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Haemophilia Treatment in the United Kingdom from 1969 to 1974

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From data collected by the Haemophilia Centre Directors of the United Kingdom and Northern Ireland (see appendix) which was compiled and analysed by ROSEMARY SPOONER

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SUMMARY. A study has been made by the Haemophilia Centre Directors of the United Kingdom and Northern Ireland. From 1969 to 1974 2600 patients with haemophilia A and 388 with haemophilia B attended Haemophilia Centres for treatment.

Of these patients, 71 are known to have died in the survey period. A record is presented of the amounts and types of therapeutic materials used each year during this time. The incidence of jaundice and anti-factor VIII and anti-factor IX antibodies was recorded.

Since 1967 increasing amounts of cryoprecipitate and of factor VIII and factor IX concentrate have greatly improved the prospect for treatment of patients suffering from haemophilia A and haemophilia B. Since 1969 the Directors of Haemophilia Centres have collected data about the amounts and types of therapeutic material used to treat patients having haemophilia A (factor VIII deficiency) or B (factor IX deficiency) and about the complications of treatment. It is hoped that this information will help in the formulation of National Policy for the provision and use of therapeutic materials and help to define the types of organizations required for the care of these patients. These two diseases have been considered because between them they account for more than 95% of all patients having serious congenital coagulation defects which require treatment by coagulation factor replacement.

In a report on the first 3 years of this survey in 1974 (Biggs, 1974), the amount of factor VIII used to treat haemophilic patients was expressed as the number of blood donations (donor units) which were needed to supply the therapeutic material, this was helpful in assessing the amount of blood required to supply factor VIII from the United Kingdom blood transfusion service. The concept of donor units was also used to see if the occurrence of jaundice in patients could be related to the number of donors contributing to the factor VIII that they had received. Analysis of the data did not suggest any significant correlation.

Since the data was collected for the first report, improved methods for detecting hepatitis B surface antigen have been developed and commercial human factor VIII has become available and used in increasing amounts. It seems that commercial donors have had a higher incidence of hepatitis than unpaid donors (Maycock, 1972; Alter *et al*, 1972; Prince, 1975), although commercial suppliers are now making efforts to reduce the potential infectivity of their product. Much of the commercial human factor VIII is made by plasmapheresis from

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commercial donors. Thus the source of blood used to make factor VIII could have been more important than the number of donations contributing to pools of plasma and in any case the number of donations contributing the commercial factor VIII is seldom known. Also the amount of factor VIII activity derived from one donation will depend on the amount of plasma removed from each donation and on the subsequent fractionation procedures. Therefore it now seems more generally useful to express factor VIII as units of activity. The data collected from 1969 to 1971 has thus been converted to factor VIII activity units for comparison with the data collected from 1972 to 1974.

The unit of factor VIII was originally defined as the amount of activity in 1 ml of citrated normal plasma as collected for testing in the laboratory. The unit is now established in a freeze dried International Standard preparation. Considerable effort was expended in an attempt to ensure that 1 International unit of factor VIII would correspond to the same amount of factor VIII activity as 1 ml of average normal human plasma (Bangham *et al*, 1971). But since the International Standard for factor VIII has been available it has become apparent that there are consistent differences between the assay results of different laboratories. These differences can give rise to annoying discrepancies. For example, an individual laboratory may find that, using the International Standard, the activity of a given human plasma pool may not have exactly 1.0 unit of factor VIII per ml but may deviate from the mean of the fresh normal samples used in the initial establishment of the standard.

Recalibration of the local standard may mean that the amount of factor VIII activity derived from a given amount of plasma will be expressed as a numerically different number of units than before the standard was introduced. There may be an apparent fall in the amount of factor VIII produced though in fact no change will have occurred. Alternatively a commercial factor VIII may be found to contain a smaller number of factor VIII units than claimed on the label and since the preparations are paid for by the unit much money can be involved in the discrepancy. In due time it is to be hoped that these laboratory to laboratory variations will be eliminated. A unit of factor IX is similarly related to the activity of average normal plasma. This activity is in process of being established as an International Standard.

The number of factor VIII units from each donation used to make cryoprecipitate was assessed in Oxford when 200–220 ml of plasma were collected from each donation. We found that on average 79 units of cryoprecipitate factor VIII were derived from each donation (Biggs *et al*, 1974). The unit assessed in Oxford in 1974 would now correspond to about 65 iu cryoprecipitate factor VIII per donation. At that time the cryoprecipitate from four other centres was tested and found to have less than 70 'units' of factor VIII activity per donation. Clearly if 180 ml of plasma is collected (instead of 200 or 220 ml) then less factor VIII can be made from each donation. At present it is widely accepted that about 70 units of factor VIII are derived from each donation when cryoprecipitate is made, and this figure has been used to calculate the factor VIII activity of cryoprecipitate. At some centres better results are claimed (Cash, 1975) for the yield of factor VIII in cryoprecipitate but it is probable that 70 u/donation is a generous estimate for the yield of factor VIII per donation, if all centres are included.

When National Health Service (NHS) freeze dried factor VIII is considered, data collected in Oxford showed that the yield of factor VIII activity in the intermediate potency factor VIII was very similar to that of cryoprecipitate (Biggs *et al*, 1974). If high potency factor VIII is

made then the yield of activity is less than that for intermediate potency factor VIII. A general guide to the yield of factor VIII in different preparations is given in Table V. The amount of freeze dried factor VIII made within the NHS is still much less than that required to treat all haemophilia A patients but commercial human factor VIII is now available in large amounts. It is the purpose of the present communication to review the data collected over the last 6 years and to consider the effects of the availability of commercial human factor VIII.

The Numbers of Patients having Haemophilia A or Haemophilia B

The total numbers of patients attending for treatment during the 6 year period at those Centres which have contributed to the survey are shown in Table I. It will be seen that a total of 2988 patients with either haemophilia A or B are known at the Centres making returns. Of these, 2600 have haemophilia A and 388 (13%) have haemophilia B. In comparison with males

TABLE I. Numbers of patients having haemophilia A or B included in the 1969–1974 survey, showing the age distribution on 31 December 1974

Age	*Haemophilia A*		*Haemophilia B*		*Normal males*
	Total	*%*	*Total*	*%*	*(%)*
0–4	129	4.96	22	5.67	8.4
5–9	289	11.11	39	10.05	8.4
10–19	646	24.85	107	27.58	15.0
20–29	509	19.58	72	18.56	14.8
30–39	329	12.65	39	10.05	12.2
40–49	222	8.54	36	9.28	12.6
50–59	158	6.08	21	5.41	12.0
60–69	84	3.23	15	3.86	10.0
70+	42	1.62	10	2.58	5.7
Unknown	130	5.00	18	4.64	
Dead	62	2.38	9	2.32	
Total	2600	100	388	100	99.1

in the normal population there is still a marked preponderance among haemophiliacs of patients in the 10–30 age group. In due course it is to be presumed that most of the patients in this age group will live to be middle-aged and old and that there will be a substantial increase in the number of living patients.

Seventy-one patients having haemophilia A and B are known to have died during the survey period. The age at death of the patients who died is given in Table II. In the case of haemophilia A, 17.7% of the patients who died had factor VIII antibodies whereas (see Table XIV) only 6% of all patients have factor VIII antibodies. Information about the deaths of patients was not specifically requested until 1973 and thus the information for the whole period of the study may not be complete. The causes of death for haemophilia A patients are shown in Table III. It will be seen that rather more than half died from bleeding or from the complications of treatment.

In the early statistics the average age at death of severely affected haemophilic patients was less than 20 years. Thus the age at death seems to have more than doubled as a result of factor VIII therapy. It is easy to see that a doubling of the average age at death of patients must of itself lead to a doubling of the number of living patients. Thus in the next 50 years there must be a very substantial increase in the number of living haemophiliacs. As these haemophiliacs

TABLE II. Age at death of patients having haemophilia A or B

Age	*Haemophilia A*		*Haemophilia B*
	All cases	*Patients with factor VIII antibodies*	
0–4	3	0	1
5–9	1	0	0
10–19	6	2	2
20–29	9	1	1
30–39	5	1	2
40–49	14	2	0
50–59	8	2	2
60–69	12	2	1
70+	4	1	0
Total	62	11	9
Average age at death	42.3	46.3	33.6

TABLE III. The cause of death of haemophilia A patients

Cause of death	*No. of cases*
Intracranial bleeding	16
Other types of bleeding	3
Operations and complications	4
Jaundice	5
Reaction to plasma infusion	1
Cardiovascular disease	9
Cancer	7
Miscellaneous (not haemorrhagic)	4
No information	13
Total	62

will live relatively normal lives and may be expected to produce children, a second increase in the number of haemophiliacs will be caused by the birth of sons to the daughters of present-day haemophiliacs. In addition Haldane (1947) calculated a mutation rate to the haemophilic gene at a rate of 3.2×10^{-5} per generation. Thus estimates of the amounts of therapeutic materials needed to treat haemophilic patients will need frequent revision.

The degree of severity of the defect in haemophilia A and B patients is indicated to some extent by the level of the patient's clotting factors (Table IV). Those with less than 2% of factor VIII or IX include all of the severely affected patients. It will be seen that of the patients for whom we have records, 61% of haemophilia A patients are severely affected and for haemophilia B the proportion is 50%.

In 1974 we estimated that there were probably 3000 haemophilia A patients in the United Kingdom and we might therefore be reaching a stage when most of the existing patients are known at the Haemophilia Centres and have come to one of the Centres for treatment at least once in the 6 year period. On the other hand, new patients are being added very regularly year by year to those already included in the study at the Centres in addition to those born during the survey period. As previously noted, the number of patients must be increasing and the continued collection of data is essential.

TABLE IV. Degree of severity of haemophilia A or B

Level of clotting factor (% of average normal)	*Factor VIII deficient patients*		*Factor IX deficient patients*	
	No.	*%*	*No.*	*%*
Less than 2%	1589	61.11	191	49.22
2–10%	586	22.54	121	31.19
10%+	334	12.85	54	13.92
Unknown	91	3.50	22	5.67
Total	2600	100	388	100

The Amounts and Types of Therapeutic Material Used

The types of therapeutic materials used at the Centres to treat haemophilia A and B patients are set out in Table V. For haemophilia A the materials are: plasma, cryoprecipitate, NHS freeze dried concentrate and commercial factor VIII concentrate. Plasma is now little used. Cryoprecipitate is a simple concentrate made from plasma at all Regional Transfusion Centres. Cryoprecipitate is much superior to plasma for the treatment of haemophilia A patients but the material is very variable from one sample to another and the potency cannot be known before it is used. For each dose the assumption must be made that the material is of low potency, thus there is a tendency to use more material for each patient than is probably needed. The NHS freeze dried concentrate is an 'Intermediate Potency' preparation made from pools of plasma derived at present from pools of from 200 to 750 blood donations. The material is of assayed and labelled potency of about 5 u/ml and made up for use by adding sterile water for injection. Commercial factor VIII concentrate is available from several companies and each batch is derived from 1000–4000 litres of plasma collected by plasmapheresis from paid donors. Since about 400 ml of plasma is derived from each donor each batch contains plasma from more than 2500 individual donors. The material is of higher purification than the NHS concentrate.

A characteristic that must be considered is the loss of activity of the various preparations

during fractionation (Table V). There is some loss during the preparation of plasma and even further loss during the preparation of frozen plasma used as starting material for fractionation. The preparation of cryoprecipitate and NHS concentrate involve some loss of factor VIII but the loss from the NHS freeze dried concentrate is less variable than that from the preparation of cryoprecipitate. The preparation of the commercial concentrate of higher potency involves more loss of activity than does that of the NHS freeze dried concentrate. Were the NHS freeze dried concentrate converted to a 'high potency' preparation similar to that made by commercial companies about twice as much plasma would be required to produce a given quantity of factor VIII.

TABLE V. Factor VIII and factor IX activities of various therapeutic materials

Preparation	*Factor VIII or factor IX (u/ml of solution as made up for administration)*	*Yield during preparation*	*Recovery of activity in the patient (u/u/kg/dose) (see text)*
Plasma	0.6 VIII	80	0.02
Cryoprecipitate	2–10*	10–40	0.016–0.018
NHS factor VIII	5–6	30–35	0.016–0.020
Commercial human factor VIII	20–30	15–20	0.018–0.022
Plasma	0.9 IX	100	0.004–0.015
NHS factor IX concentrate	30–40	60	0.004–0.015

* The concentration depends on the volume of fluid added to the cryoprecipitate to variation in factor VIII level between donors and to the care taken in preparation of various batches.

A final measurement, the recovery of activity in the patient's plasma, needs mention. To obtain a measurement of response, the dose is expressed in u/kg of the patient's weight. For a dose of 1 u/kg the maximum rise in plasma factor VIII to be expected is 0.024 units/ml or 0.024 u/u/kg dose (see Table V). The observed rise in plasma factor VIII for various preparations is given in Table V and varies from time to time and from preparation to preparation from 0.016 to 0.022 u/u/kg. Using this concept it is possible to calculate the dose in a particular patient which is likely to give desired rise in plasma factor VIII.

For haemophilia B (factor IX deficiency or Christmas disease), plasma and NHS factor IX concentrates are the therapeutic materials used and the main difference from factor VIII lies in the recovery of activity which is about half of that of factor VIII.

The amounts of therapeutic material used at the Haemophilia Centres making returns are shown in Tables VI–IX. Returns for the Oxford Centre are shown separately. It will be seen that at Centres other than Oxford the amount of cryoprecipitate used has increased steadily over the years (Table VII). This increase has been due to the efforts made by the Regional Transfusion Centres. In 1974 cryoprecipitate still accounted for nearly 80% of all material used. By contrast, at the Oxford Centre cryoprecipitate has never constituted more than 43% of material used and since 1971 the proportion of cryoprecipitate has fallen steadily (Table VIII). In Oxford, plasma previously used to make cryoprecipitate is now fractionated to make

TABLE VI. Factor VIII preparations used at Haemophilia Centres in the United Kingdom during 1969–74, showing the calculated amount in factor VIII units and the types of materials used

	1969		1970		1971		1972		1973		1974	
	Amount	%	*Amount*	%	*Amount*	%	*Amount*	%	*Amount*	%	*Amount*	%
Plasma	1194120	17.17	1077956	13.16	801480	6.78	618030	5.60	665080	4.20	691960	3.37
Cryoprecipitate	4734940	68.09	6226569	76.04	7951160	67.25	8387830	75.98	11840590	74.80	14443810	70.29
NHS VIII concentrate	1024940	14.74	884450	10.80	3070690	25.97	1938975	17.56	2448085	15.47	2731515	13.29
Commercial VIII concentrate	Nil		Nil		Nil		94530	0.86	875260	5.53	2680775	13.05
Total	6954000		8188975		11823330		11039365		15829015		20548060	
No. of centres	37		35		36		37		40		47	
No. of patients*	1022		1108		1154		1234		1434		1634	
Average amount of factor VIII used per patient	6804		7391		10246		8946		11028		12575	

* Excluding those not transfused and adjusted for duplicates.

TABLE VIII. Factor VIII preparations used in Oxford to treat haemophilic patients during 1969–74, showing the calculated amount in factor VIII units and the types of materials

	1969		1970		1971		1972		1973		1974	
	Amount	%	*Amount*	%	*Amount*	%	*Amount*	%	*Amount*	%	*Amount*	%
Plasma	332160	32.09	446040	32.21	196800	13.16	9750	0.49	Nil		Nil	
Cryoprecipitate	227640	21.99	378840	27.35	606550	40.55	624270	31.45	371630	16.59	95000	3.86
NHS VIII concentrate	475440	45.93	560070	40.44	692370	46.49	1350765	68.06	1471215	65.67	1500480	60.89
Commercial VIII	Nil		Nil		Nil		Nil		397350	17.74	868805	35.25
Total	1035240		1384950		1495720		1984785		2240195		2464285	
No. of patients treated	175		166		179		195		217		219	
Average amount of factor VIII used per patient	5916		8343		8356		10178		10323		11252	

TABLE IX. The number of Christmas disease patients treated at Haemophilia Centres in the United Kingdom during 1969–74 and the amounts of factor IX preparations given to them

Year	Centres with Christmas disease patients	No. of patients treated	Factor IX (units)				Average amount factor IX units per patient
			Plasma	NHS conc.	Other conc.	Total	
1969	Oxford	37	59049	349384	—	408433	11039
	Others (23)	112	942630	86445	—	1029075	9188
	Total (24)	142*	1001679	435829	—	1437508	10123
1970	Oxford	35	21600	333945	—	355545	10158
	Others (23)	101	906356	225566	(Konyne)	1131922	11207
	Total (24)	131*	927956	559511	—	1487467	11355
1971	Oxford	25	2400	550993	—	553393	22136
	Others (26)	108	623400	22129	—	1245529	11533
	Total (27)	132*	625800	1173122	—	1798922	13628
1972	Oxford	38	Nil	771732	—	771732	20309
	Others (28)	138	266260	1256862	(Konyne & Bebulin)	1523122	11037
	Total (29)	172*	266260	2028594	—	2294854	13342
1973	Oxford	43	Nil	654884	—	654884	15230
	Others (34)	168	73892	2394170	15120	2483182	14781
	Total (35)	204*	73892	3049054	15120	3138066	15383
1974	Oxford	35	Nil	492740	—	492740	14078
	Others (43)	212	156800	4179140	37700	4373640	20630
	Total (44)	237*	156800	4671880	37700	4866380	20533

* Adjusted for duplicates. ( ) = Amounts not stated.

NHS concentrate. The amount of NHS concentrate used in Oxford reflects close proximity and the good co-operation between the Oxford Regional Transfusion Service and the Plasma Fractionation Laboratory which has enabled plasma to be fractionated to make all valuable components rather than used for cryoprecipitate and red cells alone. The commercial human factor VIII was introduced to the United Kingdom in 1972 and in 1974 constituted 13% of all factor VIII used in the United Kingdom.

The average amounts of factor VIII used per patient per annum in the United Kingdom is shown in Table VI. The amount used per patient is still increasing and reached the figure of 12 575 units in 1974. Some of the patients included in the survey attended several centres. In making the calculations for Table VI all of the material used by a patient has been collected together, no patients are counted twice and the figures give a true estimate of the use of factor VIII per patient at haemophilia centres in the United Kingdom from which returns have been received. In Table VIII (Oxford statistics) it will be seen that the use per patient is slightly less than the average for all centres. About half of the patients treated in Oxford reside outside the territory of the Oxford Regional Health Authority and some of them attend regularly for treatment at other centres and only come to Oxford in exceptional circumstances. These patients are thus the *same* patients seen at some other centre. Material given to these patients at their usual centres is not included in the Oxford statistics. Table VII gives the use of factor VIII at centres other than Oxford. In this table also the average number of units used per patient per annum is less than in Table VI. This is because some patients usually treated at these centres were sometimes treated at Oxford and some patients usually treated at Oxford attended other centres while on holiday or travelling for other reasons. Table VI eliminates all duplicates of patients seen at more than one centre.

There has been a steady increase in the amount of factor VIII used. As more factor VIII has become available it has been used. There is no doubt that it would be valuable to present all of the NHS factor VIII as a freeze dried preparation.

Similar statistics for factor IX are given in Table IX. It will be seen that the average use per patient of factor IX reached 20 533 u/patient per annum in 1974. The high use of factor IX is probably related to the low recovery of factor IX activity in the factor IX deficient patient's plasma. In recent years factor IX has been used in increasing amounts for patients other than those with congenital factor IX deficiency (Christmas disease). Factor IX has been used to reverse excessive coagulation defects caused by oral anticoagulant therapy, it has been used in liver disease patients and for patients with factor VIII deficiency who have antibodies directed against factor VIII. Some of these other uses of factor IX were not anticipated in planning the national needs for factor IX. When new uses are found for a therapeutic substance which is made within the NHS there is need for frequent exchange of information between clinicians, fractionation specialists and planners if adequate amounts are to be maintained.

Home Therapy

The survey data have not included any information about the numbers of patients receiving home therapy. Cryoprecipitate is much less satisfactory for home therapy than are the freeze dried preparations. Thus an increase in the number of patients on home therapy is likely substantially to increase the demand for freeze dried preparations to replace cryoprecipitate.

When considering the introduction of patients to home therapy is it usual to give priority

to the most severely affected patients who need most frequent treatment. Thus when home therapy is first used at a Centre the amount of factor VIII used per home therapy patient per annum will be much higher than the average for all patients. For example the first seven patients who started home therapy in 1971 at Oxford have used 33 400 units of factors VIII per patient per year over the 5 year period from 1971 to 1975. As more mildly affected patients are included in the home therapy programme a fall will occur in the amount of material used per patient. In 1975 54 haemophilia A patients were receiving regular home therapy from Oxford and on average 17 623 units of factor VIII were used per patient. Similar figures from Newcastle in 1975 were 18796 units per patient per year for 38 different haemophilia A patients. Since very mildly affected patients will probably not receive home therapy in the near future the use of factor VIII per patient on home therapy is likely to remain higher than that for all patients (Table VI).

The Occurrence of Hepatitis in Patients Treated for Haemophilia A or Haemophilia B

There are a number of important considerations to be taken into account in assessing the incidence of hepatitis in patients treated for haemophilia A and B. The first of these concerns the definition of hepatitis. In the survey years 1969–72 we collected data about patients who were known to be ill having clinical jaundice. In 1973 and 1974 some Haemophilia Centre Directors made returns for patients who had abnormal liver function tests (LFTs) but who were not ill. It is true that early and mild cases of hepatitis will be detected by raised LFTs. On the other hand, many Haemophilia Centre Directors have not carried out LFTs on their patients and thus for this survey we include only those patients judged to have clinical jaundice.

In the previous survey much attention was paid to the number of donations used to treat patients. This was called the 'donation exposure'. It was found that only 1.95% of patients who received plasma or cryoprecipitate developed jaundice. These patients were exposed to the least number of donations. 3.22% of the Oxford patients developed jaundice and these patients had been exposed to most NHS concentrate and thus to most donations. The difference between 1.95% and 3.22% is not significant and it seems that the NHS concentrate made from unpaid donors is not more likely to cause jaundice than cryoprecipitate.

In 1972 the commercial human factor VIII was used for the first time in the United Kingdom. This material is made from very large pools of plasma collected from paid donors some of whom have lived in poor districts of the United States cities and the similar situations of other countries. It has been shown that such commercial blood has been 10 times more likely to transmit hepatitis than blood collected from unpaid donors by National Transfusion Services (Maycock, 1972). The commercial factor VIII was introduced to the United Kingdom in 1972 and since then its use has increased until 1974 when 13% of all material used to treat haemophilia A patients was commercial. Commercial factor IX is sold in the United Kingdom but since there are adequate amounts of NHS factor IX available little of the commercial material is used.

Jaundice in haemophilia A or B patients may be due to a number of different causes. The most carefully studied is that due to hepatitis B virus the presence of which can be detected in therapeutic materials by testing for hepatitis B surface antigen or antibody. The tests for this antigen are improving rapidly and each test invented detects smaller amounts of virus. At any

time material giving positive tests is excluded from use in patients. Even the most sensitive tests probably do not exclude trace amounts of virus so that susceptible patients may still be infected. The hepatitis B virus causes jaundice of varying severity after a long incubation period (6 weeks to 6 months) and patients so infected may have positive blood tests for hepatitis B surface antigen or the corresponding antibody.

Many patients who develop jaundice do not develop hepatitis B surface antigen or antibody in their blood and it is to be presumed that they have been infected by some other virus or have developed jaundice from some other cause. Hepatitis A virus (infective hepatitis) has been implicated in some cases and there are probably long incubation period viruses resembling hepatitis B virus but which do not produce any detectable antigen or antibody in patients. In addition patients may develop jaundice from haemolysis due to blood group antibodies contaminating factor VIII (Rosah *et al*, 1970; Seeler, 1972; Tamagnini *et al*, 1975).

TABLE X. The incidence of jaundice in haemophilia A patients

Year	*All cases*			*Oxford cases*		
	Patient-treatment-years	*No. of incidents of jaundice*	%	*Patient-treatment-years*	*No. of incidents of jaundice*	%
1969	1022	20	1.96	175	4	2.29
1970	1111	26* (27)	2.34	166	5	3.01
1971	1154	16	1.39	179	8	4.47
1972	1234	18	1.46	195	3	1.54
1973	1434	26* (28)	1.81	217	8	3.69
1974	1634	85† (101)	5.20	219	16 (20)	7.30
Total	7589	186		1151	44	
Mean	1265	31	2.45	192	7.3	3.80

The numbers in parentheses indicate the total including patients with raised LFTs who were not ill.

* One patient was jaundiced twice in the year.
† Five patients were jaundiced twice in the year.

Patients undoubtedly differ in their susceptibility to virus hepatitis. Many haemophilic patients have positive blood tests for hepatitis B antibody; such patients are presumably resistant to infection with hepatitis B virus and may be resistant to other similar viruses. Patients who have received few previous infusions are more likely to be susceptible to infection when they receive infected material since they have had little opportunity to acquire immunity.

In considering the incidence of hepatitis it is important to bear all these various factors in mind. The statistics about the incidence of jaundice in patients having haemophilia A or B are shown in Tables X and XI. We have assessed the number of episodes of jaundice occurring each year. Some patients have been jaundiced more than once in the same year and many patients have been treated in several years. The incidents of jaundice each year have been

TABLE XI. The incidence of jaundice in haemophilia B patients

Year	*All cases*		*Oxford*	
	Patient-treatment-years	*No. of incidents of jaundice*	*Patient-treatment-years*	*No. of incidents of jaundice*
1969	142	2	37	1
1970	131	0	35	0
1971	132	2	25	2
1972	172	4	38	1
1973	204	2	43	0
1974	237	7 (10)	35	0
Totals	1018	17; 1.67%	213	4; 1.88%

The number in parentheses indicates patients having raised LFTs who were not clinically ill.

TABLE XII. Cases of hepatitis in haemophilia A patients treated in Oxford during 1974

Case	*No. of different batches of factor VIII given to patients*		*Probable donor exposure*
	NHS	*Commercial*	
1	1	2	5400
2	12	—	4800
3	7	3	10300
4†	9	1	6100
5†	3	1	3700
6	3	1	3700
7	4	1	4100
8	1	—	400
9†	3	2	6200
10	4	2	6600
11	2	—	800
12	2	—	800
13*	—	2	5000
14	3	2	6200
15*	—	1	2500
16	7	1	5300

Cases 1–9 showed some change of HB_s Ab or HB Ag at the time of developing hepatitis, patients 10–16 had no change in HB Ab or HB_s Ag.

* The patients received only commercial concentrate but one patient developed jaundice while actually receiving the material.

† By careful analysis hepatitis in these patients could have been due to one batch of commercial concentrate but two of them also received batches of NHS concentrate which gave positive tests for HB_s Ag.

expressed as a percentage of the number of patients treated in that year which we have called 'patient-treatment-years'. There have been a total of 7589 patient-treatment-years for 2600 haemophilia A patients. There was overall increase in the percentage of jaundiced haemophilia A patients in the year 1974 but the increase was not large. At least some of the 1974 cases of jaundice were associated with the use of one or two particularly infective batches of commercial concentrate (Craske *et al*, 1975). In most cases it is not possible to incriminate a particular batch or type of material since patients receive different sorts of material. For example the materials received by the 16 patients who developed jaundice in Oxford in 1974 are listed in Table XII. Nine of the patients probably had hepatitis B virus and in the remaining seven the type of infection was uncertain. Jaundice in haemophilia B patients has remained constant over the years averaging 1.9% of all patient-treatment-years (Table XI). Rather more cases of jaundice were reported in 1974 than in previous years but the increase is not significant.

TABLE XIII. Incidence of jaundice analysed by severity of haemophilia A

Factor VIII	1969	1970	1971	1972	1973	1974	*Totals*	%
0–2	19	22	11	17	23	66	158	84.95
3–5	1	2	1	0	2	5	11	5.91
6+	0	2	4	1	1	9	17	9.14
Totals	20	26	16	18	26	80	186	100.00

The haemophilia A patients who developed jaundice during the 6 year period have been analysed according to the level of factor VIII in their plasma (Table XIII). It will be seen that the majority of patients who had jaundice were severely affected haemophiliacs. This is rather surprising since one would expect the mildly affected patients to be most susceptible since they are less likely to have immune antibodies. On the other hand, the severely affected patients are most often exposed to infection. Of the five patients who died of hepatitis in the 6 year period four had received no material other than cryoprecipitate. 16 patients developed jaundice more than once in the survey period. The patients have been analysed according to the age of occurrence of jaundice and the distribution does not differ significantly from that of the ages of all haemophilia A patients in the survey. The an-icteric cases were all less than 20 years old. 21 haemophilia A patients who became jaundiced had antibodies to factor VIII.

The Occurrence of Factor VIII or Factor IX Antibodies in Patients having Haemophilia A or B

The numbers of haemophilia A patients having factor VIII antibodies is given in Table XIV. It will be seen that in no year of the survey period has there been an increase in the number of new cases detected. The percentage of patients having factor VIII antibodies has remained constant averaging 6.75%. In 49% of all cases the antibody was detected before the patient reached the age of 20. Eleven patients having factor VIII antibodies died in the survey period (Table II); this is 17.7% of all patients who died. The average age at death, 46.27, is not significantly different from the age at death of all patients (see Table II). Only five haemophilia

TABLE XIV. The incidence of factor VIII or factor IX antibodies in patients having haemophilia A or B

	Haemophilia A				*Haemophilia B*			
Year	*Cumulative total number patients in survey*	*Cumulative number with factor VIII antibody*	*%*	*New cases detected*	*Cumulative total number patients in survey*	*Cumulative number with factor IX antibody*	*%*	*New cases detected*
1969	1050	79	7.52	21	142	4	2.82	0
1970	1418	97	6.84	18	185	5	2.70	1
1971	1703	113	6.64	17	223	5	2.24	0
1972	1977	130	6.58	17	276	5	1.81	0
1973	2281	150	6.58	19	322	5	1.55	0
1974	2600	165	6.35	15	388	5	1.29	0
Mean			6.75					

B patients are known to have developed anti-factor IX antibodies and no new cases have been detected since 1970.

DISCUSSION

From the data collected for the first United Kingdom report (Biggs, 1974) and by the MRC Working Party (Biggs *et al*, 1974) it was concluded that 'An assessment of the total amount of factor VIII) likely to be required for all types of treatment puts the total in excess of 500 000 blood donations annually or about 40 million units of factor VIII'. In 1974 the 1634 haemophilia A patients treated at 47 Haemophilia Centres used on average 12 575 units of factor VIII each. We do not yet know how many patients are treated at hospitals not designated as Haemophilia Centres.

The estimate of 40 million units of factor VIII would provide treatment for 3181 patients at the 1974 level of treatment at Haemophilia Centres. There is no reason to suppose that this

TABLE XV. The use of factor VIII in different countries

Country	*Population (millions)*	*Haemophiliacs per 10^5 population*	*Units of factor VIII used per patient per annum*
France*	50	6.6	14000
Belgium*	9.7	4.6	13500
Finland*	5	5.0	7200
Switzerland*	6	6.6	8750
U.S.A.†	200	10.0	12000
U.K.	55	6.0	12575

* From an International Forum organized by *Vox Sanguinis* (1976).
† From NILH Survey (1972).

treatment level was optimum. It seems that the estimate made in the previous report is unlikely to be excessive. An analysis of current practise in other countries is given in Table XV. It will be seen that in three of the five countries the current use of factor VIII is similar to that in the United Kingdom.

It was concluded in the previous report that at least half and preferably all of the factor VIII should be freeze dried. In 1974 70% of the factor VIII used was still presented as cryoprecipitate. At Oxford about 25% of the haemophilia A patients, including those most severely affected, are on home therapy. These home therapy patients receive about half of the factor VIII used in Oxford (Table VIII). If a similar proportion of patients at other centres were given home therapy (and since freeze dried material should be used for home therapy) it follows that at least half of the supply should be freeze dried. It can also be argued that it is much safer to use freeze dried factor VIII for operation cases and dental extractions since the dose and hence the response can be predicted more certainly for freeze dried concentrate than for cryoprecipitate. These operation cases account for about 20% of factor VIII used for cases treated in hospital. The estimate for home therapy cases is based on data which includes material used for operations in these home therapy patients. It may be deduced that at least 60% of the factor VIII should be freeze dried.

In 1974 13% of the factor VIII used in the United Kingdom was bought from commercial companies. The proportion used in 1975, computed from incomplete statistics, is likely to be about 20%. It seems inevitable that, as the commercial factor VIII is available, it will be used to supplement NHS freeze dried factor VIII for those patients and those episodes of bleeding where freeze dried factor VIII is to be preferred to cryoprecipitate. As previously stated (see also Table VI) 75% of all factor VIII used in 1974 was in the form of plasma or cryoprecipitate. A fourfold increase in NHS freeze dried factor VIII would be needed to supply enough factor VIII for the basic needs of haemophilic patients if the average use per patient were to stay the same and if 25% of patients were on home therapy.

The cost of supplementing the NHS factor VIII by commercial concentrate in 1974 was about £300 000. In 1975 unpublished data indicate that it was about £500 000. We have the scientific and technical knowledge to make all of the factor VIII that is needed within the United Kingdom using blood that is collected in the United Kingdom. The sooner this objective of self reliance is reached the less costly will the treatment for haemophilia A patients become. There are reasons other than cost which should encourage every effort to have the supply of factor VIII made from United Kingdom blood. For one thing our haemophilic patients should not be dependent on commercial blood donors recruited in other countries. Also blood from these donors may be more likely to transmit infection than the blood of voluntary donors. In addition it must be undesirable for a major source of supply of factor VIII to be from foreign companies whose policy may be affected by political and other decisions outside the United Kingdom.

APPENDIX

The Directors of 48 Haemophilia Centres who Contributed Data to the Survey and who Participated in the Preparation of the Manuscript

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