APPENDIX C

U.K. HAEMOPHILLIA HEPATITIS WORKING PARTY

ANNUAL REPORT FOR THE YEAR 1982-3. THE COMMITTEE HAS MET THREE TIMES DURING THE YEAR. SUBJECTS CONSIDERED WERE:

a) Prospective studies of hepatitis in mildly affected haemophiliacs.

b) Evaluation of the infectivity of heat treated factor VIII or IX using a protocol based on the prospective studies described in (a)

c) Hepatitis Surveillance. Details of the years 1980 and 1981 and preliminary figures for 1982 are available.

In addition, work has been started on putting all the past patient data from the 1974-6 survey of Hemofil and Kryobulin associated hepatitis on the Regional Computer of the Oxford Regional Health Authority.

d) Hepatitis B vaccine.

e) The Acquired Immune Deficiency Syndrome.

A surveillance system for the reporting of cases was set up. Two cases have so far been reported in the U.K. which conform to the CDC criteria. This subject will be considered separately at the meeting.

a) Prospective studies of hepatitis in infrequently treated haemophiliacs

This study was started at Oxford in 1981 and the first 30 patients followed after 1 transfusion of factor VIII concentrate for at least 6 months are described in a paper which will shortly appear in the British Medical Journal. Of the 30 studies, 4 patients were excluded because they had evidence of chronic liver disease, 2 patients received cryoprecipitate and did not develop hepatitis. Of the remaining 24, 17 patients contracted non-A, non-B hepatitis, 9 after their first transfusion of factor VIII concentrate. Seven of these were after transfusion of one batch of NHS factor VIII with a pool size of between 1,200 and 2,600 plasma donations (mean 1,600). This interesting result confirms that the risk of contracting non-A, non-B hepatitis is 100% on first exposure, whether NHS or commercial factor VIII. All 5 patients treated with U.S. commercial factor VIII contracted hepatitis whether or not they had previously received factor VIII. No cases of hepatitis B were observed, although 12 patients had evidence of past hepatitis B. The incubation period of the non-A, non-B hepatitis varied from 1 - 12 weeks.

Of the patients who had hepatitis, 12 have been followed for at least 1 year and 4 of these have evidence of continuing liver disease.

b) Evaluation of the infectivity of heat treated factor VIII using a protocol based on the prospective study, since no tests for non-A, non-B hepatitis are yet available.

The recent development of new preparations of factor VIII where attempts have been made to reduce the contamination of preparations by hepatitis viruses by heat treatment has made it necessary to devise protocols for the evaluation of the residual infectivity of these preparations, since no tests of infectivity are available for non-A, non-B hepatitis viruses. A protocol drawn up by the

Working Party based on the experience of the prospective study was circulated to interested Haemophilia Centre Directors. It was hoped that a sufficient number of patients with no previous treatment with concentrate would be identified, so that formal trials could be conducted as part of collaborative evaluation of each product on the basis of exemption from a clinical trial certificate.

An internationally based trial was started with the Travenol product, and an Armour product will be available for evaluation in the next 3 months. However, the problem of AIDS has overshadowed these developments, as the ethical problem of exposing mild haemophiliacs to commercial material must be considered by each Director.

This is summarised in the enclosed discussion paper (Appendix C(i)).

c) Hepatitis Surveillance. See attached Appendix C(ii).

d) Hepatitis B vaccine

This has been shown to be immunogenic in haemophiliacs, and results of the Oxford trial are being analysed. However, problems of possible contamination of the course plasma by a putative AIDS related agent has complicated this situation. WHO recently reviewed the situation and has recommended that any vaccine derived from human plasma should include at least 2 inactivation steps, one of which should be exposure to formalin. The only vaccine which fulfills these criteria is the Merck, Sharp and Dohme vaccine, the only vaccine licensed in the U.K.

A formal follow-up of subjects who took part in the 1978 New York trial of the Merck vaccine is in progress. While there is no evidence of risk to persons who received the vaccine in the New York trial, it would be wise to exercise caution in the use of vaccine until the formal follow-up period is completed. The theoretical risk of AIDS must be balanced against the risk of contracting hepatitis B.

Recommendations regarding the use of hepatitis vaccine in Haemophilia Centres is given in Appendix C(iii).

J. Craske
Chairman, U.K. Haemophilia Centre Directors Hepatitis Working Party

28.9.83

APPENDIX C(i)

U.K. HAEMOPHILIA CENTRE DIRECTORS HEPATITIS WORKING PARTY

Factors to be considered in the Selection of Hepatitis Reduced Products for Clinical Trial - Evaluation of residual infectivity for Hepatitis Viruses

Several manufacturers will shortly be in a position to offer trial batches for evaluation of their residual infectivity according to the trial protocols recently considered by the Reference Centre Directors and circulated to all Directors.

These products seem to be of 3 types:-

1) The freeze dried product is heated in the presence of compounds (e.g., sucrose) which stabilise the factor VIII activity, but reduce the quantity of infective virus in the product by pasteurisation. Heat inactivation is applied to the point where there is no sifnificant loss of factor VIII coagulent activity. The temperature is usually 60°C , the exact conditions are a commercial secret, but the heat is known to be applied after the freeze drying process.

Two such products are:-

(i) Hemofil T (Exception from Clinical Trial Certificate obtained) - trial now underway

(ii) Factorate HT - available in 3 months

2) The plasma is treated with chemicals (e.g., β-propiolactone + U.V. light in the presence of detergent) or (Tween 80) which render the viruses uninfective while preserving the coagulent activity. The products involved are:-

Factor VIII manufactured by BIOTEST in West Germany - no plans are likely to involve trials of this product in the U.K. There is about a 25% loss of factor VIII activity.

Kryobulin (Immuno) - still under development; available later this year?

3) The product is pasteurised by heating at 60°C in the presence of stabilisers for factor VIII, but this is done under conditions where hepatitis B virus may be inactivated. The strains of non-A, non-B hepatitis virus which are used experimentally in chimpanzees have been found to be more heat labile than hepatitis B and are assumed to be destroyed by this process. Unfortunately this reduces the factor VIII activity by 50% and this means that the product price would be high (? 40p per factor VIII unit).

Behringwerke A.G., manufacturers of Germany have developed such a product which has undergone clinical trial in Germany. It is unlikely that they would consider applying for a British product licence unless an approach was made to them. Since their unheated product is not marketed here this may take some time.

Hemofil T is at present available for clinical trial. An exception for a Clinical Trial Certificate was granted by the British Licensing Authority on 1.6.83.

Factorate HT will be available within 3 months, and presumably exception for a Clinical Trial Certificate will be obtained in due course.

Opinion i) The degree of heat treatment received by both American products may lessen the infection risk for non-A, non-B hepatitis viruses, but by what degree can only be ascertained by clinical trial in human subjects.

It is unlikely that the hepatitis B virus infection will be significantly affected by the heat treatments used in the above products. Hepatitis B vaccine will have to be used to eliminate this risk.

ii) Both the German products from Behringwerke and Biotest seem to be likely to have a significant reduction of their contamination rates with hepatitis B and non-A, non-B viruses, but the significant loss of factor VIII activity will increase the price of this product and might produce shortages of supply if the demand was high. Thirty-one batches have been used in a clinical trial with, so far, no cases of hepatitis. However, details of the precise classes of patient studied are not yet available.

iii) The Acquired Immune Deficiency Syndrome (AIDS) and transfusions of factor VIII. So far 16 cases of this syndrome which fit the criteria used by the Centre for Disease Control (CDC) Atlanta, Georgia, have been reported in the U.S.A. Five cases have been reported from Europe. This includes the suspect case notified to me recently in the U.K. Though the incidence in U.S. haemophiliacs is low (1 case per 1,500 persons at risk) and there is, as yet, no hard evidence relating specific products or batches to particular cases, the infective theory for the causation of this disease is still the one that fits all the known facts about AIDS.

Consideration must, therefore, be given to the possibility that factor VIII concentrate prepared from plasma donations obtained in the U.S.A. might be contaminated with a putative infectious agent associated with the cause of AIDS.

Since there is no information as to the physical characteristics of such an agent, the materials used to reduce the risk of transfusion hepatitis, such as heat treatment, cannot be relied upon to render factor VIII concentrate manufactured from the same plasma free from such an agent. The only product which may be free from the risk, and is made from U.S. commercial plasma, is the Merck, Sharp and Dohme hepatitis B vaccine and this is treated with formalin, pepsin at pH2 and 8 molar urea. All the commercial heat treated products and the Biotest brand of factor VIII are made in part from plasma obtained from commercial sources in the U.S.A. There is, as yet, no product which is not made from sources likely to carry a risk of a putative virus associated with AIDS being present in the plasma pool from which the factor VIII is fractionated and which is heat treated.

This will cause a problem when the criteria for clinical trials of these products in the U.K. have to be considered. Since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B hepatitis.

There is, therefore, a considerable ethical problem when considering the evaluation of the new heat treated products for their residual infectivity in clinical trials in patients infrequently treated with factor VIII who have no prior exposure to freeze dried concentrate.

It is to be hoped that a hepatitis reduced product will be available from NHS sources before long.

J. Craske
Chairman, U.K. Haemophilia Centre
Directors Hepatitis Working Party

11.7.83.

APPENDIX C(ii)

Incidence of Acute Hepatitis in Patients with Congenital Coagulation Defects Treated by U.K. Haemophilia Centres During 1980-82

The attached tables show the preliminary results of analysing the information received from Haemophilia Centres regarding patients treated during 1980-1982. Five Haemophilia A patients had 2 attacks of hepatitis during a treatment year and one carrier of Christmas disease is thought to have had 3 attacks, one not related to treatment. These cases are being investigated further. Seven additional cases of suspected hepatitis were reported to us; 4 of these cases were of hepatitis which was not related to treatment with blood products and 3 were jaundiced patients who had some illness other than hepatitis. Further analysis of the data is underway and we hope to be able to give a more detailed report at the next meeting.

J. Craske
Rosemary J.D. Spooner
Oxford Haemophilia Centre.

5th October, 1983.

Table 1

Cases of Acute Hepatitis Reported by Haemophilia Centre Directors in 1980-82

Coagulation Defect	Treatment year	Total number of Patients treated in the year with blood products	Hepatitis Type and Number of Cases*					Patients who developed acute hepatitis	
			A	B	Non-A/B	Not yet** classified	Total	Number***	% Total treated
Haem. A	1980	2,139	-	12(6)	41(4)	1	54(10)	51	2.38
	1981	2,230	-	15(7)	27(5)	4(3)	46(15)	46	2.06
	1982	2,247	-	19(9)	40(4)	7(3)	66(16)	64	2.85
Haem. B	1980	357	-	-	2	-	2	2	0.56
	1981	368	-	2(1)	3(1)	2	7(2)	7	1.90
	1982	384	1	1	3(1)	-	5(1)	5	1.30
Von Willebrands	1980	246	-	1	9	-	10	10	4.07
	1981	286	-	1	7	-	8	8	2.80
	1982	270	-	1	4	2	7	7	2.59
Haem. A Carriers	1980	27	-	-	-	-	Nil	Nil	-
	1981	42	-	-	1	1	2	2	4.76
	1982	34	-	-	1	1	2	2	5.88
Haem. B Carriers	1980	12	-	-	-	-	Nil	Nil	-
	1981	9	-	-	-	-	Nil	Nil	-
	1982	11	-	-	2	1(1)	3(1)	2	18.18
Total for the 3-years		4,060	1	52(23)	140(15)	19(7)	212(45)	206	5.07
% Total Hepatitis cases		-	0.47	24.53	66.04	8.96	100	-	-

*Figure in brackets () = number of asymptomatic cases

**Cases still under investigation

*** Figures adjusted to allow for patients who had more than one acute attack of hepatitis in the year.

Table 2

Number of Haem. A Patients Treated with only One Type of Therapeutic Material in any one year and the number of these patients who developed Hepatitis

Material Type	Treatment Year	No. Patients treated in year with only the one type of material	No. of Cases of Hepatitis*				Haem. A Patients who had Hepatitis	
			Hep. A	Hep. B	Non-A/B Hep.	Total No. Cases	No.	% of treated patients
Armour (Factorate)	1980	121	-	2(1)	2(1)	4(2)	4	3.31
	1981	147	-	2	3(1)	5	5	3.40
	1982	154	-	2(1)	1(1)	3(2)	3	1.95
Hyland (Hemofil)	1980	53	-	1	2(2)	3(2)	2**	3.78
	1981	35	-	-	1	1	1	2.86
	1982	53	-	-	1	1	1	1.89
Cutters (Koate)	1980	29	-	-	3(2)	3	3	10.34
	1981	20	-	-	2	2	2	10.00
	1982	45	-	-	3(2)	3(2)	3	6.67
Immuno (Kryobulin)	1980	46	-	-	3(1)	3(1)	3	6.52
	1981	41	-	-	2	2	2	4.88
	1982	31	-	1	-	-	1	3.23
Speywood (Humanate)	1980	2	-	-	-	-	Nil	0
	1981	6	-	-	1(1)	1(1)	1	16.67
	1982	0	-	-	-	-	Nil	0
NHS Conc. - Elstree	1980	150	-	4	3(1)	7(1)	6**	4.00
	1981	270	-	5	3(2)	8(2)	8	2.96
	1982	259	-	2(1)	6(2)	8(3)	7**	2.70
NHS Conc. - Oxford	1980	76	-	-	1	1	1	1.32
	1981	111	-	-	6(3)	6(3)	6	5.41
	1982	72	-	-	3(1)	3(1)	3	4.17
NHS Conc. - Edin.	1980	46	-	-	-	-	Nil	0
	1981	54	-	-	1	1	1	1.85
	1982	75	-	-	-	-	Nil	0

(cont.

Table 2 (cont.)

Material Type	Treatment Year	No. Patients treated in year with only the one type of material	No. of Cases of Hepatitis *				Haem. A Patients who had Hepatitis	
			Hep. A	Hep. B	Non-A/B Hep.	Total No. Cases	No.	% of treated patients
Cryoprecipitate	1980	361	-	-	1	1	1	0.28
	1981	355	-	-	-	-	Nil	0
	1982	305	-	-	1	-	1	0.33

*Figure in brackets () = number of patients who had not previously received treatment with concentrates

**1 Patient had 2 acute episodes (Non-A/B hepatitis, followed by B).