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Jaundice and Antibodies Directed against Factors VIII and IX in Patients Treated for Haemophilia or Christmas Disease in the United Kingdom

ROSEMARY BIGGS

on behalf of the Directors of 37 Haemophilia Centres in the United Kingdom (see Appendix II)

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SUMMARY. A study has been made of the incidence of jaundice and of antibodies directed against factors VIII and IX in patients treated for haemophilia and Christmas disease at 37 Haemophilia Centres in the United Kingdom during 1969–71. Records of 1837 patients were received and of these, 1625 (88.5%) had haemophilia and 212 (11.5%) had Christmas disease. The incidence of jaundice in all patients for the 3-yr period was 3.48%. The average annual incidence of episodes of jaundice among patients treated in each year was 1.83%. The use of freeze dried concentrate (in comparison to cryoprecipitate) did not cause a dangerous increase in episodes of jaundice. The incidence of antibodies directed against factor VIII was 6–7%. The proportion did not increase over the 3-yr period. There was no evidence of a familial tendency to develop antibodies directed against factor VIII.

In 1967 a meeting was held of the Directors of 32 of the then existing 36 Haemophilia Centres of Great Britain. It was decided to study the incidence among haemophilic and Christmas disease patients of transfusion hepatitis and of antibodies to blood clotting factors VIII and IX for these complications are the most alarming to be associated with the treatment of these patients. Haemophilia is a rare disease and Christmas disease is even rarer, so that the above-mentioned complications of its treatment are rarer still. It was anticipated that if the experience in our densely populated islands were pooled it might provide valuable information, unlikely to be accumulated by any one Centre elsewhere in the world. Special forms were prepared on which to record the varieties and amounts of therapeutic material used and the incidence of jaundice and of antibodies (inhibitors) to coagulation factors during the years 1969, 1970 and 1971. An analysis of the data obtained is presented in this report. In addition to information about hepatitis and factor-VIII antibodies, the survey has given an idea of the amounts of therapeutic materials used per patient, the number and age distribution of patients treated at the Centres and the reasons for which treatment was given.

Transfusion hepatitis is a disease caused by several viruses which may occur in donor plasma. There is every reason to suppose that these viruses may be present in the various protein fractions used to treat haemophilia and Christmas disease (cryoprecipitate, human

Correspondence: Dr Rosemary Biggs, Oxford Haemophilia Centre, Churchill Hospital, Headington, Oxford OX3 7LJ.

antihaemophilic globulin [HAHG] and factor-IX concentrate). The incidence of the Hepatitis B virus in the donor population was of the order of 1 per 800 donations at the time that these observations were made (Wallace *et al*, 1972). Since then the screening of all donors for Hepatitis B antigen has been instituted and the incidence of samples grossly contaminated with Hepatitis B virus is now certainly less. Screening, however, is unlikely to remove all infected samples because more than one virus is involved and because the screening method is not sufficiently sensitive to detect all samples infected with Hepatitis B virus.

The theoretical danger of exposure to infection increases with the number of donations contributing to the doses of treatment material used. For a particular patient the number of donations to which that patient has been exposed (donation-exposure) can be calculated provided that very complete records are kept. In fact, from the returns received, it is not possible to calculate the donation-exposures for all Centres since the batch numbers for concentrates were not given. Details of donation-exposures are available for the Oxford patients, who number about 200 each year. The Oxford patients have therefore been analysed separately in relation to the incidence of jaundice.

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

RESULTS

AGE DISTRIBUTION

Records were received concerning 1837 different patients with haemophilia and Christmas disease treated at the Centres in 1969, 1970 and 1971. The age distribution of the patients on 31 December 1971 is given in Table I. When this is compared with that of the general normal male population it is seen that an abnormally high proportion of the patients are in the 5–30 yr age groups. This may be a true reflection of the age distribution of the patients because some who would have been in the older age groups may have died before modern treatment became available. If this is the case then the number of haemophilic patients is likely to increase as a result of improved survival of patients who are now young. On the other hand, it is possible that a proportion of the older patients do not choose to come to hospital for treatment.

The patients who developed jaundice in the 3-yr period have the same age distribution as all the patients. The patients with antibodies to coagulation factors have a possible small bias towards the older age groups (Table I).

AMOUNTS OF THERAPEUTIC MATERIAL USED

Table II shows the total amounts of material used to treat haemophilic patients in the three years of the survey. The figures are expressed in terms of blood donations, that is the number of donations from which plasma used to make the various products was derived. The increase

TABLE I. Age distribution on 31 December 1971 of haemophilia and Christmas disease patients included in the 1969–71 survey, showing the incidence of antibodies to factors VIII and IX in these patients and the incidence of jaundice, the age grouping of the jaundiced patients being their age at the time they were jaundiced

Age group (yr)	*General male population 1971 (%)*	*Haemophilia*				*Christmas disease*			*Haemophilia and Christmas disease*		
		No. of patients	*%*	*With antibodies*		*No. of patients*	*%*	*No. of patients with antibodies*	*No. of patients*	*No. episodes of jaundice*	*% of treated patients who developed jaundice*
				No. of patients	*%*						
0–4	8.4	91	5.60	3	3	15	7.08	—	106	Nil	—
5–9	8.4	227	13.97	10	10	19	8.96	1	246	4	6.25
10–19	15.0	408	25.16	28	28	55	25.94	3	463	18*	28.13
20–29	14.8	333	20.49	25	25	42	19.81	—	375	9	14.06
30–39	12.2	231	14.22	13	13	33	15.57	—	264	14*	21.87
40–49	12.6	132	8.12	4	4	16	7.55	—	148	11	17.19
50–59	12.0	83	5.10	7	7	12	5.66	—	95	4	6.25
60–69	10.0	43	2.65	4	4	7	3.30	1	50	3	4.69
70+	5.7	19	1.17	1	1	4	1.89	—	23	1	1.56
Unknown	—	41	2.52	1	1	6	2.83	—	47	—	—
Dead	—	17	1.05	4	4	3	1.41	—	20	—	—
Total		1625		100 (6.15%)		212		5 (2.36%)	1837†	64 (3.48%)	

* One patient is reported to have been jaundiced twice during the survey period.

† Of this total, 34 patients were not transfused during the survey period and were thus not exposed to any risk of developing jaundice.

TABLE II. The total amounts of therapeutic material used to treat haemophilia at the Haemophilia Centres from 1969 to 1971

Year of treatment	*No. of Centres making returns*	*No. of patients treated*	*Blood donations used*	
			Total	*Per patient*
1969	36	1014	86045	84.9
1970	33	1005	105531	105.0
1971	35	1100	132743	120.7

in the number of donor units per patient from year to year reflects the increase in material made available at the Centres.

Table III shows the numbers of patients subjected to major surgical procedures and to dental extraction during 1969 and 1970. Information about surgical and dental cases was not collected in 1971. It will be seen that a small and decreasing proportion of the total material is used for these cases. It should be noted that owing to shortage of material a number of major surgical operations have been deferred. Most of the therapeutic material is used to treat patients who have spontaneous bleeding or bleeding following minor trauma.

HEPATITIS

Sixty-two patients with haemophilia or Christmas disease have had 64 episodes of clinical jaundice during the three years of the survey. The main symptoms of the illness are presented in Table IV. It will be seen that the diagnostic features of the illness, in addition to jaundice, were pale stools, dark urine, nausea and anorexia.

The annual incidence of jaundice for the 3-yr period in all Tables but Table I relate to 'patient treatment years'. Year by year at the various Centres many of the same patients are treated. If the annual statistics are to be considered separately it must be assumed that every exposed patient is at risk every year. This annual review of jaundice is obviously important

TABLE III. The material used to treat haemophilia and Christmas disease patients for major surgical operations and dental extractions

	1969	1970
Surgery (returns from 17 Centres)		
No. of cases	44	34
Blood donations used	9986	9278
% Total units used for all episodes of bleeding, including haemarthroses, etc.	10.81	8.13
Dental extractions (returns from 28 Centres)		
No. of cases	173	133
Blood donations used	7201	6610
% Total donor units used for all episodes of bleeding, including haemarthroses, etc.	7.76	5.79

for this small group of multitransfused patients since it will be the criterion by which the effect of donor selection on the infectivity of factor-VIII preparations may be judged. The average annual incidence in the 3-yr period was 1.83% (Table VIII). The incidence of jaundice may also be considered in relation to the total number of different patients treated in the 3-yr period. In this case the incidence was 3.48% of the 1837 patients treated during the three years (Table I). Most of the patients who developed jaundice were severely affected haemophilia or Christmas disease patients whose ages ranged from 8 to 70 yr. Of the patients who developed jaundice during the three years, two (3.2% of those infected) have died of acute hepatic failure.

The calculation of a relationship between jaundice and the materials administered to patients involves the consideration of the long incubation period, the size of pools used to make batches of concentrate, and the total number of donations given to each patient. Concentrates used to treat the much rarer Christmas disease patients are derived from the same blood as that used to treat haemophilic patients. Thus the most useful information about the total amounts of material used and the amount per patient is derived from considering the haemophilic patients separately. The information required to make these calculations is based on treatment given in Oxford (Tables V and VI).

TABLE IV. Symptoms suffered by the 62 haemophilia and Christmas disease patients who developed clinical jaundice during the survey period

Symptom	*No. affected*
Anorexia	41
Nausea	36
Vomiting	20
Abdominal distension	30
Dark urine	45
Pale stools	32
No information	12
No. of patients who had two attacks	2
No. of patients who died of hepatitis	2

The Incubation Period

Since the incubation period of Hepatitis B virus is of the order of 6 weeks to 5 mth, the jaundice developed by a particular patient may be related to material received as long as 5 mth previously. Thus it is not reasonable to relate the incidence of jaundice in a particular year to material given in exactly the same period of time. In the present calculations, materials given, summated from January to December in each year, have been related to cases observed from the beginning of June of one year to the end of May in the next. This is an arbitrary decision but it seemed as reasonable as any other. By this method patients who developed jaundice prior to 31 May 1969 are excluded as are those who became jaundiced after 1 June 1972. Eight patients with jaundice who were observed at the Centres during January–May 1969 and 11 cases during June–December 1972 are thus excluded from the survey.

TABLE V. Material given to haemophilic patients treated in Oxford from 1969 to 1971

Year	*No. of patients*	*Material*	*Donations used for Oxford patients*	*Donation-exposures*	*No. of pools*	*Mean pool size (donations)*
1969	174	Plasma	2768	2768		
		Cryoprecipitate	3252	3252		
		Factor-VIII concentrate	6792*	73951	83	160
1970	166	Plasma	3717	3717		
		Cryoprecipitate	5412	5412		
		Factor-VIII concentrate	8001*	115599	72	192
1971	179	Plasma	1640	1640		
		Cryoprecipitate	8665	8665		
		Factor-VIII concentrate	9891*	153919	80	192

* The donations contributing to pools (no. of pools × mean pool size) is always larger than the donations actually used in Oxford since much of the material was used at other centres.

The Effect of Pool Size

If plasma or cryoprecipitate is used to treat a particular patient then the whole of the plasma or cryoprecipitate from each donation is infused into a single patient. The probability of any single donation being infected will depend on the incidence of hepatitis in the population. The probable number of infected doses included in a period of treatment will be: the number of donations multiplied by the incidence of infected donations. If the incidence of infection is assumed to be 1 in 800 donations (0.00125) and the number of donations used to make plasma and cryoprecipitate to treat haemophilic and Christmas disease patients in Oxford in 1969 was 6319, then the probable number of infected donations would be: $0.00125 \times 6319 = 7.9$. Excluding the unlikely event that one patient might by chance receive two infected doses, it is likely that eight patients would have been exposed to virus as a result of receiving plasma or cryoprecipitate.

TABLE VI. Material used to treat Christmas disease patients in Oxford from 1969 to 1971

Year	*No. of patients*	*Material*	*Donations used for Oxford patients*	*Donation-exposures*	*No. of pools*	*Mean pool size (donations)*
1969	34	Plasma	299	299		
		Factor-IX concentrate	2036*	50052	40	439
1970	36	Plasma	110	110		
		Factor-IX concentrate	4229*	44162	26	384
1971	23	Plasma	20	20		
		Factor-IX concentrate	4169	48138	37	300

* The donations contributing to pools (no. of pools × mean pool size) is always larger than the donations actually used in Oxford since much of the material was used at other Centres.

When batches of material made from large pools are considered the problem is more complex. If, for example, a particular patient receives four infusions, one from each of four batches of dried material, each batch being derived from a pool of 200 donations, then he has been exposed to 4 × 200 different donations of blood and he would be said to have had 800 donation-exposures. Complications arise if the same batches of material are given to other patients. Suppose another patient receives four identical doses from these same batches. This second patient has also had 800 donation-exposures. If the 'exposures' for the two patients are added up then the patients have been exposed to 1600 donations which is absurd since in all only 800 donations contributed to the pools. Thus the donation-exposure cannot be used directly to calculate the probability of the patients being exposed to virus. If the total donation-exposure is known and also the total number of donor units used is known, then it is possible to calculate the number of patients receiving material from each batch. In the simple example given the total number of donation-exposures was 1600, the total donations from which the material was derived was 800, the number of patients receiving material from each batch was 1600/800 = 2 (see also Appendix I).

TABLE VII. Incidence of jaundice in haemophilic and Christmas disease patients treated at Oxford during 1969, 1970 and 1971

Diagnosis	*Year*	*No. of patient-treatment-years*	*Patients probably exposed to virus each year*	*Jaundice*		
				No.	*% of all patients*	*% of patients probably exposed to virus*
Haemophilia	1969	174	107	5	2.87	4.67
	1970	166	115	5	3.01	4.35
	1971	179	121	7	3.91	5.78
Total		519	343	17	3.27	4.96
Christmas disease	1969	34	34	1	2.9	2.9
	1970	36	34	0	0	0
	1971	23	23	2	8.69	8.69
Total		93	91	3	3.23	3.30
Grand total		612	434	20	3.27	4.60

For 1969, the total donation-exposures arising from the use of factor-VIII concentrates for haemophilic patients in Oxford was 73 951 and the donations contributing to the pools were 11 392. Thus according to the above calculation the pools were on average given to 73 951/11 392 = 6.5 patients. This calculation gives a low average for the Oxford patients since a proportion of the material was used in the other Centres. The material from the pools actually used in Oxford was equivalent to 6792 donations. Thus the total number of Oxford patients exposed to each batch was 73 951/6792 = 10.8. It should be noted that the large number of patients receiving doses from each batch of freeze dried factor VIII is due to the great shortage of the material. Were more material available it should be possible to reserve whole

TABLE VIII. Incidence of jaundice in haemophilic and Christmas disease patients, June 1969 to May 1972

Year	No. of patient-treatment-years		Episodes of jaundice		Jaundice (%)	
	Oxford	Other	Oxford	Other	Oxford	Other
1969	208	940	6	15	2.88	1.59
1970	202	925	5	19	2.47	2.16
1971	202	1027	9	10	4.45	0.97
Total	612	2895	20	44	3.26	1.55
Grand total	3507		64		1.83	

batches of material for single patients and thus greatly reduce the overall number of donation-exposures.

The donation-exposures of the patients may be used to calculate the average number of patients receiving material from each batch. Other data known are the average size of the plasma pools contributing to each batch, the number of batches used and the number of patient treatment years. From these data an estimate can be made of the probable number of patients exposed to virus each year. An example of the calculation is given in the Appendix. The results of these calculations are given in Table VII. The observed incidence of jaundice can then be related to the total number of patients treated (3.27%) and to the number of patients probably exposed to virus (4.60%).

Patients at other Centres may also be compared with those at Oxford (Table VIII) which shows that the incidence of jaundice is lower at the other Centres than at Oxford. Patients at Oxford receive more concentrate and thus more donation-exposures than patients elsewhere. The incidence of jaundice among patients who were not exposed to freeze-dried pooled material during the survey period is given in Table IX. In this case the number of patients exposed to virus is taken to be the number of donations used in the year divided by 800: it was assumed that no patient received two infected donor contributions. It will be seen that the overall incidence of jaundice was less than that in the Oxford patients when expressed

TABLE IX. Incidence of jaundice at Centres where no freeze-dried concentrates were used

Year	No. of Centres	No. patient-treatment-years	Blood donations used	No. patients probably exposed to virus (donations/800)	Jaundice		
					No. of cases	% of all patients	% of patients probably exposed to virus
1969	20	461	40127	50.16	12	2.60	24
1970	17	270	22884	28.61	5	1.85	17.48
1971	20	449	50316	62.89	6	1.34	9.54
Total		1180	113327	141.66	23	1.95	16.23

as a percentage of the total number of patients treated. When the incidence of jaundice is assessed as a percentage of the patients probably exposed to virus, the incidence is substantially higher than for the patients treated with concentrate. This result may derive from some fallacy in the assumptions on which the calculations are based but may suggest that a multi-transfused patient exposed to a whole donation of infected plasma is more likely to be infected that one exposed to infected material diluted in a pool. The calculations also suggest that if all of the patients were exposed to virus diluted in large pools then the incidence of jaundice would not be much greater than 5% since the patients at present treated with concentrate already have a high risk of being exposed to virus.

Hepatitis associated antigen and antibody were tested for by various methods in patients at seven Centres and of 302 patients tested about 30% were antigen or antibody positive (Table X). Judging from the proportion of Oxford patients probably exposed to virus (Table VII) rather more than half of those exposed became antigen or antibody positive but of these only about 10% were noticeably ill.

TABLE X. Hepatitis B associated antigen/antibody returns from seven Centres

	No.	%
No. of patients tested	302	100
Antigen positive	9	2.98
Antibody positive	84	27.81

The observed fact of the low incidence of clinical illness associated with jaundice in these multiple-transfused severely affected patients may well not apply to mildly affected patients who are not often transfused. This supposition is supported by the data of Kasper & Kipnis (1972) who showed an incidence of hepatitis of four in 290 patients (1.4%) who had had more than 10 previous infusions and eight in 53 (15%) for patients with less than 10 previous infusions. A similar conclusion may possibly be drawn from our observations on the treatment of 22 carriers of haemophilia and Christmas disease. These 22 women with low plasma concentrations of factor VIII or IX were treated for 24 operative procedures, including major surgery and dental extraction, with material derived from a total of 1408 blood donations. Two of these patients (11.1%) developed jaundice.

ANTIBODIES AGAINST FACTORS VIII AND IX

The danger of developing antibodies against factors VIII and IX 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 genetically related patients and the other concerned the amount and type of therapeutic material used. In addition a cumulative total of patients who have antibodies has been kept during the three years 1969–71. In Table XI it will be seen that the

TABLE XI. Cumulative table of patients with haemophilia and Christmas disease and the incidence of factor-VIII and factor-IX antibodies

Year	*No. with haemophilia*	*No. with Christmas disease*	*% with antibodies*	
			Haemophilia	*Christmas disease*
1969	1014	134	7.00	2.98
1970	1251	179	6.87	2.79
1971	1625	212	6.15	2.36

proportion of patients who have factor-VIII antibodies year by year has remained at about 6–7%. This Table is somewhat inaccurate since we have limited information about patients who have died during the period of the Survey. The incidence of antibodies against factor IX is very low: over the whole survey period only five cases were encountered. Table I shows the age distribution of the patients with antibodies to factors VIII and IX.

Genetic Study

The purpose of this study was to see if patients related to a patient having antibodies were more liable to develop antibodies than other patients. The first question to ask was how many haemophilic patients were seen during 1968 at the different Centres and how many of these had factor-VIII antibodies. In all 1126 patients were seen in 1968 and of these 61 had antibodies, giving an incidence in the haemophilic population of 5.43%.

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 who had antibodies. The results of this survey are given in Table XII. It will be seen that the overall incidence of antibodies in this group of patients with more than one haemophilic person was 4.46% (41/919), which is not significantly different from the general survey for 1968 (5.43%).

Of the 369 families studied, 38 had one or more members with antibodies. On average these families would have a total of 38×2.49 members = 95 members.

Of these 95 patients, 38 are propositi and known to have antibodies. These must be subtracted from the total leaving 57 patients who were at risk to develop antibodies. Of these, three are known to have antibodies, giving an incidence of: $3/57 = 5.26\%$.

This figure is essentially 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

TABLE XII. The incidence of factor-VIII antibodies in haemophilic families

No. of families containing more than one patient	*Total no. of patients*	*Average no. of patients per family*	*No. of families including patients with antibody*	*No. of patients with antibodies*
Haemophilia				
369	919	2.49	38	41
Christmas disease				
53	126	2.37	1	2

noted that the numbers are small, even for haemophilia. The figure for patients with Christmas disease were too small for any conclusions to be made about a familial tendency to develop antibodies, though it may be noted that only two patients with antibodies were recorded at the time of the genetic study (1968–69) and that these were members of the same family and neither had received large numbers of infusions.

The Relation between Material Given for Treatment and the Development of Factor-VIII Antibodies

This study concerned haemophilic patients seen during 1969–71 for whom records were kept. Of the 1625 patients with haemophilia, 100 had antibodies to factor VIII.

The first piece of information about these patients concerns the date at which the factor-VIII antibodies were detected:

Year factor-VIII antibody detected					
Prior to 1968	1968	1969	1970	1971	No information
30	22	19	15	13	1

The techniques for diagnosis of these antibodies are improving but the number of new cases reported each year does not seem to be increasing, as one would expect if patients were more readily immunized by concentrated factor VIII.

The next information concerned the type of preparation used before 1969 for the 71 haemophilic patients who had antibodies at that time. There were very few patients who had received only one type of material. An analysis of the patients receiving various materials is as follows:

Whole blood	Plasma	Cryoprecipitate	HAHG	Animal AHG	No information
53	58	49	38	23	2

It will be noted that 23 of these 71 patients had received animal AHG before 1969, which is certainly a high proportion if comparison is made with all treated patients (12 patients out of 1014 patients treated during 1969 were given animal AHG concentrate and of these six were given the material because they already had antibodies at the time of treatment). A separate analysis by Rizza & Eipe (1970) of 52 patients known to have received animal AHG in Oxford

TABLE XIII. The amount of factor VIII expressed as factor-VIII units received by patients who developed factor-VIII antibodies in the survey period in comparison with all patients treated over the same period of time

Year	*Patients who developed antibodies during the year*			*All treated patients*		
	No. of patients	*Factor-VIII units received during the 12 mth prior to development of antibodies*		*No. of patients*	*Factor-VIII units received*	
		Mean	*Range*		*Mean*	*Range*
1969	19	33323	1500–159250	986	21920	500–439250
1970	15	26458	1500– 69500	985	26705	500–445750
1971	13	52235	2600–192000	1075	30800	500–573000

since 1954 and who were known not to have had factor-VIII antibodies at the time of treatment showed that eight (15%) of them subsequently developed antibodies. There would thus seem to be an increase in the incidence of antibodies in patients treated with animal AHG.

During the period of the survey 47 haemophiliacs developed antibodies to factor VIII. These patients received amounts varying from 1500 to 192 000 units of factor VIII (1 unit of factor VIII is the amount present in 1 ml of fresh normal plasma) during the 12 mth prior to the development of antibodies. The amounts of material received per patient in the three years in comparison with the amounts received by other patients are shown in Table XIII. There is some possibility that exceptionally high dosage of human factor VIII may promote the formation of antibodies.

THE TOTAL AMOUNTS OF MATERIAL USED AND REQUIRED AT THE HAEMOPHILIA CENTRES

The amount of material used in terms of blood donations per patient has increased steadily over the three years of the survey (Table II). This increase reflects increased supply. For Christmas disease patients there is now enough material to give all of the treatment estimated

TABLE XIV. Materials used during 1971 at 35 Centres to treat haemophilia and Christmas disease patients

	Amount (donations)	% *Total*
Plasma	9526	6.71
Cryoprecipitate	116227	81.84
Concentrates (factor VIII)	16256	11.45
Concentrates (factor IX)	(14523)*	(9.28)
Total	142009	100

* The factor IX is made from donations used for preparing factor VIII and thus is not included in the total donations.

to be required in the form of concentrate. The position is much less satisfactory with regard to haemophilia and factor VIII. The supply of factor-VIII containing preparations has been dealt with in detail in another context (Biggs *et al*, 1974). The two most valuable materials now made are cryoprecipitate and freeze-dried factor-VIII concentrate (Table XIV). The total amount of these preparations at present available is inadequate. The material supplied to Haemophilia Centres in 1971 permitted the administration of concentrate or plasma derived from 120.7 donations per patient.

Although the availability of cryoprecipitate has greatly improved the treatment of haemophilic patients it has serious disadvantages in comparison with freeze-dried concentrate. Cryoprecipitate is variable in potency from batch to batch and from one Centre to another (Biggs *et al*, 1974). Moreover cryoprecipitate is time-consuming to make up in the ward or out-patient department and is not the most suitable preparation for home therapy. There is no doubt that the great majority of those who treat haemophilic patients would prefer to

receive the factor VIII in the form of a stable freeze-dried preparation of good solubility and known reliable activity.

An assessment of the total amount likely to be required for all types of treatment puts the total in excess of 500 000 blood donations annually or about 40 million factor VIII units (Biggs *et al*, 1974). Of this material at least half (and preferably all) should be supplied in the form of a freeze-dried preparation in order that home therapy can be instituted on a reasonable scale.

In considering the feasibility of supplying concentrates of factor VIII in the amounts required, it should be noted that the blood needed to supply factor VIII is not additional to that required to treat other patients. The supply of factor VIII depends on facilities, personnel and planning to use all parts of the donated blood. Thus red cells, platelets and various plasma fractions (e.g. albumin, gamma globulin, plasma protein fraction and factor IX) may be used separately as indicated by clinical considerations. About 1.5 million donations of blood are obtained annually by the Blood Transfusion Service in the United Kingdom. The amount of factor VIII estimated to be required would involve fractionating one-third to one-half of the total donated blood, but all the other special fractions also have valuable uses.

DISCUSSION

The clinical value of early treatment of haemophilic patients in the saving of life and the prevention of crippling is now well established. This treatment is known to carry two main hazards: (1) the transmission of viral hepatitis; (2) the development of specific antibodies against coagulation factors.

The data on hepatitis suggest that severely affected and multi-transfused patients with coagulation defects do not have a high incidence of clinical illness associated with jaundice. Present calculations suggest that if all of the patients were exposed to virus contained in pools of plasma 4–5% of them might develop clinical illness. The proportion of patients exposed to virus is likely to decrease in future rather than to increase since donations grossly infected with Hepatitis B antigen will be excluded by universal donor screening. The present low infection rate for these particular multi-transfused patients may be due in part to resistance to infection following immunization from multiple transfusions. It is also possible that the actual amount of infected material infused may affect the development of jaundice; if large amounts of material are to be used there may be a positive advantage in using concentrate derived from pooled material in which any virus present is diluted. Large pools of plasma may also contain Hepatitis B antibody which may reduce the infectivity of any virus that may be present.

The data on the development of antibodies are so far reassuring. There does not seem to be a large component attributable to genetic predisposition, and, so far, no sustained increase in the proportion of patients with antibodies has been observed. There is some evidence of a higher incidence of antibodies in patients who had previously received animal AHG therapeutically and there is also an indication that exceptionally high dosage of human factor VIII may promote antibody formation. At present the incidence of antibodies seems to be about 6% of all patients. From the point of view of recording the incidence of antibodies in all 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 a clear indication if the proportion of patients with factor-VIII antibodies starts to increase.

The evidence about the incidence of jaundice and antibodies in patients with haemophilia and Christmas disease does not suggest that either of these complications is clearly related to the type of human material used. Thus there would seem to be no disadvantage to the patient in greatly increasing the amount of freeze-dried concentrate and planning ultimately to replace cryoprecipitate by concentrate. In fact its greater reliability, suitability for home therapy and ease of administration, together with serious overall shortage of material, indicate the urgent need for increased production of freeze-dried concentrate.

Present estimates suggest the need for at least a 20-fold increase in the amount of freeze-dried concentrate of factor VIII made in the United Kingdom.

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APPENDIX I

The probability of exposure to hepatitis virus of patients treated in Oxford in 1971 with concentrates and other preparations containing factor VIII.

Data and Definitions

1. Total number of patients treated = 179.
2. Number of batches of concentrate used = n = 80.
3. Mean number of donations per batch = $\overline{D}_n$

$$\overline{D}_n = \frac{\sum^n_1 D_1 + D_2 + D_3 + \ldots D_n}{n} = 192 \text{ donations}$$

4. Mean number of patients exposed to each batch of material = $\overline{P}_n$

$$\overline{P}_n = \frac{\sum^n_1 P_1 + P_2 + P_3 + \ldots P_n}{n}$$

5. Total donations = $n\,\overline{D}_n$ = 15 360
   Donations used in Oxford = 9891
   Donations used elsewhere = 5469

6. Donation-exposures of patients $= \sum^{n}_{1} P_1D_1 + P_2D_2 \ldots P_nD_n$
$= \bar{P}_n\bar{D}_n.n = 153\,919$ (for Oxford patients)

$$\bar{P}_n = \frac{\bar{P}_n\bar{P}_n n}{n\bar{D}_n} = \frac{\text{Donation-exposures}}{\text{Donor units}}$$

7. Number of patients treated with concentrates = 120
Total number of patients treated = 179

Assumption that the incidence of hepatitis in the donor population is 1 in 800 and that patients treated elsewhere with batches of concentrate used in Oxford had donation-exposures similar to those in Oxford.

Calculation

1. The probability of each batch being infected is 192/800 = 0.25
The probable number of batches which are not infected
= number of batches $\times e^{-0.25}$
= $80 \times 0.78 = 62$
probable number of infected batches = $80 - 62 = 18$
2. Number of Oxford patients exposed to each batch = 153 919/9891 = 15.5
Each patient is on average exposed to $18 \times 15.5/120 = 2.32$ infected samples.
The number of patients not exposed to virus =
number of patients $\times e^{-2.32}$
= $120 \times 0.1 = 12$
number exposed = $120 - 12 = 108$
3. Number of single donations (cryoprecipitate and plasma) given in Oxford in 1971 = 10 305. Of these 10 305/800 = 13 probably carrying virus.
The number of patients probably exposed to virus in 1971 was $108 + 13 = 121$.

APPENDIX II

The Directors of 37 Haemophilia Centres who Contributed Data to the Survey and who Participated in the Preparation of the Manuscript

Dr P. G. Arblaster, Treloar Haemophilia Centre, Lord Mayor Treloar Hospital, Alton, Hants.
Dr P. Barkhan, Department of Haematology, Guy's Hospital, London, S.E.1.
Dr Rosemary Biggs, Oxford Haemophilia Centre, Churchill Hospital, Oxford.
Professor E. K. Blackburn, Department of Haematology, The Royal Infirmary, Sheffield.
Dr A. L. Bloom, Department of Haematology, University Hospital of Wales, Cardiff.
Dr T. H. Boon, Royal Victoria Infirmary, Newcastle-upon-Tyne.
Dr T. Black, Liverpool Royal Infirmary, Pembroke Place, Liverpool.
Dr I. A. Cook, Regional Blood Transfusion Centre, Raigmore Hospital, Inverness.
Professor W. M. Davidson, Department of Haematology, King's College Hospital, Denmark Hill, London, S.E.5.
Dr Audrey A. Dawson, Haematology Unit, University Medical Buildings, Foresterhill, Aberdeen.

Dr Katherine M. Dormandy, The Haemophilia Centre, Royal Free Hospital (N.W. Branch), London, N.W.3.

Professor A. S. Douglas, Department of Medicine, Glasgow Royal Infirmary. (Present address: University Department of Medicine, Foresterhill, Aberdeen.)

Dr J. O. P. Edgcumbe, Department of Pathology, Royal Devon and Exeter Hospital, Exeter.

Professor R. M. Hardisty, Department of Haematology, Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Professor F. G. J. Hayhoe, Haematology Clinic, Department of Medicine, University of Cambridge.

Dr C. A. Holman, Department of Haematology, Lewisham Hospital, London, S.E.13.

Professor J. G. Humble, Department of Haematology, Westminster Hospital, London, S.W.1.

Dr A. Inglis, Department of Pathology, Cumberland Infirmary, Carlisle.

Professor G. I. C. Ingram, Department of Haematology, St Thomas's Hospital, London, S.E.1.

Dr M. C. G. Israels (now retired) and Dr I. W. Delamore, Department of Clinical Haematology, The Royal Infirmary, Manchester.

Dr G. C. Jenkins, Department of Haematology, The London Hospital, Whitechapel Road, London, E.1.

Dr M. J. Meynell, Department of Haematology, Queen Elizabeth Hospital, Birmingham.

Dr R. S. Mibashan, Department of Haematology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, W.12.

Professor P. L. Mollison, Department of Haematology, St Mary's Hospital, Paddington, London, W.2.

Professor M. G. Nelson, Department of Clinical Pathology, Royal Victoria Hospital, Belfast.

Dr J. R. O'Brien, Central Laboratory, St Mary's General Hospital (East Wing), Portsmouth.

Professor T. A. J. Prankerd, Department of Haematology, University College Hospital, Gower Street, London, W.C.1.

Dr S. G. Rainsford, Lord Mayor Treloar College, Froyle, Nr Alton, Hants. (Dr Rainsford contributed information about the boys at the Lord Mayor Treloar College before and after the establishment of the Haemophilia Centre at Alton.)

Dr A. B. Raper, Department of Haematology, The Royal Infirmary, Bristol.

Professor J. L. Stafford, Department of Haematology, St George's Hospital, Blackshaw Road, Tooting, London, S.W.17.

Dr D. Stern, Royal Victoria Hospital, Boscombe, Bournemouth.

Dr H. Sterndale, Isle of Thanet District Hospital (Margate Wing), Margate.

Dr J. Stuart, Department of Haematology, The Children's Hospital, Ladywood, Birmingham.

Professor J. W. Stewart, Bland-Sutton Institute of Pathology, The Middlesex Hospital, London, W.1.

Dr L. M. Swinburne, St James's Hospital, Leeds.

Dr J. J. Taylor and Dr R. Scheuer-Karpin, Department of Pathology, Kingston General Hospital, Hull.

Dr G. R. Tudhope, Therapeutics Unit, Maryfield Hospital, Dundee.

Dr R. L. Turner, Department of Haematology, The Royal Infirmary, Bradford.

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