HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY
REPORT FOR YEAR 1980-81

This has been the third and final year of the retrospective hepatitis survey financed by the D.H.S.S. This report will deal with some preliminary results of the 3 year survey, and propose further subjects for further study by the Hepatitis Working Party (W.P.)

HEPATITIS SURVEILLANCE

Table 1 shows the preliminary results of hepatitis reports where there was enough information to categorise these incidents as being related to factor VIII or IX therapy. Cases not considered to be associated with replacement therapy have been excluded. A total of 283 episodes of hepatitis were reported by the Haemophilia Centre Directors, including 253 patients; 26 patients had 2 attacks of hepatitis and 4 patients 3 attacks. Of the total of 283, 197 were non-B hepatitis and therefore probably non-A, non-B, and 86 incidents were hepatitis B. Table 1 classifies each incident according to the brand of product implicated in each incident. The differing proportions of incidents related to each brand does not reflect the relative incidence of hepatitis due to each product. Hemofil and Kryobulin were used in the U.K. 2 to 3 years before the other commercial products, and the relative amounts of other products have varied since due to market forces. Further evidence concerning the relationship of different types of hepatitis to different brands of concentrate is given later in this report.

From the patient's point of view most episodes of acute hepatitis were mild. Hepatitis B still occurs related to all types of product, but the incidence has continued to decline. This must be attributed to the improved methods of donor screening for HB_sAg and quality control of the products.

COMPLICATIONS

The question of the significance of chronic hepatitis observed by several groups of workers in liver biopsies of patients with chronically elevated transaminases is still unanswered. Current investigations are attempting to relate the results in different groups of patients to their transfusion history, and there is strong evidence that different types of non-A, non-B hepatitis are related to different products (see later). Most patients in this group are still entirely symptomless. The natural history of there disease in non-haemophiliacs is still not known, though there is some evidence to suggest that some patients with liver biopsy appearances of chronic active hepatitis have a better prognosis than patients with similar histology on liver biopsy whose liver disease is considered to be of non-viral origin. There have been no further deaths directly or indirectly attributed to liver disease in the past year.

FACTORS AFFECTING THE INCIDENCE OF HEPATITIS

a) Incidence of hepatitis due to commercial versus NHS associated hepatitis

Table (2) compares the figures for B and non-B hepatitis in patients receiving only one product in any year for the years 1977-9 and was presented in last years report. It shows that there is a 4-20 times higher incidence of overt non-A, non-B hepatitis associated with U.S. Commercial concentrate compared with NHS. There is no demonstrable effect with hepatitis B probably due to the effect of screening plasma donations for HB_sAg. We have, as yet, no data for symptomless hepatitis, but a prospective study of patients treated with factor VIII or IX is planned at several Centres.

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b) History of transfusion with concentrate

Table 3 analyses 137 cases of non-A, non-B hepatitis by transfusion history. The chief finding is that 70-80% of cases of non-A, non-B hepatitis were associated with the first dose of concentrate that the patient received. Four out of 91(4.4%) cases occurred where US Commercial concentrate was the implicated brand, in which the patient gave a history of 1-3 years treatment with these products. In contrast. 6 out of 46 (13.7%) cases occurred associated with NHS concentrate or Kryobulin (both intermediate factor VIII concentrate) occurred where the patients had previously been treated with NHS factor VIII or Kryobulin.

Table 4 gives an example of the current pattern of non-A, non-B hepatitis. Most of the patients treated with any batch of concentrate will be immune to non-A, non-B hepatitis, since batches of concentrate of any brand are contaminated with one (or more) serotypes of these agents. Recently a batch of Kryobulin was investigated when 3 cases were reported to be associated with transfusion of this batch. The only criteria one can use when assessing possible immunity to reinfection is a history of previous exposure to a similar product. Table 4 shows that 13/57 (22.8%) patients treated were probably not immune to non-A, non-B hepatitis and of these, 4 developed hepatitis, giving an attack rate of possible susceptibles of 30.8%, excluding symptomless cases.

c) Screening of donors for hepatitis B

Hepatitis B is still present at a low level but donor screening appears to have eliminated any difference between Commercial and NHS concentrate in this respect - see table 2.

d) Occurrence of different serotypes of virus in different products

Apart from different sources of donor, there are 2 different types of factor VIII concentrate available in the U.K.

1) High purity factor VIII made by variants of the glycine/PEG method of fractionation (U.S. Commercial factor VIII concentrate) and

2) Intermediate factor VIII (NHS factor VIII and Kryobulin).

Table 5 shows the differences between 2 products, Hemofil (a commercial U.S. Concentrate) and Kryobulin (an intermediate factor VIII) with respect to the chance that a patient will contract non-A, non-B hepatitis with the first batch of material that he receives or a second or subsequent batch. With Hemofil in 1974-5 there was a 20 times greater chance of contracting overt non-A, non-B hepatitis with the first batch than with the second or subsequent batch. In contrast, there was an equal chance when treated with the first or subsequent batch of Kryobulin of contracting overt non-A, non-B hepatitis.

One of 2 explanations is likely for this. The first is that the attack rate of Hemofil associated hepatitis was much higher than that associated with Kryobulin. The attack rate of Hemofil associated non-A, non-B hepatitis in 1974-5 was (12.9%) and that of Kryobulin was (10.1%) - Unpublished data - Hepatitis Working Party.

These differences therefore cannot be explained by differences in attack rates above. The second possible explanation is that Hemofil is contaminated with one serotype of non-A, non-B hepatitis and that Kryobulin contains 2 or more serotypes.

That the second explanation is the more likely and is confirmed when the data relating to multiple attacks of non-A, non-B hepatitis are examined (table 6). Six patients developed 2 attacks of non-A, non-B hepatitis where the first was associated with U.S. Commercial concentrate (all similar to Hemofil) and the second with Kryobulin or NHS material. However no multiple cases were observed where U.S. Commercial concentrate was implicated in both attacks. In contrast, 4 patients had 2 attacks of non-A, non-B hepatitis associated with intermediate products. In 2 instances the first and second were associated with NHS factor VIII and in the second 2 the first was associated with Kryobulin in both patients, and the second attack with Kryobulin in one and FEIBA in the second. The right hand column in table six gives the ratio of hepatitis associated with different products in the proportion in which they occurred in this series.

One hypothesis to explain the results of the survey is that high purity U.S. Commercial factor VIII is contaminated with one virus, and the intermediate factor VIII being a 'cruder' product contains 2 non-A. non-B viruses. Therefore it is likely that one agent is removed in the fractionation process for high purity concentrate. There is as yet no evidence to suggest whether the U.S. Commercial associated agent is the same as one of these in the intermediate concentrates.

REINFECTION

Some recent evidence suggests that reinfection with non-A, non-B viruses may occur in haemophiliacs when transfused with a large quantity of factor VIII where a large dose of virus is present. This has been shown to occur with hepatitis B prior to the introduction of screening of plasma donations for HB$_S$Ag. It is possible that the cases associated with second or subsequent batches of Hemofil (see page 1) represent instances of this, though there may be other explanations.

FUTURE OF HEPATITIS SURVEILLANCE

The Working Party has considered the results of surveys collected so far and we wish to make the following recommendations:-

1) That the survey should continue by the pursuance of the surveillance scheme to follow changes in incidence of hepatitis related to changes in types of treatment and of blood products.

2) There is little information about the incidence of subclinical hepatitis. Some work on commercial contrate has been carried out at the Royal Free Hospital. However, there is a need for a prospective study comparing different products, and an application for a project grant has been made to the Medical Research Council to support a multicentre study in patients coming to operation. A feasibility study has so far shown that 4 out of 4 of patients studied who had had no previous transfusion of concentrate developed non-A, non-B hepatitis.

Table 1

FACTOR VIII/IX ASSOCIATED HEPATITIS 1974-9

CASES ASSOCIATED WITH DIFFERENT BRANDS

Type of Hepatitis	Brand Memofil	Kryobulin	Factorate	Koate	Profilate	NHS Elstree	NHS Oxford	Cryoprecipitate	NHS IX
B	32	7	11	1	3	23	4	2	3
Non-B	87	25	22	10	6	21	10	9	7
Total	119	32	33	11	9	44	14	11	10

A Total of 283 episodes were reported involving 253 patients. 26 patients had two attacks of Hepatitis and 4 patients had three attacks.

Total 283 Non-B 197; Hepatitis B 86.

Table 2

FACTOR VIII ASSOCIATED HEPATITIS : COMMERCIAL AND NHS BLANKS

ATTACK RATES IN PATIENTS RECEIVING ONE PRODUCT

Year	Brand	Cases of Hepatitis						
		Non-B (Overt)	B (Overt)	B Symptomless	Total Overt Hepatitis	Total Transfused	Ratio Commercial/NHS Non-B	Ratio Commercial/NHS B
1977	Commercial	3 (2.67)	2 (1.78)	0	5 (4.46)	112	4.76	0.79
	NHS	1 (0.56)	4 (2.23)	0	5 (2.79)	179		
1978	Commercial	14 (7.7)	1 (0.5)	0	15 (8.3)	180	19.7	0.79
	NHS	1 (0.39)	2 (0.63)	0	3 (0.96)	313		
1979	Commercial	10 (6.32)	1 (0.63)	0	11 (6.96)	158	21.73	(Not significant)
	NHS	1 (0.29)	0	0	1 0.29)	342		

Table 3

FACTOR VIII AND IX ASSOCIATED NON-A, NON-B, HEPATITIS 1974-80

ASSOCIATION WITH PREVIOUS TRANSFUSION HISTORY

Total Cases Non-A, Non-B, Hepatitis 137

Previous Transfusion History

	Freeze Dried Concentrate	Yes	No	Total
Current Attack of Hepatitis		31	106	
1. Associated with U.S. Commercial Concentrate		18(20%)	73(80%)	91
2. Associated with NHS or Immuno Concentrate		13(28%)	33(72%)	46

TRANSFUSION HISTORY - EFFECT OF TRANSFUSION OF DIFFERENT BRANDS OF CONCENTRATE

Brand Implicated	No. Cases Transfused U.S. Commercial	No. Cases Transfused NHS or Immuno	Total Previous Concentrate	Total No. Previous Concentrate
U.S. Commercial	4	15	18	91
NHS or Immuno	6	8	13	46

Table 6

MULTIPLE ATTACKS OF NON-A, NON-B HEPATITIS IN HAEMOPHILIACS

Brand Implicated First Attack	Second Attack	No. Patients	No. of Cases Associated each Brand Expressed as Ratio Second to First Attack
U.S. Commercial	Kryobulin (Immuno)	3	18/91
U.S. Commercial	NHS or Cryo	3	29/91
U.S. Commercial	U.S. Commercial	0	45.5/45.5
Kryobulin	FEIBA (IX) or Kryobulin	2	9/9
NHS VIII	NHS VIII	2	14.5/14.5
Kryobulin	NHS	0	18/29