31

SECOND ANNUAL REPORT ON PROJECT NUMBER

J/S240/78/7

1. TITLE

Studies of the epidemiology and chronic sequelae of factor VIII and IX associated hepatitis in the United Kingdom.

2. AIM

(a) To study the incidence and types of factor VIII and IX related hepatitis in the U.K. by requesting the Directors of Haemophilia Centres to report cases as soon as they occur to the Oxford Haemophilia Centre using standard record forms; the effect of batch size, Hepatitis Surface Antigen (HB_sAg) screening of donors, the source and numbers of donations used to make each brand of concentrate are studied. Paired sera, faeces, urine and implicated batches of concentrate are collected for study where possible from acute non-B hepatitis cases. Studies of the incidence of acute hepatitis B, both overt and symptomless are carried out. An attempt is made to provide an "early warning" system to identify implicated batches of concentrate. Serological studies of the prevalence of HB_sAg, Anti-HB_s, Hepatitis A antibody and antibodies to other viruses have been carried out at Oxford.

The hepatitis reports for 1977, 1978 and 1979 (those received by 31.7.80) have been reviewed and compared with the results of the 1974-75 Hemofil Survey (1) and the results of a survey of Kryobulin associated hepatitis in 1976 (2).

(b) To assess the incidence of chronic liver disease due to factor VIII associated hepatitis by following up of patients with known infected batches of concentrate. Patients are examined for clinical and laboratory evidence of chronic liver disease. The prevalence of antibody to hepatitis B and abnormal transaminases in household contacts of haemophiliacs are also being assessed.

One hundred and forty eight patients at Oxford on long term factor VIII have been followed up in 1979-80. In addition the haemophilia B patients on NHS factor IX therapy have been separately assessed. The results of this survey are given in Appendix II.

3. COST AND DURATION

Approved budget £25,462.43. Duration 3 years from September 1978 but research fellow in hepatitis at Oxford supported for 2 years only. He has now completed his 2 year term.

4. PERSONS ENGAGED WHOLE OR PART-TIME ON THIS PROJECT

Dr. J. Craske, Consultant Virologist, Manchester Public Health Laboratory

Dr. C.R. Rizza, Consultant Physician in Charge, Oxford Haemophilia Centre

Miss R.J.D. Spooner, Research Assistant, Oxford Haemophilia Centre

Dr. S. Ghosh, Research Fellow in Hepatitis, Oxford Haemophilia Centre

Dr. Joan Trowell, Lecturer in Medicine, Nuffield Department of Clinical Medicine, The John Radcliffe Hospital, Oxford

Dr. C.A. Ludlam, Consultant in Charge, Haemophilia Centre, Edinburgh Royal Infirmary, (Dr. D. Davies retired from the Working Party January, 1980)

Dr. Richard Lane, Director, Blood Products Laboratory, Elstree. (Dr. D. Ellis retired in December, 1979)

5. STAGES COMPLETED

(a) First and second years surveillance of cases of hepatitis reported to the Oxford Haemophilia Centre. Review of cases notified in years 1974-77. Records of cases notified in the 1974-76 surveys of Hemofil and Kryobulin related hepatitis and, the data for 1977 and 1978 have all been entered in computer files at the Oxford Regional Health Authority. Preliminary analysis of data for 1977-79 has been carried out.

(b) Review of patients on long term factor VIII therapy at Oxford Haemophilia Centre:-

Total number of patients; 179 investigated in first year; 124 have been tested for hepatitis A and B serology.

In addition, 12 patients with Haemophilia B out of this sample were assessed separately.

In 1979-80, 148 of the patients initially reviewed in 1978 were available for follow-up.

An assessment of the value of the measurement of serum bile acids as a measure of chronic liver disease in haemophiliacs was carried out - see Appendix II.

(c) Studies of hepatitis A and B serology and liver function tests in household contacts of haemophiliacs on home treatment were also started.

(d) A preliminary study of liver function tests and hepatitis B serology was also undertaken in patients with a mild coagulation defect (VIII >2%) or with Von Willebrands Disease who attended the Haemophilia Centre for treatment or were admitted for operation.

6. PROGRESS MADE IN RELATION TO RESEARCH PLAN

(1) Hepatitis Surveillance.

In addition to the 209 cases of hepatitis identified for the period 1974-1977, a further 75 cases of hepatitis were identified in 1978-79 as being associated with factor VIII or IX therapy. Table 2 details the numbers of cases of B and non-B hepatitis reported in 1977-79. The cases in 1979 are those reported up until 31.7.80. Data from 16 Haemophilia Centres are still awaited for 1979.

It will be seen:-

(a) that there is a slight decline in the cumulative attack rate in 1978-79 for the total overt cases of hepatitis. This would be expected with repeated exposure of a finite number of patients to an infective agent. The level of non-B hepatitis has shown no evidence of decreasing when the cumulative attack rate is allowed for.

(b) Hepatitis B is still present at a reduced level despite the general requirement in the U.S.A. that all donor plasma be screened for HB_sAg by RIA before pooling for the preparation of commercial concentrate.

The change in incidence of overt* hepatitis B in patients first exposed to Hemofil factor VIII concentrate is given in the top 2 lines of table 2. Batches Q - V were made from donations screened by HB_sAg by counterimmunoelectrophoresis (CIE). Those used to make batches W - ZA were screened by radioimmunoassay (RIA).

(a) CONSTANT PATTERN OF FACTOR VIII AND IX ASSOCIATED HEPATITIS

Table 3 shows the detailed results of the cases of B and Non-B hepatitis reported to Oxford as being associated with factor VIII and IX therapy in the 1977 treatment year. A total of 66 cases of hepatitis-like illness were reported. Of these, 5 were excluded from the analysis of the results for the reasons indicated under "other categories". Similar results were obtained from the 1978 and 1979 returns (Table 4). Only cases reported to 31.7.80, have been included for 1979 and the results of a further 16 Haemophilia Centres are still to be analysed. The trends for the last three years are similar and are summarized in Table 4. The detailed returns for 1977-79 showing cases associated with different brands of factor VIII and IX therapy are given at the end of the report as Appendix I.

NON-B HEPATITIS

The results of the first annual report have been confirmed in that every case where hepatitis A and other viral serological tests have been carried out indicate that this is Non-A, Non-B hepatitis. However, cases

* Overt hepatitis in this report means acute hepatitis with symptoms and signs of the disease.

where the results of tests are not available have been included in this survey where all the other criteria suggest that they are similar and, therefore, these cases will still be referred to in this report as Non-B hepatitis.

Table 4 shows that similar cumulative attack rates for non-B hepatitis occur for all brands of commercial factor VIII. Possibly higher attack rates are associated with patients with Von Willebrands disease (Table 5 - 1979) even though the numbers of patients treated are small. The largest number of cases was associated with the big increase in the use of American factor VIII between 1977 and 1979, (from 315 to 672 patients treated in one year with this product). In contrast, the use of Kryobulin over this period declined between 1977 and 1978 with a slight increase in 1979. The 1974-75 Hemofil survey showed that overt non-B hepatitis was 20 times more likely to occur with the first batch of concentrate transfused than with second or subsequent batches (3).

Epidemiological observations (3) also suggest that the non-B hepatitis associated with U.S. commercial factor VIII might be different from that associated with other products such as NHS factor VIII and Kryobulin.

The observed variations in attack rates are, therefore, likely to be due to (1) the varying population of patients receiving a brand of concentrate in different years who have previously been treated with the same or different products in previous years, (2) previous treatment with NHS factor VIII, Kryobulin or U.S. commercial. When all these factors are taken into account, it is our opinion that the incidence of non-B hepatitis associated with different U.S. products is similar, and has not altered significantly since that associated with the first batches of Hemofil in 1974. The hypothesis used to explain the variations in attack rates will be tested over the next six months by examining the effect of previous treatment with incidence of hepatitis using the data already collected.

NHS FACTOR VIII

The incidence of non-B hepatitis associated with NHS VIII and Kryobulin may be lower than associated with U.S. commercial, but factors such as those already mentioned may affect that with NHS concentrate. This has been used in some Centres for over 10 years and, therefore, a higher proportion of patients may have had past exposures. Since 1976 the donor pool size for each batch of Elstree factor VIII (NHS) has increased from 500 to 3,500 donors, whereas that of factor VIII made at Oxford and Edinburgh is still approximately 500 (4). The effects of this factor on the incidence of hepatitis is considered later.

An attempt was made to compare the incidence of overt non-B hepatitis due to U.S. commercial and NHS factor VIII as shown in Table 5. The attack rates of hepatitis in patients who were treated with only one product in any treatment year are shown for these 2 groups for both non-B hepatitis and hepatitis B. The incidence of hepatitis due to each product can be added together since each patient does not appear more than once in any of the treatment groups in one year. While the incidence of hepatitis B does not show any difference, probably reflecting donor screening for HB_sAg, there is a 4 - 20 times increased incidence of overt hepatitis associated with U.S. commercial compared with NHS factor VIII. Further analysis of the data may show whether this is a true estimate.

HEPATITIS B

Cases of overt hepatitis B have been reported both associated with commercial and NHS factor VIII (Tables 4 and 6) and are at approximately the same level of prevalence with all products. The absence of reported cases with Kryobulin in 1978, Hemofil in 1977-79 and NHS (Elstree) in 1979 may be due to the fact that the fall in total patients transfused in these years was reflected in a smaller number of patients receiving first transfusions of concentrate who were susceptible to hepatitis B infections. Similarly, the cases associated with Armour factor VIII in 1977-79 may be associated with the relatively large increase in the number of patients first transfused with this product during these years who were, therefore, susceptible to hepatitis B infection. The absence of cases of hepatitis B associated with NHS (Oxford) VIII and Profilate (see Appendix II) is probably due to the small number of patients receiving these products.

Further analysis of the data may show whether or not there are other factors affecting the apparent variation in the incidence of overt hepatitis B.

SYMPTOMLESS HEPATITIS B VIRUS (HB) INFECTION

Table 7 shows the results of a survey carried out of the prevalence of hepatitis B surface antibody (Anti-HB_s) and hepatitis B core antibody (Anti-HB_c) using radioimmunoassay tests (Ausab and Corab - Abbott Laboratories Ltd.) in different groups of patients. A positive test for Anti-HB_s was considered to be a ratio of $\frac{\text{counts/min of test serum}}{\text{counts/min negative control serum}} > 20$

Values below this are likely to be due to: a) passive antibody from recently transfused concentrate or: b) non-specific reactions (ratio <3). Cases of doubt were resolved by retesting fresh serum specimens obtained before a further transfusion. In some cases it was still not possible to assess immune status, as

severely affected patients receive 2-3 transfusions per week. Patients in the doubtful group usually fell into this category. The results show however, that there is a high correlation between previous transfusion of factor VIII concentrate and immunity to hepatitis B. Therefore, severely affected patients on regular therapy with concentrate are likely to be immune to hepatitis B, even though in some cases passively acquired Anti-HB_s cannot be excluded. The results of testing for Anti-HB_c confirm this picture. Fig. 1 shows the relationship of the ratio obtained in the Ausab test as defined above to the number of days since the last infusion of factor VIII concentrate or cryoprecipitate, and shows the role of passive acquired antibody. Some of the high ratios in the 8-45 day category are likely to be due to a secondary antibody response to HB_sAg in the transfused concentrate, possibly partially complexed with Anti-HB_s.

The results of the survey indicate that:-

(1) 85-90% of patients with severe factor VIII or IX deficiency have antibody to hepatitis B virus and are therefore immune to reinfection.

(2) The proportion of carriers of hepatitis B virus (3/132) is no higher than in non-haemophiliacs with a similar exposure to HBV. Therefore, hepatitis B is not likely to be a major cause of chronic liver disease in this group.

(3) Infection with HBV is highly correlated in British haemophiliacs with the use of large pool concentrate, both NHS and commercial. Many patients with a severe coagulation defect (VIII <2%) are exposed to hepatitis B infection below the age of 5 years. Much of the infection in young children is symptomless, as only a few children below 5 years of age give a history of overt illness compatible with hepatitis B.

(4) Patients with mild coagulation defects (VIII - >2%) often do not require regular factor VIII therapy, and only require concentrate to cover an operation or other major accident. They are not treated until they are 30-40 years old, but are more likely to suffer from overt hepatitis B than young children when first transfused with concentrate - see Table 8.

SYMPTOMLESS NON-B HEPATITIS

Studies of post transfusion hepatitis in the U.S.A. associated with whole blood indicate that a high proportion of cases of non-A, non-B hepatitis are symptomless, and are only detectable by following patients prospectively by studies of serum transaminase levels (5). The Hemofil

survey (3) showed that though 52 out of 417 patients contracted overt non-B hepatitis when first transfused with concentrate, only 3 out of 497 patients transfused with a second or subsequent batch of Hemofil contracted overt hepatitis. The fact that a patient was 20 times less likely to contract overt hepatitis if he had previously been transfused with an infected batch of concentrate can be attributed to the acquisition of immunity to reinfection through a symptomless infection after the first transfusion. However, prospective liver function tests were not done. This suggests that the symptomless infections are due to the same agent as the overt cases.

Of the patients at Oxford, 30% of patients with abnormal transaminases (categories 3 and 4 appendix I) gave a history of overt hepatitis. This suggests that a significant proportion of the cases of chronic liver disease in haemophiliacs started as cases of acute overt non-B hepatitis. Overt jaundiced cases of hepatitis B however, rarely progress to a carrier state or chronic hepatitis (6).

A prospective study at the Royal Free Hospital has shown that of 10 patients contracting non-B hepatitis after first transfusion of factor VIII concentrate, 7 were entirely symptomless (7). One of 3 patients followed prospectively after overt non-B hepatitis after concentrate has progressed to probable chronic liver disease 28 months later (8).

Table 9 shows the results of a preliminary survey of aspartate aminotransferase (AST) estimations carried out on haemophilia A and Von Willebrands disease patients with mild coagulation defects (VIII - >2%) in which patients were bled within 3 months of their first transfusion of Oxford NHS factor VIII or other brands of concentrate.

Of a total of 9 patients who received one transfusion of NHS (Elstree) or U.S. commercial factor VIII (about 1-2,000 VIII units) 4 had abnormal (AST's) grade 3 or 4, whereas, all 5 patients who were transfused once with Oxford factor VIII had normal AST's. The pool size of Oxford factor VIII (NHS) is 500 donations (100 litres plasma) whereas that of Elstree factor VIII (NHS) is 3,500 donations (700 litres) (4).

The results suggest that a factor VIII concentrate made from a small pool of donors might be useful for replacement therapy for patients with mild coagulation defects to cover operations or other minor procedures. It is proposed to submit a request for a research grant to the Small Grants Committee to explore this question further prospectively by studying the incidence of overt and symptomless hepatitis in patients first transfused with factor VIII concentrate at Oxford. It is the opinion of the Working Party that the risk of acquiring

non-B hepatitis (overt or symptomless) after first transfusions of factor VIII concentrate (NHS Elstree or U.S. commercial) is 90-100% patients transfused. Further work may show whether Elstree factor VIII differs from U.S. commercial factor VIII in this respect.

(b) SEQUELAE OF ACUTE HEPATITIS

I) Only one patient died after an attack of non-B hepatitis during the period 1977-79. He suffered a retroperitoneal haemorrhage but it is likely that this coagulation defect was worsened by the additional problems associated with his liver disease.

Most cases of hepatitis B and non-B hepatitis are clinically mild. However, 6 cases of non-B hepatitis have been reported as "severe" in the acute stage. There is no evidence of an increased liklihood of chronic sequelae. No cases of fulminating hepatitis have been reported.

II) Subacute hepatic necrosis. One patient has been reported as suffering from subacute hepatic necrosis after an acute attack of non-B hepatitis. It is possible that this condition is considerably under-reported.

III) Recurrent jaundice of unknown aetiology. Six cases of jaundice were reported between 1977 and 1979 which were not associated with transfusion of any specific product, but the patients had a severe coagulation defect and required regular factor VIII replacement. Four of these patients were at Oxford, and are considered to be cases of chronic liver disease. The cause of recurrent jaundice in these cases will be further investigated.

IV) Chronic Liver Disease. This is considered in a separate report submitted under appendix II.

(c) TRANSFUSION HISTORY

Table 10 shows the previous transfusion histories in patients contracting non-B hepatitis. Of 91 patients whose non-B hepatitis was associated with U.S. commercial concentrate, 77 had no previous concentrate, whereas, of 29 associated with NHS factor VIII, 12 had had previous concentrate. Therefore, the association of a first transfusion of concentrate with non-B hepatitis is very strong, particularly with U.S. commercial factor VIII. Further investigations of the significance of these results are being carried out.

(d) INCUBATION PERIOD OF NON-B HEPATITIS

Fig. 2 shows the incubation period of cases of non-B hepatitis of all cases where enough information was

available since 1974, related to the associated brand of factor VIII concentrate. The mean of the incubation periods for Hemofil was 30.2 days and for NHS VIII and IX concenteate, the brands with the largest range of incubation period, was 42.2 days. However, there was no significant difference between the means when assessed by Students t test. Almost all the non-B hepatitis associated with factor VIII and IX concentrate is the short incubation type (less than 60 days).

(e) SECONDARY CASES OF HEPATITIS

Since 1974, 7 cases of secondary hepatitis B, 1 symptomless and 6 symptomatic, have been reported. In two instances the index cases were symptomless. Four overt cases of secondary hepatitis B occurred between 1974 and 1979, when 59 cases of primary overt hepatitis B were reported. This means that 1 case of symptomatic hepatitis B occurred for every 14.75 cases of primary hepatitis B.

Two cases of hepatitis B were in the parents of haemophiliacs who regularly gave factor VIII to their sons. The rest of the cases were in spouses or girl friends of the index case.

However, no cases of secondary non-B hepatitis have been reported in 164 cases in index patients so far in this survey. Two cases of hepatitis have occurred in the same household within one to two months on four occasions, but in each instance, both patients were haemophiliacs whose non-B hepatitis was associated with transfusion of factor VIII concentrate. If non-B hepatitis was transmitted with the same frequency as hepatitis B, then at least 11 secondary cases of non-B hepatitis would have been reported.

To try and assess whether symptomless infection due to hepatitis B or non-B was a significant factor in household contacts of haemophiliacs, hepatitis B serology and serum aminotransferase levels have been studied in:-

(1) parents of children on regular home therapy with factor VIII

(2) wives or girl friends of adult haemophiliacs on home therapy.

Of 10 adult relatives so far studied who regularly treat their haemophiliacs or Christmas disease children, all were negative for both Anti-HB_s and Anti-HB_c by RIA. Only one had an abnormal aspartate aminotransferase level (grade 3)*. This relative, however, is a known carrier of the haemophilia A gene, and has had past transfusion of factor VIII concentrate, and it is possible she had a symptomless attack of non-B hepatitis.

Further patients are at present under investigation.

*Grade 3 = AST between 1 + 2 X upper limit of normal on at least 2 occasions

7. VARIATIONS FROM THE ORIGINAL RESEARCH PLAN

We have not produced a detailed analysis of the degree of association of different episodes of hepatitis for different batches of factor VIII or IX. It has been noted that most of the cases of hepatitis in 1979-80 occurred in mild haemophiliacs requiring one episode of treatment with concentrate. This has increased the number of cases where only one product was transfused, but there has been a drop in the number of batches implicated where more than 2 cases are associated with B or non-B hepatitis. This is probably due to a diminution in the proportion of susceptibles being transfused with only one batch of concentrate as more and more of the total number of U.K. haemophiliacs have received treatment. Therefore, the assumptions made in appendix I of our first annual report are no longer valid. This will be discussed in more detail in the final report.

8. FACTORS CAUSING DELAY IN EXECUTION OF THE RESEARCH PLAN

It was our intention to publish a paper describing the results of a survey of hepatitis A and B antibodies in haemophiliacs treated at Oxford. It was found, however, that different batches of the 'Ausab' test for Anti-HB_s gave wide variations of the ratio of $\frac{\text{counts per min of test serum}}{\text{counts per min negative control serum}}$.

We are now in the process of standardising this test using the International Standards for Anti-HB_s which has just been issued. The paper will be then submitted for publication.

9. PUBLICATIONS PROPOSED

(1) A summary of this work so far will be published as part of a report of the symposium on Unsolved problems in Haemophilia which was held at the Royal College of Physicians and Surgeons, Glasgow, on October 1st and 2nd, 1980. The paper was entitled "The epidemiology of factor VIII and IX associated transfusion hepatitis in the U.K."

(2) A paper on hepatitis A and B serology in haemophilia (see section 8).

10. EXPECTED DATE OF COMPLETION

September 1st, 1981. Final report - October, 1981.

REFERENCES

1. Craske, J., Kirk, P., Cohen, B, and Elise M. Vandervelde (1978) J. Hyg., Camb, 80, 329-336.

2. Craske, J., R.J.D. Spooner (1976) Unpublished observations.

3. Craske, J., R.J.D. Spooner, Elise M. Vandervelde (1978) Lancet, ii, 1051.

4. Dr. Richard Lane, Personal Communication (1980).

5. Berman, M., Alter, H.J., Ishak, K.G., Purcell, R.H. et al (1979) Ann. Int. Med. 91, 1-6.

6. Dr. D.S. Dane, Personal Communication (1980).

7. Dr. Peter Kernoff, Personal Communication (1980).

8. Haemophilia Hepatitis Working Party, Unpublished Observation (1980).

TABLE 1

JAUNDICE IN HAEMOPHILIAC PATIENTS IN THE UNITED KINGDOM

Year	Total number of treated patients	Number of cases of jaundice	Per Cent	
1969	1048	19	1.81	
1970	1041	25	2.40	
1971	1143	22	1.92	
1972	1191	17	1.42	
1973	1124	26	2.31 -	Hemofil first used
1974	1634	85(101)*	5.20 (6.18)	Kryobulin first used
1975	1609	42(51)	2.61 (3.17)	
1976	1886	56(61)	2.97 (3.24)	Other commercial products)
				Koate (Cutter))
				Factorate (Armour))
				Profilate (Abbott))
1977	1968	50(54)	2.54 (2.74)	
1978	2039	41(47)	2.01 (2.30)	
1979	1935	33(40)	1.70(2.06)	

Data from Biggs, R. (1974)
Biggs & Spooner (1976)
U.K. Haemophilia Survey 1977-79.

* Numbers in brackets include asymptomatic cases.

TABLE 2

HEPATITIS B AND NON-A, NON-B HEPATITIS RELATED TO FACTOR VIII TRANSFUSIONS U.K.

Year	Batches Factor VIII	Non-B Hepatitis No. Cases (%)	Hepatitis B (Overt) No. Cases (%)	Total Hepatitis	Total Transfused	Products
1974-5	Q - V (6)	45 (14.6%)	26 (8.4%)	62*	308F[+]	Hemofil
1975	W - Z4(7)	10 (7.4%)	2 (1.5%)	12	136F	Hemofil
1975-6	K1- K12	13 (10.9%)	4 (3.4%)	17	119F	Kryobulin
1977	Not relevant	33 (1.68)	17 (0.86)	50 (2.54)	1968A[x]	All Products
1978	" "	34 (1.66)	8 (0.39)	41 (2.01)	2039A	" "
1979	" "	29 (1.49)	4 (0.20)	33 (1.7)	1935A	" "
TOTAL		164	61	215	6505	

[+]F = Patients first exposed to Commercial Concentrate

[x]A = All patients treated

* 9 patients suffered 2 attacks of hepatitis (Non-B + B) other products had multiple attacks of hepatitis studied in 1975-76. Data not included in this Survey. Percentages are of total patients in each category who were transfused.

TABLE 3

FACTOR VIII ASSOCIATED HEPATITIS - 1977

Patients Diagnosis and Material received	Cases of Hepatitis Non-B Overt only	Cases of Hepatitis B Overt	Cases of Hepatitis B Symptomless	Total Overt only	Total Patients Transfused
Haemophilia 'A'					
NHS Elstree	6 (0.66)	4 (0.44)	1	10 (1.10)	908
Oxford	3 (1.67)	0	0	3 (1.67)	180
Edinburgh	0	1 (0.81)	2	1 (0.81)	123
Cryoprecipitate	2 (0.15)	1 (0.075)	0	3 (0.23)	1329
Commercial					
Hemofil	11 (2.48)	0	1	11 (2.48)	444
Factorate	5 (1.58)	7 (2.22)	0	12 (3.80)	315
Profilate	1 (3.7)	0	0	1 (3.7)	27
Koate	1 (0.41)	1 (0.41)	0	2 (0.82)	241
Kryobulin	0	1	0	1 (0.33)	306
Commercial Unspecified	2	2	0	4	Not available
Total	33 (1.68)	17 (0.86)	4	50 (2.54)	1968
Haemophilia 'B' NHS IX	4 (1.34)	1	0	4 (1.34)	298
Von Willebrands Hemofil	1 (0.42)	0	0	1 (0.42)	237
Secondary Cases	0	1	0	1	
Deaths	None				

* One double attack hepatitis Non-B followed by hepatitis B

Two household contacts of patients contracting non-B hepatitis also had recently developed non-B hepatitis Both, however, had recently been transfused with commercial VIII concentrate and are included above.

Other categories see attached sheet (Table 3A).

TABLE 3A

OTHER CATEGORIES (NOT INCLUDED IN CALCULATION OF ATTACK RATES)

Chronic Hepatitis		1
Hepatitis Type Unknown) Related to Blood Products)		1
Glandular Fever		0
Hepatitis A		0
Hepatitis not due to Blood Products	Non-B	1
	Hep-B	0
Symptomless Non-B		1
Abnormal LFT's not Related to Hepatitis		1

Total Cases of Hepatitis like Illness = 66
(Including symptomless cases)

TABLE 4

TRENDS IN THE INCIDENCE OF FACTOR VIII ASSOCIATED HEPATITIS 1977-79

HAEMOPHILIA 'A' PATIENTS

Product	Year	Non-B (%)	Hepatitis B (%)	Total	Total Transfused
NHS Elstree	1977	6 (0.66)	4 (0.44)	10 (1.10)	908
	1978	7 (0.69)	2 (0.19)	9 (0.89)	1011
	1979	3 (0.30)	0	3 (0.30)	973
Cryo	1977	2 (0.15)	1 (0.075)	3 (0.22)	1329
	1978	3 (0.26)	0	3 (0.26)	1120
	1979	2 (0.22)	0	2 (0.22)	895
Commercial					
Hemofil	1977	11 (2.48)	0	11 (2.48)	444
	1978	5 (1.29)	0	5 (1.29)	386
	1979	5 (1.34)	0	5 (1.34)	373
Factorate	1977	5 (1.58)	7 (2.22)	12 (3.80)	315
	1978	8 (1.33)	4 (1.03)	12 (2.00)	599
	1979	10 (2.46)	2 (0.30)	12 (1.78)	672
Profilate	1977	1 (3.7)	0	1 (3.71)	27
	1978	2 (2.71)	0	2 (2.77)	72
	1979	2 (2.46)	0	2 (2.46)	81
Koate	1977	1 (0.41)	1 (0.41)	2 (0.82)	241
	1978	3 (1.17)	0	3 (1.17)	255
	1979	2 (0.39)	0	0 (0.39)	215
Kryobulin	1977	0	1 (0.33)	1 (0.33)	306
	1978	3 (1.71)	0	3 (1.71)	175
	1979	2 (0.84)	1 (0.42)	3 (1.26)	237

TABLE 5

FACTOR VIII ASSOCIATED HEPATITIS 1977-1979 PATIENTS WITH VON WILLEBRANDS DISEASE

Year	Material Transfused	Cases of Hepatitis Non-B (Overt Only)	B Overt	B Symptomless	Total Overt Only	Total Patient Transfused
1977	Cryo	0	0	0	0	198
	NHS Elstree	0	0	0	0	26
	Edinburgh	0	0	0	0	3
	Oxford	0	0	0	0	8
	Commercial					
	Hemofil	1 (20.0)	0	0	1 (20.0)	5
	Factorate	0	0	0	0	0
	Profilate	0	0	0	0	5
	Koate	0	0	0	0	8
	Kryobulin	0	0	0	0	9
	Total	1 (0.43)	0	0	1 (0.43)	237
1978	Cryo	0	0	0	0	190
	NHS Elstree	1 (3.2)	0	0	1 (3.2)	31
	Edinburgh	0	0	0	0	2
	Oxford	0	0	0	0	15
	Commercial					
	Hemofil	0	0	0	0	5
	Factorate	0	0	0	0	10
	Koate	0	0	0	0	3
	Kryobulin	0	0	0	0	3
	Total	1 (0.43)	0	0	1 (0.43)	228
1979	Cryo	0	0	0	0	176
	NHS Elstree	1 (2.12)	0	0	1 (2.12)	47
	Edinburgh	0	0	0	0	2
	Oxford	0	0	0	0	13
	Commercial					
	Hemofil	1 (20.0)	0	0	1 (20.0)	5
	Factorate	3 (25.0)	0	0	3 (25.0)	12
	Koate	0	0	0	0	1
	Kryobulin	2 (50.0)	0	0	2 (50.0)	4
	Total	8 (3.43)	0	0	8 (3.43)	233
	Commercial Brand Unknown	1	0	0	1	

TABLE 6

FACTOR VIII ASSOCIATED HEPATITIS : COMMERCIAL AND NHS BRANDS
ATTACK RATES IN PATIENTS RECEIVING ONE PRODUCT

Year	Brand	Cases of Hepatitis					Ratio Commercial/NHS	
		Non-B (Overt)	B (Overt)	B Symptomless	Total Overt Hepatitis	Total Transfused	Non-B	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 7

HEPATITIS B SURFACE (ANTI-HB_s) and CORE (ANTI-HB_c) ANTIBODY

PREVALENCE IN HAEMOPHILIA PATIENTS AT OXFORD

Treatment Group	Severity Coagulation Defect	Treatment	Anti-HB_s Positive Ria Ratio >20*	Anti-HB_s Negative Ria Ratio <3.0*	Doubtful Anti-HB_s Status Ria Ratio >3.0 and <20*	Hb_sAg Carriers	Total
Haemophilia A	<1% ($VIII_c$)	NHS+ Commercial Concentrate	102(77.3%)	11(8.3%) (1/11 Anti-HB_c Positive)	16+(12.12%) (11/16 Anti-HB_c Positive)	3(2.3%)	132
Haemophilia A (including VW carriers)	>1%	Blood Plasma or Cryoprecipitate	0	17	0	0	17
Christmas disease patients		NHS IX Concentrate	15(88%)	0	1(11.8%)	0	16

* A positive result in this survey was considered to be a ratio $\frac{\text{counts test serum}}{\text{counts negative control serum}} > 20$

Negative results were considered to be a ratio <3.0
Doubtful results with ratios less than 20 or greater than 3 may have been due to passively acquired antibody

+ Doubtful and negative results were tested for hepatitis B core antibody by 'corab' ria test. If anti-HB_c positive 'doubtful' results are included then 102 + 11 = 113 or 85.6% of severe haemophiliacs had evidence of past hepatitis B infection (excluding carriers of HB_sAg).

TABLE 8

RELATIONSHIP OF AGE TO ANTI-HB_s STATUS AND HB_sAg CARRIER STATUS

Group	Severity of Coagulation Defect	Age (Years) <5	6-10	11-20	21-30	31-40	40+	Total
Haemophilia 'A'	Severe <2% VIII	0/1	10*/12(83%)	34+/41(83%)	26+/34(76%)	18/21(86%)	17/22(77%)	102/132(77%)
Haemophilia 'A' VW + carriers Prior to first transfusion of concentrate	Mild >2% VIII	0	0	0	0	0/1	0/16	0/17
Christmas disease (Haemophilia 'B')	All patients	0	4/4	7/7	3/3	1/2	1/1	15/16

* No. positive Anti-HB_s/Total

\+ 3 patients carriers of HB_sAg.

TABLE 9

ABNORMAL ASPARTATE AMINOTRANSFERASES

WITHIN 3 MONTHS OF TRANSFUSION OF FACTOR VIII CONCENTRATE

IN PATIENTS RECEIVING FIRST TRANSFUSIONS

Brand	No. transfusions	Grade Aminotransferase (No. of Patients)				
		*(1)	(2)	(3)	(4)	Total
Oxford VIII	1	5	0	0	0	5
	2	1	0	0	0	1
	3	0	0	1	0	1
Bristree	1	1	1	2	0	4
U.S. Commercial	1	1	2	2	0	5
Cryoprecipitate Blood etc.		3	0	0	0	3
No Products		12	0	0	0	12

* Grade (1) = Normal AST

(2) = Abnormal AST on one occasion

(3) = AST between 1 + 2 x upper limit of normal on at least 2 occasions

(4) = AST more than 2 x upper limit of normal on at least 2 occasions.

TABLE 10

FACTOR VIII ASSOCIATED HEPATITIS

NON-B HEPATITIS

PREVIOUS TRANSFUSION HISTORY RELATED TO BRAND IMPLICATED

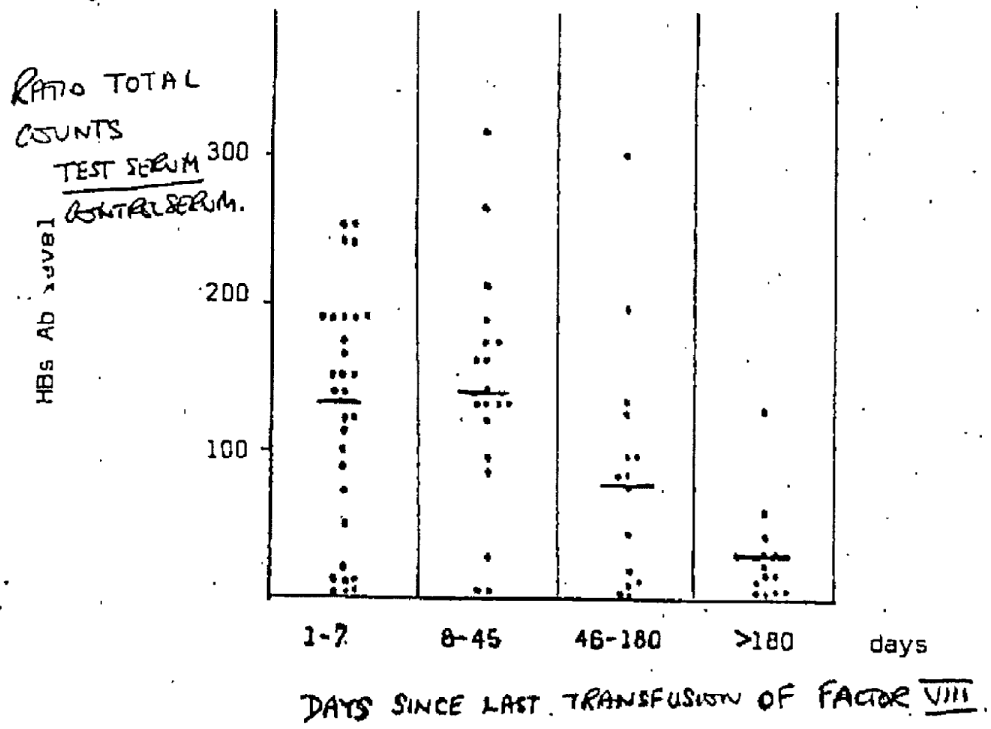
History	Brand Implicated	Number of Patients Kryobulin	NHS	U.S. Commercial	Total
Previous Freeze Dried Concentrate	Yes	9	12	14	35
	No	9	17	77	103
Total		18	29	91	138
Previous NHS only*		-	1	3	-

* Data on other cases with previous transfusion history not yet complete.

Fig 1

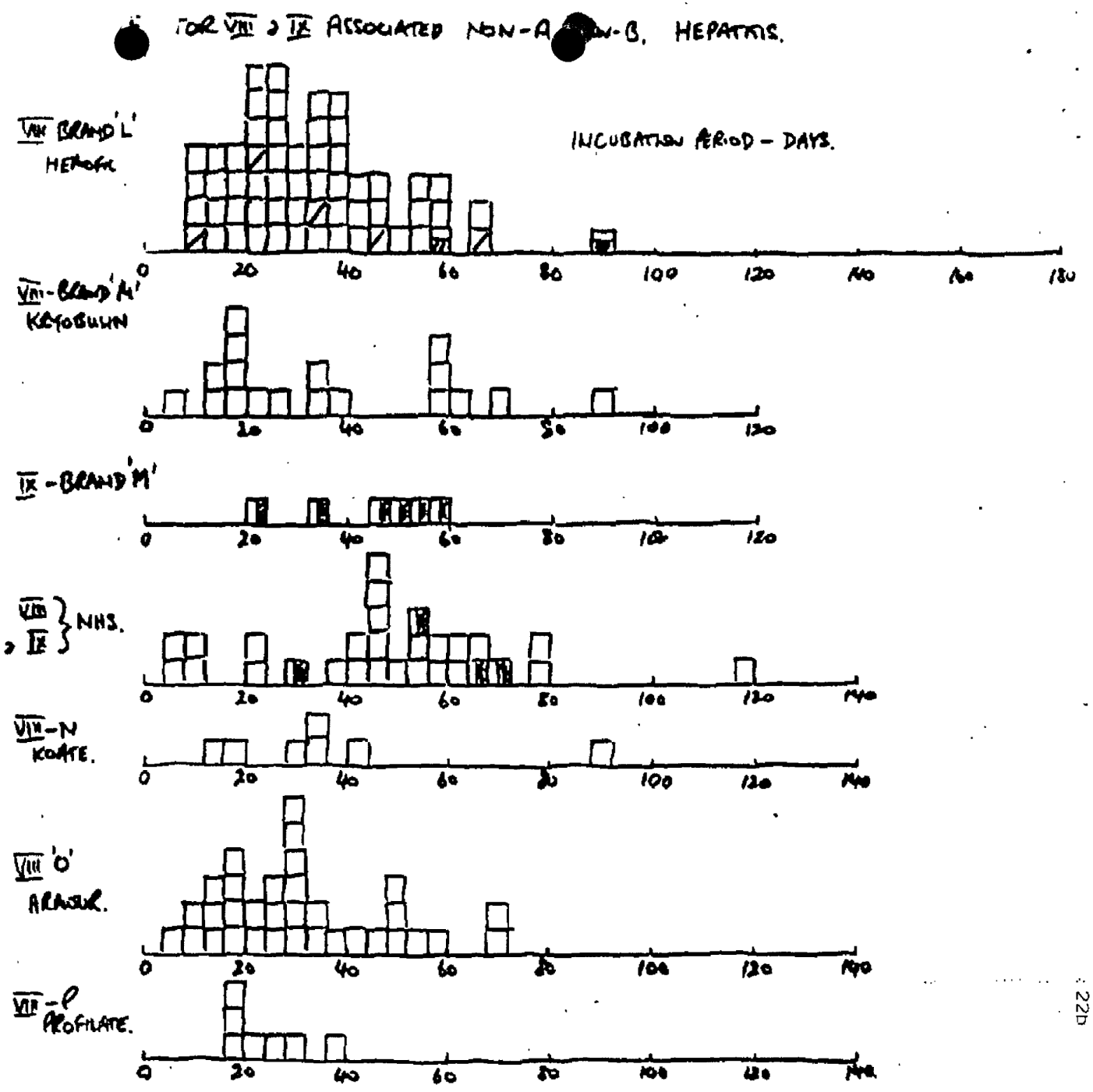
HBs Ab level in relation to last dose of factor VIII

"AUSAB" RADIOIMMUNOASSAY TEST.



DAYS SINCE LAST TRANSFUSION OF FACTOR VIII.

Fig 2.



APPENDIX I

U.K. HAEMOPHILIA HEPATITIS SURVEY RETURNS FOR 1977-79

TABLE A

FACTOR VIII ASSOCIATED HEPATITIS - 1977

Patients Diagnosis and Material Received	Cases of Hepatitis				Total Patients Transfused
	Non-B Overt Only	Overt	B Symptomless	Total (overt only)	
Haemophilia 'A'					
NHS VIII Elstree	6 (0.66)*	4 (0.44)*	1	10 (1.10)*	908
Oxford	3 (1.67)	0	0	3 (1.67)	180
Edinburgh	0	1 (0.81)	2	1 (0.81)	123
Cryo	2 (0.15)	1 (0.075)	0	3 (0.23)	1329
Commercial					
Hemofil	11 (2.48)	0	1	11 (2.48)	444
Factorate	5 (1.58)	7 (2.22)	0	12 (3.80)	315
Profilate	1 (3.7)	0	0	1 (3.7)	27
Koate	1 (0.41)	1 (0.41)	0	2 (0.82)	241
Kryobulin	0	1	0	1 (0.33)	306
Commercial Unspecified	2	2	0	4	Not available
Total	33 (1.68)	17 (0.86)	4	50 (2.54)	1968
Haemophilia 'B' NHS IX	4 (1.34)	1	0	4** (1.34)	298
Von Willebrands Hemofil	1 (0.42)	0	0	1 (0.42)	237
Secondary Cases	0	1	0	1	
Deaths	None				

* ( ) = % total patients transfused.

** One double attack hepatitis Non-B followed by hepatitis B. Two household contacts patients contracting Non-B Hepatitis also had recently developed Non-B hepatitis. Both, however, had recently been transfused with Commercial VIII concentrate.

Other categories see attached sheet (Table B).

TABLE B

OTHER CATEGORIES (NOT INCLUDED IN CALCULATION OF ATTACK RATE)

Chronic Hepatitis		1
Hepatitis Type Unknown) Related to Blood Products)		1
Glandular Fever		0
Hepatitis A		0
Hepatitis not due to Blood Products	Non-B	1
	Hep-B	0
Symptomless Non-B		1
Abnormal LFT's not Related to Hepatitis		1

Total Cases of Hepatitis like Illness = 66
(Including symptomless cases)

TABLE C

FACTOR VIII ASSOCIATED HEPATITIS - 1977 PATIENTS TREATED WITH ONLY ONE BRAND OF CONCENTRATE

Patient Diagnosis and Material Received	Cases of Hepatitis				Total Patients Treated with One Product
	Non-B (Overt Only)	B Overt	B Symptomless	Total Overt Only	
Haemophilia 'A'					
NHS Elstree	1 (0.93)	4 (3.73)	0	5 (4.67)	107
Oxford	0	0	0	0	39
Edinburgh	0	0	0	0	33
Cryoprecipitate	2 (0.39)	1 (0.19)	0	3 (0.58)	514
Commercial Hemofil	2 (3.70)	0	0	2 (3.70)	54
Factorate	1 (5.88)	2 (11.76)	0	3 (17.64)	17
Profilate	0	0	0	0	0
Koate	0	0	0	0	12
Kryobulin	0	0	0	0	29
Total	6 (0.74)	7 (0.86)	0	13 (1.61)	805
Total NHS Concentrate	1 (0.56)	4 (2.23)	0	5 (2.79)	179
Commercial Concentrate) All Brands)	3 (2.67)	2 (1.78)	0	5 (4.46)	112
Ratio Commercial /NHS	4.76	0.79			

TABLE D

FACTOR VIII AND IX ASSOCIATED HEPATITIS 1978

Patient Diagnosis and Material Received	Cases of Hepatitis				Total Patients Transfused
	Non-B (Overt Only)	B Overt	B Symptomless	Total Overt Only	
Haemophilia 'A'					
NHS Elstree	7 (0.69)	2 (0.19)	0	9 (0.81)	1011
Oxford	0	0	0	0	201
Edinburgh	0	0	0	0	121
Cryoprecipitate	3 (0.26)	0	0	3 (0.26)	1120
Commercial					
Hemofil	5 (1.29)	0	0	5 (1.29)	386
Factorate	8 (1.33)	4 (1.03)	2	12 (2.00)	599
Profilate	2 (2.77)	0	0	2 (2.77)	72
Koate	3 (1.17)	0	0	3 (1.17)	255
Kryobulin	3 (1.71)	0	0	3 (1.71)	175
Commercial Unspecified	2	2	5	4	Not available
Total	34 (1.66)	8 (0.39)	7	42 (2.01)	2039
Haemophilia 'B' NHS IX	2 (0.68)	0	0	2 (0.68)	294
Secondary Cases	0	2	0	2	
Deaths	None				

Other categories see attached sheet (Table E)

TABLE E

OTHER CATEGORIES (NOT INCLUDED IN CALCULATION OF ATTACK RATE)

Chronic Hepatitis		2
Hepatitis Type Unknown) Related to Blood Products)		3
Glandular Fever		0
Hepatitis A		2
Hepatitis Unrelated to Blood Products	Non-B	0
	B	1 + 1 Symptomless
Symptomless Non-B		1
Abnormal LFT's not) Related to Hepatitis)		0

TABLE F

FACTOR VIII ASSOCIATED HEPATITIS 1978 - PATIENTS TREATED WITH ONLY ONE BRAND OF CONCENTRATE

Patient Diagnosis and Material Received	Cases of Hepatitis				Total Patients Treated with only One Product
	Non-B (Overt Only)	B Overt	B Symptomless	Total Overt Only	
Haemophilia 'A'					
NHS VIII Elstree	1 (0.47)	2 (0.94)	0	3 (1.41)	212
Oxford	0	0	0	0	78
Edinburgh	0	0	0	0	28
Cryoprecipitate	3 (0.73)	0	0	3 (0.72)	414
Commercial					
Hemofil	3 (4.76)	0	0	3 (4.76)	64
Factorate	4 (5.79)	1 (1.44)	0	5 (7.24)	70
Profilate	2 (66.0)	0	0	2 (66.0)	3
Koate	2 (25.0)	0	0	2 (25.0)	16
Kryobulin	3 (10.34)	0	0	3 (10.34)	29
Total	19 (2.04)	3 (0.33)	0	22	930
Total NHS Concentrate	1 (0.31)	2 (0.63)	0	3 (0.96)	318
Commercial (All Brands)	14 (7.7)	1 (0.5)	0	15 (8.3)	180
Ratio Commercial/NHS	19.7	0.79			

TABLE G

FACTOR VIII AND IX ASSOCIATED HEPATITIS 1979

Patient Diagnosis and Material Received	Cases of Hepatitis				Total Patients Transfused
	Non-B Overt Only	B Overt	B Symptomless	Total Overt Only	
Haemophilia 'A'					
NHS Elstree	3 (0.30)	0	0	3 (0.30)	973
Oxford	0	0	0	0	174
Edinburgh	1 (0.57)	0	0	1 (0.57)	105
Cryoprecipitate	2 (0.22)	0	0	2 (0.22)	895
Commercial					
Hemofil	5 (1.34)	0	0	5 (1.34)	373
Factorate	10 (1.49)	2 (0.30)	3	12 (1.78)	672
Profilate	2 (2.46)	0	0	2 (2.46)	81
Koate	2 (0.39)	0	0	2 (0.39)	215
Kryobulin	2 (0.84)	1 (0.42)	1	3 (1.26)	237
Commercial Product Not Specified	2	0	1	2	Not Available
NHS and Kryobulin	0	1	0	1	" "
Total	29 (1.49)	4 (0.20)	5	33 (1.7)	1935
Haemophilia 'B' NHS IX	1 (0.34)	1 (0.34)	1	1 (0.34)*	286
Secondary Cases	0	1	1	1	
Deaths	1 (Death related to subacute or early chronic hepatitis)				

* One case of Non-B followed by hepatitis B.

Other categories see attached sheet (Table H)

TABLE H

OTHER CATEGORIES (NOT INCLUDED IN THE CALCULATION OF ATTACK RATES)

Chronic Hepatitis	2
Hepatitis type unknown) Related to Blood Products)	3
Glandular Fever	1
Hepatitis A	0
Hepatitis Unrelated to Non-B) Blood Products B)	0 0
Symptomless Non-B	2
Abnormal LFT's not related to Hepatitis	1

Total Cases of Hepatitis-like Illness = 53
(Including Symptomless Cases)

TABLE I (Appendix I)

FACTOR VIII ASSOCIATED HEPATITIS 1979 - PATIENTS TREATED WITH ONLY ONE BRAND OF CONCENTRATE

Patient Diagnosis and Material Received	Cases of Hepatitis				Total Patients Treated with One Product
	Non-B (Overt Only)	B Overt	B Symptomless	Total Overt Only	
Haemophilia 'A'					
NHS Elstree	1 (0.44)	0	0	1 (0.44)	227
Oxford	0	0	0	0	85
Edinburgh	0	0	0	0	30
Cryoprecipitate	2 (0.53)	0	0	2 (0.53)	371
Commercial					
Hemofil	2 (5.40)	0	0	2 (5.40)	37
Factorate	3 (3.61)	0	0	3 (3.61)	83
Profilate	2 (66.0)	0	0	2 (66.0)	3
Koate	1 (6.25)	0	0	1 (6.25)	16
Kryobulin	2 (10.52)	1 (5.26)	1	3 (15.78)	19
Total	13 (1.48)	1 (0.11)	1	15 (1.71)	874
Total NHS Concentrate	1 (0.29)	0	0	1 (6.29)	342
Commercial All Brands	10 (6.32)	1 (0.63)	0	11 (6.96)	158
Ratio Commercial/NHS	21.73	0			

APPENDIX II

Chronic Liver disease in Haemophiliacs - November, 1980

Hepatitis and liver dysfunction is now a recognized complication of therapy with blood products particularly coagulation factor concentrates which are usually made from pooled plasma from a large number of donors and administered at frequent intervals or for a long time. As prospective studies in non-haemophiliacs indicate that about 5% of patients with acute type B, and 20-30% Non-A, non-B hepatitis develop chronic hepatitis and as other studies show that more than three quarters of the haemophilic population is positive for anti-HB_s, it is quite likely that a large proportion of haemophiliacs will develop chronic hepatitis associated with non-A non-B hepatitis. In 1975 Mannucci et al were first to show that 45% of their patients had raised transaminase levels. Since then many reports have been published confirming their findings and liver biopsy studies in haemophiliacs have also shown a large proportion of abnormal serum enzyme levels in non-symptomatic haemophiliacs (Lesesne et al, 1977). It was decided to study haemophiliacs attending the Oxford Haemophilia Centre to find out the incidence of clinical and biochemical abnormalities, frequency of different viral antigens and antibodies related to liver disease, and also to look at other possible causes of chronic liver disease in haemophiliacs.

According to the agreed protocol of the Haemophilia Centre Directors Hepatitis Working Party, 180 patients with severe haemophilia A have been studied. The patients were given a general physical examination with particular attention to signs associated with liver disease and a medical history was taken regarding their general health and symptoms associated with chronic liver disease. Blood samples were collected at intervals of 3 to 6 months for liver function tests, HB_sAg, anti-HB_s; hepatitis 'A' virus antibody (anti-HAV) and other viral studies.

The results of the medical history, physical examination and liver function tests were analysed. On the basis of the liver function tests the patients were divided into two broad groups. The first group consisted of those with completely normal liver function tests and those showing occasional abnormal levels which in most cases can be attributed to an haematoma or other bleeding episode. The second group showed more persistent abnormalities lasting for more than six months. The last group are probably cases of chronic hepatitis and are being followed up by Dr. Trowell at the Liver Clinic.

Results

In spite of multiple transfusions and large numbers of grossly abnormal liver function tests, very few patients showed any stigmata of chronic liver disease. The most significant clinical finding was a palpable spleen (8%), other signs like spider nevi and gynaecomastia were rare (only 5 and 1 cases respectively). Total protein was raised in more than 10% of the cases, but the albumin globulin ratios was raised in 10 cases.

As discussed earlier, depending on the liver function (particularly AST) it is possible to divide the haemophiliacs into two groups but there is a steady 'flow' of patients from one group to the other, when they are observed over a period of time, though there was little change in total number (Table 1). In the last year, 10 patients of group one have converted to group two and 7 of group two have converted to group one. The second group was investigated in slightly more detail including serum immunoglobulins and BSP retention. 20% of this group showed raised IgG compared to 5% in the first group. The cases of raised IgM were more evenly distributed between the two groups (25%). About 50% of the second group showed abnormal BSP retention.

During the period of the study (March 1978 to August 1980) 8 of these patients developed acute hepatitis (4%) and only 2 of these (25%) were HB_sAg positive. In 7 out of 8 cases the liver function tests rapidly returned to normal levels. The eighth patient required treatment with corticosteroids for persistently abnormal liver function and symptoms suggestive of chronic liver disease.

110 out of 126 patients studied had evidence of past infection with hepatitis B (87.3%) as evident by detectable amounts of anti-HB_s. Prevalence of anti-HB_s positive cases increased from 77% (10 out of 13 tested) in 6-10 year age group to 86% in the 31-40 years age group 18-21 (fig. 1) though these differences were not statistically significant. There was no relation between the level of anti-HB_s and abnormal liver function tests. The patients treated with different types of factor VIII (NHS or commercial) showed no significant differences in the prevalence of anti-HB_s nor did they show any difference in the proportion of patients with abnormal liver function tests, but anti-HB_s ratio showed an inverse relation with the time interval between the last doses of factor VIII and the day on which the blood sample was collected (fig. 2). The factors affecting this result have already been considered in the main report (page 5). Only three of these patients were positive for HB_sAg.

The results of tests for hepatitis A antibody by radioimmuno assay on 124 patients showed that 26 of them or 21.0% were positive (a ratio of >2.5 in the HAVAB RIA test)* The prevalence of anti-HAV related to the age of patients is given in Table 2. An unexpected finding was the age distribution. These results are being further investigated.

Study of serum bile acid level as an index of abnormal liver function

Since the introduction of radioimmuno assay of bile acids it has been suggested that bile acid measurements may be sensitive index of liver function and hence may be an early indicator of chronic liver disease. As a pilot project, fasting blood

* HAVAB radioimmunoassay test for hepatitis A antibody - Abbott Laboratories Ltd.

samples were collected from 16 haemophiliacs who had not had a bleeding episode for at least 7 days and were tested for serum cholate and chenodeoxycholate levels. Other liver function tests were also performed on the same day. The results showed no relationship between serum bile acid levels and other liver function tests (Table 3).

Study of transaminase level following infusion with factor VIII concentrate

It has been suggested that factor VIII concentrates may contain some hepatotoxic material and that when transfused in large amounts and at frequent intervals may raise serum transaminase levels. To study this possibility five haemophiliacs with normal transaminases level were transfused with factor VIII concentrate, enough to raise the factor VIII level between 50 and 70% of normal and then the liver function tests were followed at regular intervals for 7 days to detect any change, but none of these five patients showed any significant change in transaminase levels or any other liver function tests following transfusion.

Study of hepatitis in the relatives of haemophiliacs

Following reports from other Centres of a few cases of overt hepatitis B among the relatives of haemophiliacs, particularly among those who administer factor VIII concentrate, it was decided to test the relatives of haemophiliacs, who administer concentrate during home treatment for evidence of liver dysfunction and hepatitis A and B serology. Of a total of 20 such relatives tested, 19 of them had normal liver functions and 10/10 tested were negative for anti-HB_s. The other relative who showed a high AST and ALT and a negative anti-HB_s test, was in fact a carrier of the haemophilia gene and had been treated with factor VIII concentrate in the past during an operative procedure. A study has been started to determine the incidence of HB_sAg and anti-HB_s among the spouses of haemophiliacs. This problem was also discussed in the main report (section 6e, page 9).

Mild haemophiliacs and hepatitis

The attack rate of hepatitis with a particular batch of concentrate is higher in mild haemophiliacs than in severe haemophiliacs. This is related to the frequency of past treatment with blood products. Our observations suggest that chronic hepatitis may be preceded by both overt and symptomless hepatitis. The incidence of subclinical hepatitis associated with first transfusions of concentrate is at present unknown. So it has been decided to check all mild haemophiliacs, who are receiving factor VIII concentrate for the first time, at monthly intervals for at least 6 months for liver function, HB_sAg and anti-HB_s. A further request for financial support will be submitted to the small grants committee for this project in the near future.

REFERENCES

1. Mannucci, P.M., Capitanio A., Del Nimmo E, et al., Asymptomatic liver disease in haemophiliacs. J. Clin. Pathol. 28, 620-624, 1975.

2. Lesesne, H.R., Morgan J.E. et al., Liver biopsy in Haemophilia A, Am. Internal Med. 86, 703-707, 1975.

TABLE 1 (Appendix II)

Changes in liver function tests in Oxford patients on regular treatment with Factor VIII or Factor IX concentrate between 1978-79 and 1979-80

	Haemophilia A		Christmas disease patients (1980
	1978-79	1979-80	
*Group 1	41 (23.6)**	44 (29.7)	4 (25)
Group 2	63 (36.2)	51 (34.5)	5 (31)
Group 3	47 (27.0)	31 (21)	5 (31)
Group 4	23 (13.2)	22 (14.8)	2 (13)
Total number of patients	174	148	16

* Group 1 = AST level always normal
Group 2 = AST level occasionally abnormal
Group 3 = AST level persistently abnormal (between 35 (upper limit of normal) and 70 i.u./l)
Group 4 = AST level persistently abnormal (more than 70 i.u./l)

** ( ) = % total number on regular treatment.

TABLE 2 (Appendix II)

HEPATITIS A ANTIBODY

AGE RELATED PREVALENCE IN OXFORD HAEMOPHILIA 'A' PATIENTS TREATED WITH FACTOR VIII CONCENTRATE

	Age - Years	<5	6-10	11-20	21-30	31-40	40+	Total
RIA test for Hepatitis A antibody (HAVAB)	No. Positive* / Total	0/1	0/17	3/35	4/31	6/20	13/20	26/124
	Per cent	0	0	8.6	12.9	30	65	21.0

* A positive result in this survey was considered to be a ratio of $\frac{\text{counts in test serum}}{\text{counts in negative control}}$ of >2.5

Values lower than this were considered to be due to passively transfused antibody (1.0 - 2.5) or negative (<1.0).

TABLE 3 (Appendix II

Patient No.	Cholate nMol/l	Chenodoxycholate nMol/l	Liver function (AST) 6 months preceding the sample	Anti HB_sAg level	Jaundice	Remarks
1	1.2	0.6	Always < 35 i.u.	Not tested	Nil	
2	0.9	0.6	" > 70 i.u.	Not tested	Nil	
3	3.6	0.8	" < 35 i.u.	177	Nil	
4	1.4	0.6	" > 70 i.u.	144	Nil	
5	1.6	0.6	Occasionally > 35 i.u.	172	Nil	
6	1.1	0.5	" > 35 i.u.	170	1968 (haemolytic)	
7	3.2	1.9	Always abnormal but < 70 i.u.	24	1969 1974 - Non B	
8	5.0	0.6	" < 35 i.u.	175	Nil	
9	4.6	0.7	" < 35 i.u.	Not tested	Nil	
10	4.4	1.1	" > 70 i.u.	11	1974 - B	
11	3.6	4.4	" < 35 i.u.	1	Nil	HB_sAg carrier
12	3.6	3.1	" abnormal but < 70 i.u.	97	1978?	
13	1.2	0.7	?	Not tested	Nil	
14	1.0	0.6	" < 35 i.u.	Not tested	Nil	
15	4.8	0.9	Occasionally > 35 i.u.	129	Nil	
16	13.1	14.9	" > 35 i.u.	213	1974 - Non B	
Normal range	0.2-3.2	0.2-2.9	0-35 i.u.	0-20		

Fig. 1. ANTI-Rbs ANTIBODY. CORRELATED TO THE AGE OF PATIENTS

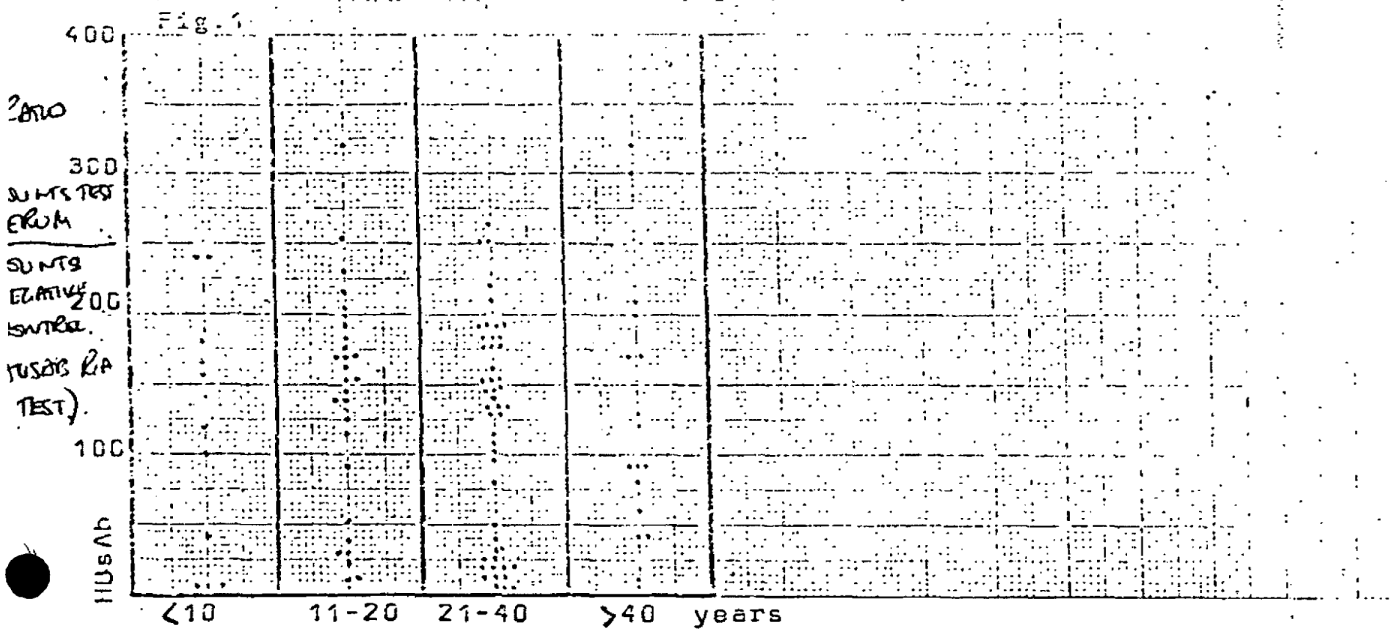


Fig. 2.

HBs Ab level in relation to last dose of factor VIII