sup>2</sup> but in adults the development of liver disease seems to depend more on the state of the individual patient than on age. We found no correlation between age and liver status, the median ages being 31 for subsided hepatitis, 25 for chronic persistent hepatitis, 25 for chronic active hepatitis, and 33 for cirrhosis. 42 of our biopsies were done blind and the frequency of

cirrhosis might have been even higher if biopsy material had been obtained from affected parts of the liver.<sup>5,6</sup> Unlike Hay et al, who used persistently raised transaminase levels as a criterion for biopsies, we studied all patients who needed surgery (in most cases orthopaedic) and who consented to biopsy, which explains why we found cirrhosis less often than Hay et al did. We found that transaminase levels rose with the severity of histological findings (see table). However, in the individual case, transaminase levels provided only a poor clue, and we agree with Hay et al that there is no relation between degree of abnormality in aminotransferase levels and the severity of the underlying liver disease.

150 patients receive regular treatment in our centre and extrapolating from the 13% frequency of liver cirrhosis found by biopsy in 45 patients we would expect there to be 19 cases of liver cirrhosis among these 150 haemophiliacs. 11 have been diagnosed (9 with clear clinical symptoms such as oesophageal varices, bleeding from oesophageal varices, or ascites and histologically so there are probably other cases of cirrhosis without specific clinical symptoms among our patients with haemophilia. When liver cirrhosis was clinically diagnosed in our patients the median age was 43. Epple et al<sup>7</sup> found that in non-haemophiliacs in the region of Germany that includes Heidelberg the median age of patients at the time of diagnosis of cirrhosis was 56. 5 of our 11 haemophiliacs with liver cirrhosis have died from hepatic failure (1 with liver cancer at necropsy) and G. Landbeck tells us that in 97 haemophiliacs who died between January, 1978, and October 1985, in West Germany liver disease was the direct cause of death.<sup>7</sup>

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#### TREADMILL TESTS FOR ANXIOUS OR DEPRESSED PATIENTS

SIR,—It is as important to identify cardiovascular disease in anxious and depressed patients as it is in other groups—indeed anxious patients may be especially at risk.<sup>1</sup> Dr Channer and colleagues (Oct 12, p 820) argue that diagnostic exercise testing is "superfluous in anxious and depressed patients with atypical chest pain". Their data do not support such a strong conclusion.

Although their discriminant analysis found that anxious and depressed patients with atypical chest pain had a high probability of a negative treadmill test, this finding was based on only 4 patients—the 4 (out of 87) who had anxiety/depression and atypical chest pain. A positive test in any of these 4 patients would have rendered the discriminant analysis insignificant, yet the exercise tests were done in such a way that the depressed patients walked for a significantly shorter time and were thus less likely to have an ischaemic endpoint response. The results would have been meaningful only if the anxious and depressed patients had reached

CORRELATION BETWEEN HISTOLOGICAL DIAGNOSES AND LIVER FUNCTION TESTS

No of patients	No of tests per patient	Histological diagnosis*	GOT (U/L)	GPT (U/L)	GGT (U/L)	Bilirubin (mg/dl)
9	10	SH	24 (8–38)	45 (9–97)	27 (7–78)	0.6 (0.3–0.9)
10	12	CPH	28 (17–54)	75 (34–229)	49 (15–92)	0.9 (0.4–2.3)
9	12	CAH	49 (15–102)	94 (26–252)	75 (17–246)	0.7 (0.3–1.2)

Mean values and ranges of liver function tests. Observation period two years.

\*SH=subsided hepatitis; CPH=chronic persistent hepatitis; CAH=chronic active hepatitis.