

AGENDA FOR MEETING OF HAEMOPHILIA CENTRE DIRECTORS TO BE HELD

at OXFORD HAEMOPHILIA CENTRE

on MONDAY, 5TH APRIL, 1971

Chairman:

1. Opening address:
2. Apologies
3. Report on the progress of the MRC Cryoprecipitate Working Party Survey of the Incidence of Transfusion Jaundice and the Incidence of Inhibitors in Haemophilic and Christmas Disease Patients (see Appendix 1)
4. Hepatitis and Australia Antigen
5. Management of patients with inhibitors
6. Factor-IX Concentrate.
7. Availability and use of factor-VIII concentrates and cryoprecipitate

LUNCH TIME

8. Classification, organization and financing of Haemophilia Centres
9. Assays: methods, standardization and automation.
10. Management of major surgery
11. Report on the EACA trial from Oxford and Cardiff (see Appendix 2)
12. Prophylactic Therapy and Home Treatment
13. Social, education and economic problems of haemophiliacs
14. A.Q.B.
15. Chairman's concluding remarks

Morning Coffee at 10.30    Lunch at 1.00    Afternoon tea at 3.30

APPENDIA 1JAUNDICE AND FACTOR-VIII ANTIBODIES IN TREATED PATIENTS  
WITH HAEMOPHILIA AND CHRISTMAS DISEASE

At a meeting of the Directors of the 36 Haemophilia Centres of Great Britain held in 1967 it was decided to make a study of the incidence of transfusion hepatitis and inhibitors, two most alarming complications of treatment of patients with coagulation defects. Haemophilia and Christmas disease are rare diseases and the above mentioned complications of treatment even rarer and so it was thought that if the experience of our densely populated islands were pooled we might be able to provide valuable information which could never be accumulated by any one Centre anywhere in the world. Special forms were prepared on which to record the varieties and amounts of therapeutic material used and the incidence of inhibitors and jaundice during the years 1969 and 1970. An analysis of the data obtained so far is included in this paper.

Transfusion hepatitis is thought to be a virus infection transmitted to the recipient by the donor plasma. There is every reason to suppose that the virus is contained in the various protein fractions used to treat haemophilia and Christmas disease (cryoprecipitate, human antihaemophilic globulin or HAHG and factor-IX concentrate). The incidence of the virus in the donor population may be of the order of 1 per 1000 (Milno et al 1971).

The danger of infection can be calculated and will be related to the number of donors used to make the material used for treatment or the number of 'donor exposures'. If large pools of plasma are used to make therapeutic concentrates the theoretical danger of infection will be increased. For the study of hepatitis the number of donor exposures was recorded. No attempt was made to record sub clinical hepatitis since the important feature from the point of view of these patients is clinical illness.

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The development of factor-VIII antibody greatly limits the effectiveness of treatment. These antibodies result from immunization of patients for whom factor VIII or factor IX are foreign proteins. It seemed that the most important features in determining the occurrence of antibodies would be genetic susceptibility to being immunized and the amounts and types of therapeutic material used. Both of these features were studied.

### Results

Records were received concerning 943 patients with haemophilia and 123 with Christmas disease who were seen during 1969 at the 30 Centres from which records were returned. The age distribution of these patients is shown in Table 1, and the human plasma protein fractions they received during the year are shown in Table 2. In addition, ten patients received animal AHG concentrates. 34 out of the total of 1066 patients did not receive treatment with plasma, cryoprecipitate, human factor VIII or factor-IX concentrate during 1969.

### Hepatitis

Twenty-nine cases of clinical jaundice in haemophilia and Christmas disease patients were recorded during the year. The main symptoms, severity and outcome of the illness are presented in Table 3. Form 3 has not yet been received for two of the patients. It will be seen that the diagnostic features of the illness were jaundice, pale stools, dark urine, nausea and anorexia. Only about half of the patients complained of abdominal discomfort or vomiting. The incidence of hepatitis was 2.8 per cent. All of the patients who developed jaundice were severely affected haemophilia or Christmas disease patients. Their ages ranged

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from 4 to 65 years. Of the 29 patients who developed clinical hepatitis three (10.3%) died. One of the patients who died was aged 9 years and had received "much cryoprecipitate" at another hospital before being admitted to a Haemophilia Centre with jaundice; the second patient who died was aged 40 and had received 299 donor units of cryoprecipitate and factor-VIII concentrate, giving a risk of exposure to 1250 donors; the third patient was aged 42 and had received 162 donor units of cryoprecipitate.

An analysis of "donor-exposures" of the patients proved rather difficult and confusing. We have made a complete analysis of the data for the Oxford patients and propose to use this as an example. In 1969, 227 patients with haemophilia and Christmas disease were treated in Oxford. 208 of these patients were treated with plasma, cryoprecipitate, human factor VIII and factor-IX concentrates, and the material given to them is summarized in Table 4; the remaining 29 patients did not require, or because of the presence of inhibitors could not be given, infusions of human plasma fractions. It will be seen that the 208 patients received 130,289 "donor-exposures", but in fact our best estimate of the number of blood donations is 15,183. The discrepancy is due to the fact that much of the material was given as concentrate made from large pools of plasma and the batches of these pools were given to several patients. It must be presumed that the patients cannot have received material from more donors than were used, thus presumably a collective estimate of average donor exposures would be:-

$$\frac{15,183}{208} = 72.99 \text{ donor exposures per patient per year ... (1)}$$

On the other hand, viewed from the point of view of the individual, the average figure would be:-

$$\frac{130,289}{208} = 626.38 \text{ donor exposures per patient ..... (2)}$$

Of the 208 patients treated in Oxford, 7 developed jaundice. If each of these 208 patients were exposed to 73 donors at random one would expect about 7.3 per cent of them to have been infected with the hepatitis virus. In fact the incidence was 3.36 per cent, which is not significantly different from the mean of all Centres. Thus the patients considered collectively have proved resistant to infection.

If the individual patient is considered, the donor exposure varied from 4 to 4,000 in the year for the patients treated in Oxford, with a mean of 626, and nearly half of the patients might have been 'expected' to develop hepatitis.

From a detailed study of the 7 Oxford patients who developed jaundice, we have calculated that they had a total risk from exposure to at least 4,482 donors during the 2-6 months prior to becoming jaundiced, the average risk per patient therefore being 640 donor exposures, which is not greater than that of the average patient (see (2) above). When calculated in the same way as the Oxford patients in (1) above, the donor exposure for the patients treated at other Centres during 1969 was:-

$$\frac{70,270}{824} = 85.27 \text{ donor exposures per patient}$$

We have not obtained sufficient information from most of the other Centres to enable us to calculate the donor exposure from the point of view of the individual as in (2) above for these patients.

For the 19 jaundiced patients from other Centres for whom we have information (out of a total of 22 jaundiced patients

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from other Centres), we have calculated that they were exposed to a minimum of 2,134 donors during the 2-6 months prior to becoming jaundiced, giving an average of 112.31 donor exposures per patient, when calculated as in (2) above. When calculated as in (1) above, these 19 patients received 1837 donor units, giving an average of 96.68 units per patient.

The therapeutic materials received by the 29 jaundiced patients in comparison with the average for all patients are shown in Table 5. It will be seen that no one material can be implicated as more likely to cause jaundice.

Other evidence on the incidence of infection is provided by a small study of the incidence of hepatitis associated antigen (HAA) and antibody in Oxford patients. Of 60 patients whose blood was examined, 11 had a positive test for antigen or antibody; of these only 1 developed clinical hepatitis.

Thus the probability of exposure to the virus deduced from incidence in the donor population and the number of donor exposures lies between 7% and 50% and the incidence of virus as indicated by the test for antigen or antibody was about 18%. The actual incidence of 2.8% of illness shows the considerable resistance of these patients to clinical infection.

We have records to date of 13 carriers of haemophilia or Christmas disease who were treated with plasma or concentrated material during 1969 and 1970 (see Table 6) and two of these developed clinical jaundice. Most of these carriers had not previously been treated with infusions and presumably they have the susceptibility to develop jaundice similar to that of the general population.

Although the surveys do not involve large numbers it is likely that the prevalence of hepatitis virus in the materials used to treat haemophilic patients is approximately as expected. The overall low incidence of clinical illness is presumably due to the fact that the patients become immunized in childhood.

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Factor-VIII Antibodies

The danger of developing factor-VIII antibodies may depend on a number of circumstances including genetic susceptibility and the amount and type of therapeutic material used. To clarify this problem two main studies were made, one concerned the development of antibodies in related patients and the other concerned the amount and type of therapeutic material used.

Genetic Study

The first question was to ask how many patients were seen during 1968 at the different Centres and how many of these had factor-VIII antibodies. It was hoped that this information would provide an estimate of the incidence of patients with inhibitor in the haemophilic population. In all 1126 patients were seen in 1968 and of these 61 had antibodies, giving an incidence in the population of 5.47%.

The second question was aimed at finding out the number of haemophilic families with more than one affected member and the number of these patients with antibodies. The results of this survey are given in Table 7. It will be seen that the overall incidence of antibodies in this group was 4.466% (41/919) which is not significantly different from the general survey for 1968 (5.47%).

Of the 369 families studied, 36 had one or more members with antibodies. On average these families had:-

36 x 2.49 members ——— 90 members (89.64)

Of these 90 patients, 36 are propositae and known to have antibodies. These must be subtracted from the total to give 54 patients who were at risk to develop antibodies. Of these, three are known to have antibodies giving an incidence of:-

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$3/54 = 5.5$  per cent

This figure is the same as that for the general population of haemophilic patients and thus does not suggest a familial tendency to develop antibodies. It must of course be noted that the numbers are small even for haemophilia. The figures for patients with Christmas disease were far too small though it may be noted that one family had two members with factor-IX antibodies and these two were the only ones with antibodies recorded.

The Relation Between Material Given for Treatment and the Development of Antibodies

This study concerned patients seen during 1969 for whom records were kept. Of the 943 patients with haemophilia 62 had antibodies to factor VIII and of the 123 Christmas disease patients 3 had antibodies to factor IX. The first piece of information about these patients concerns the date at which the diagnosis was made:-

Diagnosis Prior to 1968	Diagnosis in 1968	Diagnosis in 1969
24	20	18

Of course the techniques for diagnosis of these antibodies is improving and there is no certainty that the patients diagnosed in 1968 and 1969 did not have their antibodies at an earlier date. However as time passes this back log of patients will be eliminated.

The next study concerned the treatment prior to 1969 received by the 62 patients who had antibodies. There were very few patients who had received only one type of material. An analysis of the patients receiving various materials is as follows:-



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Whole Blood	Plasma	Cryoprecipitate	HAHG	Animal AHG
52	58	50	37	22

It will be noted that 22 of these 62 patients had received animal AHG prior to 1969 which is certainly a high proportion if comparison is made with all treated patients (10 patients out of 1066 patients treated during 1969 were given animal AHG concentrate). On the other hand an unknown proportion of the 22 patients received animal AHG because they had antibodies. Of the 10 patients treated with animal AHG concentrate during 1969, 3 patients were given the material because they already had inhibitors and 7 patients were given it to 'cover' operations. One of the 7 surgical patients, who underwent emergency laparotomy, developed an inhibitor while receiving animal AHG concentrate. A separate analysis by Rizza and Eipe (in preparation for publication) of 52 patients known to have received animal AHG in Oxford since 1954 and who were known not to have inhibitors at the time of treatment showed that 8 (15%) of them subsequently developed antibodies. There is thus an increase in the incidence of antibodies in patients treated with animal AHG.

The 18 patients who were diagnosed as having antibodies during 1969 received treatment varying from 0 to 85,750 units of factor VIII during the year before the inhibitor was detected (1 unit is the amount present in 1 ml of fresh plasma). The average amount per patient was 18,600 units. The Oxford patients including all patients with and without inhibitors probably each received on average 13,113 units of factor VIII. Thus the treatment received by patients with antibodies who developed antibody in 1969 seems to have been slightly more than the average for all patients. Of course treatment may have been withheld from many of these patients once the diagnosis of antibody had been made.

It would seem that there is little evidence to connect the development of antibody with any of the things studied.

The Total Amounts of Therapeutic Material Used at the Haemophilia Centres

The total ideal requirements of material for treating patients with coagulation defects is not known. The material used during 1969 to treat a total of 1032 haemophilia and Christmas disease patients at the 30 Centres from whom records were received was derived from 84,906 donors (Table 2). This is certainly an underestimate of requirements. For example at Oxford there is a waiting list of patients requiring non-urgent surgery. It would require material from 10,000 donors to carry out these operations. Moreover the introduction of home treatment would probably increase the amount of material used. A record of this total figure year by year will give an estimate which will level off to the ideal requirements. This figure could form the basis for an estimate of the amount of concentrate that might be required.

Discussion

The clinical value of free and early treatment of haemophilic patients in the saving of life and prevention of crippling is now well established. This treatment is known to carry two main hazards:-

- 1) The transmission of infective hepatitis.
- 2) The development of specific antibodies against coagulation factors.

The data on hepatitis suggest that patients with coagulation defects are very resistant to clinical hepatitis. Hepatitis transmission must be related to the number of 'donor exposures' of the patients. This number will increase with the

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use of dried concentrates made from large pools of donors. These concentrates have advantages in treatment in that the potency is known and they are convenient to make up and administer. The problem in recommending an increased manufacture of these lies in the possible increase in hepatitis and antibodies. From the point of view of clinical hepatitis this danger seems to be small though the high incidence of Australian antigen and antibody in haemophiliacs suggests that they do become infected. We feel that the increased risk of clinical illness is not so great as to overbalance the advantages of the use of concentrates.

The data about the development of antibodies is so far fragmentary and inconclusive. There does not seem to be a large component attributable to genetic predisposition. There is so far no evidence of a steady increase in patients with antibodies. Of the patients seen at Centres in 1968, 5.47% had antibodies and in 1969 the figure was 6.1%, but we have results only for the years 1968 and 1969 and a category for patients prior to this date. There is possibly a slightly higher incidence of antibodies in patients who received animal AHG therapeutically. At present the incidence of inhibitors seems to be between 5% and 6% of all patients.

From the point of view of recording the incidence of inhibitors in the patients in Great Britain this study provides basic information of the greatest importance. As far as we know no other large population of patients has been studied in this way. As the years pass we shall have some indication if the proportion of patients with inhibitors starts to increase.

The choice between different available concentrates is a difficult one. The incidence of jaundice in treated patients must increase with the number of donor exposures and the number of donor exposures must increase using concentrates derived

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from large pools. However the greater reliability, ease of administration, and economy of manufacture are in favour of concentrated materials. Perhaps now that the virus associated Australian antigen can be studied a method will be found to remove the antigen from concentrated materials, though of course its removal may not necessarily remove the virus.

TABLE 1

Age distribution of the 1066 Haemophilia and Christmas disease patients treated at 30 Haemophilia Centres during 1969, showing the number in each age group and this number as a percentage of the total number of patients. The Table also shows the number and percentage of patients in each age group who were jaundiced or had inhibitors during 1969/early 1970.

Age Distribution	Haemophilia and Christmas		Jaundice		Inhibitors	
	Total	%	No.	%	No.	%
0-5	122	11.44	1	0.82	1	2.45
6-10	152	14.25	4	2.63	4	2.63
11-20	303	28.42	11	3.63	20	6.60
21-30	204	19.13	3	1.47	15	7.35
31-40	108	10.13	4	3.70	11	10.18
41-50	69	6.47	4	5.79	2	2.89
51-60	43	5.03	1	2.32	5	11.63
61-70	18	1.68	1	5.55	2	11.11
71+	6	0.56	-	-	-	-
Age not known	41	3.84	-	-	-	-
Total:	1066	-	29		62	
% total No. patients		-		2.8		5.82
Mean age:	21.9					

TABLE 2

Amount of plasma, cryoprecipitate and human factor VIII and factor-IX concentrate used to treat 1032 patients at 30 Haemophilia Centres during 1969

Material	No. of Donor Units	% Total
Plasma	11,435	13.46
Cryoprecipitate	59,715	70.34
Concentrates	13,756	16.20
Total:	84,906	100.00

$\frac{84,906 \text{ units}}{1,032 \text{ patients}} = \text{average of } 82.27 \text{ units per patient}$

TABLE 3

Symptoms suffered by the 29 haemophilia and Christmas disease patients who developed clinical jaundice during 1969/early 1970

<u>Symptom</u>	<u>No. affected</u>
Jaundice	27
Anorexia	22
Nausea	20
Vomiting	15
Abdominal distension	15
Dark urine	27
Pale stools	19
No information	2

TABLE 5

Material used to treat haemophilia and Christmas disease patients during 1969, showing the percentage of patients receiving various types of materials during the year and the percentage of jaundiced patients who received these materials.

Material	% all patients	% jaundiced patients
Plasma only	11.96	7.69
Cryoprecipitate only	43.32	46.15
Concentrates only	7.02	7.69
Plasma and Cryoprecipitate	14.32	15.38
Plasma and Concentrates	8.10	7.59
Cryoprecipitate and Concs.	3.64	7.59
All types	7.79	7.59
Nil	4.50	-



TABLE 6

The age, factor VIII or factor-IX level and therapeutic materials received by carriers of haemophilia or Christmas disease during 1969 and 1970

Patient	Age	Severity	Materials	Doses	Total	
					Donor Units	Donor Exposure
<u>1969</u>						
AL*	30	12% f.VIII	Plasma & Cryo.	24	387	387
EJ	37	20% "	Cryoprecipitate	6	81	81
MM	43	1% "	Plasma & Cryo.	5	11	11
PC	36	22% f.IX	IX conc.	1	12	235
MJ	33	28% "	"	2	20	675
JT	32	6% f.VIII	VIII conc.	1	8	148
JJ	49	48% f.IX	IX conc.	1	8	475
<u>1970</u>						
EO	50	29% f.VIII	VIII conc.	1	12	246
JT*	33	6% "	Cryoprecipitate	4	56	56
JB	10	15% f.IX	IX conc.	11	60	960
DH	56	42% f.VIII	VIII conc.	1	12	271
DR	40	27% "	"	1	24	24
SS	27	45% "	"	4	68	425
Total:				62	759	4,044
Mean donor exposure:						311.07

\*subsequently jaundiced

TABLE 7

Number of families	Total number of patients	Average number of patients per family	No. of patients with inhibitor	
			In one family	In different families
	Haemophilia			
369	919	2.49	6	35
	Christmas Disease			
53	126	2.37	2	-