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Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia Based on Studies Made during 1969–72

REPORT OF THE MEDICAL RESEARCH COUNCIL'S BLOOD TRANSFUSION RESEARCH COMMITTEE WORKING PARTY ON THE CRYOPRECIPITATE METHOD OF PREPARING AHF CONCENTRATES

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Haemophilia is the commonest of the hereditary haemorrhagic states associated with a coagulation defect; it is caused by the lack from the blood of an essential coagulation factor called factor VIII. Improvements in transfusion and fractionation techniques in recent years have made it possible to separate factor VIII from blood while preserving other components for use by other patients. The present communication is an attempt to assess the advantages and disadvantages of various therapeutic materials containing factor-VIII activity and to estimate the total amount likely to be needed in this country each year. The assessment of the amount of material required involves an estimate of the number of haemophilic patients in the country and of the amount of concentrate that each might reasonably require per annum. The supply of factor-VIII concentrate in the form of cryoprecipitate has greatly increased in recent years and this preparation has revolutionized the treatment of patients with haemophilia. The provision of cryoprecipitate at the present level of production has involved a major effort on the part of the transfusion centres.

In assessing an ideal or desirable level of production of factor-VIII concentrates and the form in which these should be supplied, the feasibility of co-ordinating such a programme with the overall activities of the transfusion service must naturally be considered. From the point of view of the Blood Transfusion Service it is necessary to know the actual amount of fresh whole blood which needs to be fractionated to provide the material; this is the main concern of the present study. For this reason the results have been assessed as the number of blood donations required to supply the material needed. This concept is not precise or fixed since the amount of blood required is greatly affected by the yield of activity of a clotting factor during fractionation. For example, if the yield of activity were doubled the blood required for fractionation would be halved. The welfare of the patient depends on the amount of activity he receives in terms of clotting factor units. When available, the data have been expressed in terms both of blood donations and of clotting factor units.

The supply of factor-IX concentrate has not been considered because no additional blood is required for its preparation. It is made from the same plasma which is used to make factor VIII. In additional there is sufficient factor-IX concentrate now available to treat all of the

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factor-IX-deficient patients in the United Kingdom. The situation is quite different in the case of factor VIII, where more than half of the Directors of the 42 Haemophilia Centres consider that the present supply of factor-VIII concentrate is inadequate.

The Number of Haemophilic Patients in the Population

The estimates of the number of haemophiliacs per 100 000 of a Caucasian population have varied from 2 to 10 (Table I). In Great Britain 1608 different patients are known to have attended Haemophilia Centres during the years 1969–71. We know that this underestimates the total number of patients since some centres did not make returns and because only a little more than half of the cryoprecipitate (factor-VIII concentrate) made by the Blood Transfusion Service was sent to the Haemophilia Centres in 1971, the rest being supplied to general hospitals for the care of patients. It must be supposed that some patients are being treated at hospitals other than Haemophilia Centres.

TABLE I. The incidence of haemophilia in various populations

Country	*Author*	*Estimate per 100 000 of population*
Denmark	Andreassen (1943)	2
	Sjølin (1960)	4
Sweden	Ramgren (1962)	4
Spain	Martin-Villar *et al* (1971)	2.3
Chile	Larrain *et al* (1972)	3.5
Brazil	Rosenberg (1972)	7–10
U.S.A.	NHLI Study (1972)	6 severe, 10 mild + severe
Great Britain	Present estimate	4–5.5

With the passage of time, as more patients attend the Haemophilia Centres for treatment, the estimate of the total number of patients will become more precise. The range may be narrowed by consideration of the patients treated at the Oxford Haemophilia Centre from 1963 to 1971. During the survey period (1969–71) 331 haemophilic patients were treated. During the period 1963–69, 170 patients were seen in Oxford who are not recorded as having attended any of the Haemophilia Centres for treatment during the period 1969–71. Presumably these patients attended centres other than Haemophilia Centres. Had the same tendency of patients towards treatment at General Hospitals occurred among patients attending other centres then the total number of haemophiliacs requiring treatment would be:

$$(1608 \times 501)/331 = 2434$$

Another source of information concerns the supply of cryoprecipitate to hospitals other than those taking part in the survey during 1971. Were this material (derived from 113 648 donations) used at the rate of 120 donations per patient (the average recorded at the participating centres for 1971) then an additional 947 patients must have been treated. This estimate would give a total of 2555.

Thus the lower limit is about 2434. We suggest, for purposes of calculation, an upper limit

of 3000, which would be about 5–6 per 100 000 of the population and reasonably in line with other estimates.

The Factor-VIII Preparations at Present Used to Treat Haemophilic Patients

At present the treatment of bleeding in a haemophilic patient consists of giving a calculated dose of an anti-haemophilic factor (factor VIII) preparation as soon as any symptoms of spontaneous bleeding arise and of giving enough material during and following operations to maintain normal haemostasis.

Each of the 1102 haemophilic patients treated at Haemophilia Centres during 1971 received on average 8447 units of factor VIII. (The unit of factor-VIII activity is based on the amount present in 1 ml of fresh normal citrated plasma and is now established in an International Standard Preparation.) More than 85% of this material was for 'on demand' treatment (which is given whenever the patient feels that a haemorrhage is occurring); and only about 15% was used for major surgery and dental extraction. At many Haemophilia Centres the Directors feel that they could use at least twice as much material as they receive and that the present shortage of materials leads to dangerous selection between more or less urgent cases for treatment and the accumulation of patients on long waiting lists for non-urgent operations.

Some materials available for the treatment of haemophilic patients are listed in Table II.

TABLE II. Therapeutic materials for the treatment of haemophilia

Material	*Factor-VIII activity (u/ml)*	*Possible post-infusion level of plasma factor VIII (% normal)*	*Approx. donor units* made during 1971*
Whole blood	0.3	4–6	—
Plasma	0.6	15–20	44000
Cryoprecipitate	3–5	100+	220000
Freeze-dried concentrate	7–8	100+	25000
Commercial concentrate† (Travenol)	25	100+	—

* These figures exclude the amounts produced in Scotland.
† Preparation approximately 8 × purification of cryoprecipitate.

Whole blood contains too low a factor-VIII level to be useful in treating patients except where blood replacement is required: its administration cannot raise the factor-VIII concentration in the recipient's plasma above 5% of the average normal. Plasma is somewhat more effective and is useful for the treatment of spontaneous bleeding when other materials are not available. When plasma is given frequently to haemophilic patients, however, it can lead to the production of antibodies to plasma constituents such as IgA, and to serious and even dangerous reactions. Thus where purified preparations are available these are always to be preferred. They are, in any case, essential when high plasma concentrations of factor VIII are required, as is the case following dangerous bleeding, for post-operative haemostasis and in certain patients who have factor-VIII antibodies. In fact less than a quarter of the

material at present prepared for the treatment of haemophilic patients in the United Kingdom is in the form of plasma (Table II).

COMPARISON OF FREEZE-DRIED CONCENTRATE AND CRYOPRECIPITATE

At present two types of factor-VIII concentrate are prepared in the United Kingdom, cryoprecipitate and freeze-dried concentrate. In 1971, 220 000 blood donations were used to make cryoprecipitate in England, Wales and Northern Ireland, while plasma from 25 000 donations was used to make freeze-dried material (Table II). The preponderance of cryoprecipitate is due to the fact that this preparation can be made at all Transfusion Centres. From a long-term point of view cryoprecipitate is not necessarily the best preparation for treatment.

The information required to decide which type of concentrate is to be preferred involves a consideration of:

1. The yield of factor-VIII activity in the different fractionation procedures and the recovery of this activity when the concentrate is administered to patients. A very large loss of activity during fractionation or failure to recover the *in vitro* activity in the patient would be disadvantageous.
2. The convenience of the material in preparation and in use considered in relation to the use of blood products for all purposes.
3. The reliability of the material from batch to batch.
4. The complications which might attend treatment with the various preparations.
5. The cost of production of the material.

1. *The Yield of Factor-VIII Activity in Cryoprecipitate and Factor-VIII Concentrate Made in Oxford*

Very large amounts of these concentrates are required to treat haemophilic patients and loss of factor-VIII activity during processing can very greatly affect the cost of production of the material. The ease or difficulty of carrying out the procedure can also affect the cost since such consideration will influence the number of staff and the space required.

Fig 1 shows the yield of factor-VIII activity in cryoprecipitate and freeze-dried concentrate made in Oxford during 1971 and the first 3 mth of 1972. The freeze-dried material was made by a modification of the method of Newman *et al* (1971), the details of the procedure varying somewhat from one month to the next. The cryoprecipitate was made by pooling the plasma from two donations in a blood bottle; the contents were then frozen and the cryoprecipitate was obtained from the plasma as required. At most centres cryoprecipitate is presented as the product of single donations in plastic bags.

The overall yield of factor-VIII activity is calculated as follows:

$$\% \text{ Yield} = \frac{\text{Volume of concentrate} \times \text{Activity of concentrate} \times 100}{\text{Volume of starting plasma} \times 0.9}$$

0.9 is a factor which makes allowance for the fact that the starting plasma contains a larger volume of citrate than the standard plasma used for assay.

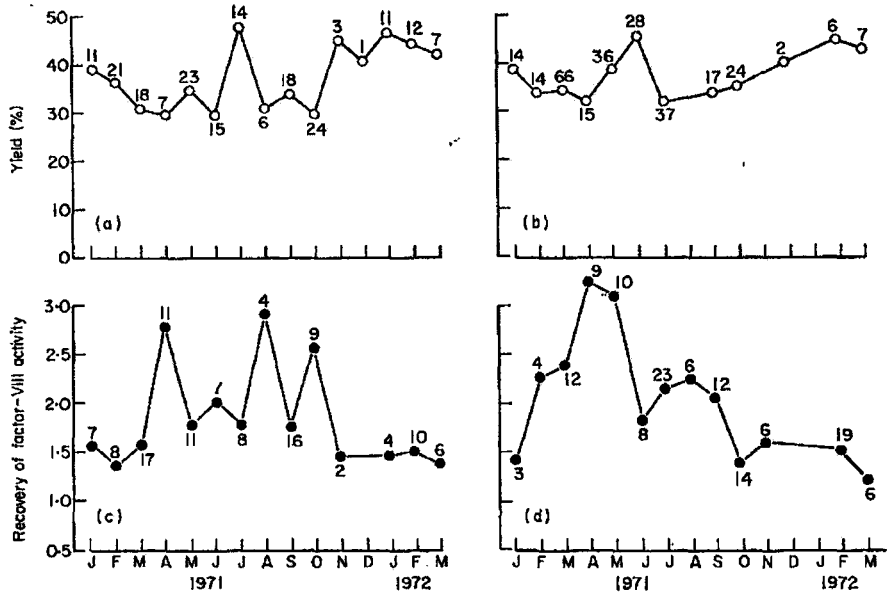

FIG 1. (a) and (b) The yield of factor-VIII activity in different batches of material made and used in Oxford throughout 1971 and during the first 3 mth of 1972. (a) Freeze-dried factor VIII. (b) Cryoprecipitate.

(c) and (d) The recovery of factor-VIII activity in the plasma of severely affected haemophilic patients expressed as percentage rise in factor VIII per unit of dose activity per kg of patient's weight. (c) Using freeze-dried factor VIII. (d) Using cryoprecipitate. The numbers on the graphs refer to the number of assays on which the points are based.

The yields for cryoprecipitate and concentrate are given in Fig 1. The mean yield for cryoprecipitate was 36% and that for concentrate was 37%. There is thus no difference between the two procedures from the point of view of average yield of factor-VIII activity. These figures, of course, only apply to the procedures used in Oxford.

In addition the *in vivo* recovery of activity for the two materials was measured over the same period of time. This *in vivo* recovery is defined as the rise in the patient's plasma factor-VIII level, expressed as percentage of the average normal per unit of factor VIII administered, per kg of the patient's body weight. The maximum possible recovery of activity by this method is 2.4% (Biggs & Macfarlane, 1966). This figures of 2.4%/kg assumes a plasma volume of 41 ml/kg in the patient and assumes that the factor VIII contained in the dose is all recovered in the patient's plasma. It is also assumed that the volume of the dose does not significantly alter the patient's plasma volume. For many years the freeze-dried concentrate has given a value of about 1.6%/kg on average at the Oxford Centre. The results for 1971 gave a mean value of 1.6%/kg for cryoprecipitate and 2.0%/kg for the concentrate. These data, taken from the same group of patients over the same time interval, show that there is no significant difference between the average yield of factor-VIII activity made by the two procedures but that the freeze-dried concentrate activity may have been rather better recovered in the patient.

The fluctuations in values shown in Fig 1 probably have many causes, such as changes in factor-VIII assay standards or unusually good recovery of factor-VIII activity in some patients. The yield and *in vivo* recovery of activity are not assessed independently. The yield of activity is calculated from the assay of doses given to patients and the recovery of activity in the patients is calculated using the same dose assays. If for some reason the dose value is wrongly assessed and the concentration in the patient correctly measured (or vice versa) the discrepancy will be seen in the recovery of activity in the patient. For example, a high yield of activity in the material may be achieved by an improved fractionation procedure, but if this yield is associated with a consistently low recovery of activity in the patient, then the adoption of that particular fractionation procedure would have to be delayed for further study.

2. *Convenience of Manufacture and Convenience and Safety in Use*

Cryoprecipitate is easier to produce than freeze-dried concentrate if small amounts of concentrate are required. On a large scale the manipulation, storage and reconstitution of thousands of single bags of cyroprecipitate may be much less satisfactory than a co-ordinated large-scale fractionation which produces a stable freeze-dried preparation containing good factor-VIII activity.

The way in which the preparation is made available to the doctor can much affect patient safety.

(a) *Cryoprecipitate.* The material is usually presented frozen in plastic bags, each bag containing cyroprecipitate prepared from plasma from one blood donation. In Oxford the blood for making cryoprecipitate is collected in plastic bags. These are centrifuged within 6 hr of collection and the plasma from two bags is pooled in British Standard Transfusion bottles. These bottles are frozen at −30°C in a refrigerator with large refrigeration capacity and stored at −30°C until needed. On the day before cryoprecipitate is to be made the bottles are well spaced out in a cold room at 2–6°C. When all the ice has melted the cryoprecipitate is collected by centrifuging at 1000 *g* for 30 min. The supernatant plasma is removed aseptically and used for further fractionation. The cryoprecipitate, still in the bottles, is refrozen until needed. The amount of cryoprecipitate given in a single dose may vary from the product of four to the product of 40 blood donations. At most centres reconstitution involves thawing the contents of single bags, pooling the material in the bags, washing out the bags and adding the washings to the already pooled material. The work involved and the time taken are considerable.

The procedure for making up cryoprecipitate for administration to patients varies very much from one centre to another. In some Regions the work is done in the blood transfusion service and in others by experienced Haemophilia Centre staff, but at many hospitals it is probable that the doses are reconstituted by house officers and nurses who have little previous experience in this particularly time-consuming occupation. The process is open to many abuses unless skilled staff are employed. If the material is thawed at too high a temperature activity will be lost. If the bags are not washed out, up to half of the activity may be left inside. If cryoprecipitate were presented to the clinician as the pooled product from five or 10 donations, many of these difficulties would be eliminated from the hospital but the actual work would be transferred to the transfusion service. There would be little overall reduction in effort although the final product given to the patient would be more reliable in activity.

TABLE III. Factor-VIII values of cryoprecipitate, showing the number of samples tested at five centres, the number of cryoprecipitates per dose (cryo) and units of factor VIII per donation (U). The two-stage method was used for the assay of factor VIII at all but Centre 2.

Sample*	Centre 1		Centre 2†		Centre 3		Centre 4‡		Centre 5			
									1971		1972	
	Cryo	U	Cryo	U	Cryo	U	Cryo	U	Cryo	U	Cryo	U
1	10	100	5	66	8	43	11	48	10	81	6	24
2	8	120	7	15	8	45	10	39	9	94	8	79
3	8	100	5	39	17	80	14	51	8	27	9	44
4	8	130	5	60	10	80	14	62	10	27	8	34
5	16	87	7	51	20	31	10	60	9	69	8	28
6	16	112	10	12	20	44	10	83	8	39	10	55
7	12	80	5	48	15	70	6	34	9	65	8	68
8	10	98	8	62	10	35	8	61	8	85	10	69
9	12	92	7	63	10	58	12	44	10	54	7	32
10	26	74	10	35	8	77	12	50	8	49	8	51
11	14	49	10	26	8	41	10	69	8	83	9	76
12	20	48	10	40	8	45	11	47	7	97	9	25
13	12	66	10	62	8	40	10	40	10	75	10	36
14	18	50	5	19	10	49	12	63	8	79	10	40
15	12	47	10	64	6	53	6	51			6	57
16	20	37	10	60	6	69	14	50			9	47
17	8	88	10	101	6	60					10	29
18	14	89	7	29	10	69					8	22
19	6	46	7	40	8	61					8	38
20	12	43	10	32	5	60					8	42
21	12	95	8	45							10	56
22	12	100	10	51							8	37
23											9	34
24											10	27
25											8	28
26											8	27
27											8	60
28											8	45
29											10	24
30											8	48
31											7	70
32											9	66
33											10	72
34											8	88
35											8	59
36											10	66
37											10	27
38											8	56
39											10	38
40											6	99
Mean	13	79.5	8	46	10	55.0	10.6	53.2	8.8	66.0	10.3	48.0
Range		37–130		12–101		31–80		34–83		27–97		22–99

* The samples tested at the different centres were different but the results were based on the same assessment of the factor-VIII unit.

† One-stage factor-VIII assay.

‡ Each bag was assessed separately.

Small alterations in the process of manufacture will affect the yield, but none of the material for clinical use is assayed before it is administered and thus the activity of the dose is not known before it is given to the patient. This preparation must be stored in a deep freeze at a temperature not higher than −30°C.

(b) *Freeze-dried concentrate.* This is presented in bottles each containing about 400 units of factor-VIII activity. The factor-VIII content of the particular material is indicated on the bottle. Each bottle is reconstituted by adding 25, 50 or 100 ml of sterile pyrogen-free distilled water (Water for Injection B.P.). The amount required for one dose may vary from one to 10 bottles, depending on the weight of the patient and the reasons for treatment. The dose is given by intravenous infusion or by injection using a syringe, depending on the volume to be used.

The United Kingdom material at present available over the whole country is of varying solubility. Relatively insoluble material can be more difficult to use but the best material dissolves almost instantly even at room temperature. There is no reason, given adequate staff and facilities, why all the material should not be equally soluble. Material which has good solubility is very convenient to use, easy to make up and the dose can be determined accurately. This preparation, in its freeze-dried state, may be stored for over a year at 4°C without significant loss of activity.

3. *The Reliability of Material from Batch to Batch*

Table III gives the results of a study of the factor-VIII activity of cryoprecipitate in 1971–72 at five Haemophilia Centres. It will be seen that the dose assays do not reflect variation of single donor units of blood since each dose was made up of pools of from five to 26 donors. The assayed factor-VIII values of the samples are very variable from one sample to another which suggests variable yield from time to time at each Transfusion Centre. There are also large differences among the centres.

The freeze-dried material made in large batches is stable on storage and can be assayed to give a reliable estimate of dose activity.

4. *Complications of Treatment*

At the time of making the survey of jaundice in haemophilic patients from which the present conclusions are drawn the incidence of HB Ag was 1 per 800 donors. Freeze-dried concentrate was made from pools of plasma derived from about 200 donors. A pool of plasma derived from many donors has a predictably greater chance of containing the hepatitis virus than plasma from a single donation. There is always theoretically a greater chance of a patient contacting hepatitis if he is treated with a freeze-dried preparation than if plasma or cryoprecipitate are used. But there is the possibility that the development of jaundice may be dose-related in these particular multi-transfused patients and that single infected bottles may be more dangerous to the individual patient than pooled material in which the virus is diluted and which may contain HB Ab. In fact the frequency of hepatitis in severely affected patients did not seem to increase very greatly with increased use of freeze-dried concentrate (Biggs, 1974). The conclusion is also supported by data collected in the United States (Kasper & Kipnis, 1972). On the other hand, mildly affected haemophilic patients, to whom very little treatment is given, do seem to have a higher incidence of hepatitis if large-pool fractions are

used. Kasper & Kipnis (1972) showed this, as did also the British survey, where female carriers of haemophilia treated with concentrate had a high incidence of hepatitis.

Since the majority of patients are in the multi-transfused category, the increased risk of exposure to hepatitis would not seem to be an important disadvantage to the use of concentrates from pooled material. Hepatitis associated with the presence of HB Ag is decreasing now that donors are being screened for the presence of this antigen; it is not expected, however, that screening will entirely eliminate this complication because of the relative insensitiveness of the methods suitable for routine use and because there may be more than one serological type of HB Ag.

The incidence of factor-VIII antibodies does not seem to be related to the type of material used.

5. *Cost of Preparation of Factor-VIII Concentrates*

The cost of preparing cryoprecipitate or freeze-dried concentrate in Great Britain cannot be computed because it is a matter of opinion to know how much of the cost of the transfusion service as a whole should be included in the estimate for one product. Various estimates have placed the cost of making one clotting factor unit at between 1.25 and 1.5 pence. These estimates are certainly too low because they exclude important items of expenditure. The commercial concentrate of factor VIII now available cost 10 pence per unit and using these the cost per annum of treating haemophilic patients might be £3–4 million. The cost of preparing material of equal value within the transfusion service would undoubtedly be less.

AMOUNTS OF FACTOR-VIII CONCENTRATES REQUIRED TO TREAT HAEMOPHILIACS IN GREAT BRITAIN

On Demand Treatment

Assessment of the amounts of material required cannot be based on the amounts at present given since this is known to be less than optimum at most centres. Careful observation of the 50 haemophilic boys resident at Lord Mayor Treloar College (Rainsford & Hall, 1973) gives an average number of bleeds per boy per year of 25 and these 25 bleeds required altogether about 30 doses of material. Each of these doses may be assessed on a more general basis as 'the material required to raise the plasm factor-VIII level to 20%'. It is assumed that an average patient's weight is 50 kg (95 patients were weighed at the Oxford Haemophilia Centre in 1971 and the average weight was 51.6 kg). It can be calculated that 2.4% is the maximum rise in factor VIII that can be expected following a dose of 1 u/kg (Biggs & Macfarlane, 1966). The minimum amount of material that could be required to cause a rise of 20% in a patient weighing 50 kg is thus:

$$(50 \times 20)/2.4 \text{ units} = 416.7 \text{ units}$$

On average only about 66% of the dose activity is recovered in the patient's circulation. Thus the average dose per patient would be:

$$416.7 \times (100/66) \text{ units} = 631 \text{ units}$$

In practice, using the concentrate, patients receive one or two bottles for a dose since it

would clearly be very wasteful to be too precise. Since the preparation of concentrate is associated with a loss of about 60% of the factor VIII starting activity the amount of plasma from which 631 units could be derived would be:

$$631 \times (10/4) = 1577 \text{ ml of donor plasma}$$

Suppose each donor provides 200–220 ml plasma, then each treatment should on average require material from seven or eight donors. The amount required if cryoprecipitate were used would depend on the recovery of factor VIII in the preparation. With low recovery the number could be as high as 12 donations for each treatment. The theoretical estimate of material from seven or eight donations per dose is unlikely to overstate the case since, as can be seen from Table III, the average amounts of cryoprecipitate given to each patient often exceeded 10 donations per dose.

These calculations may be considered according to the distribution of concentrate to various types of patient. Fig 2 shows the distribution of bleeds per year per boy based on

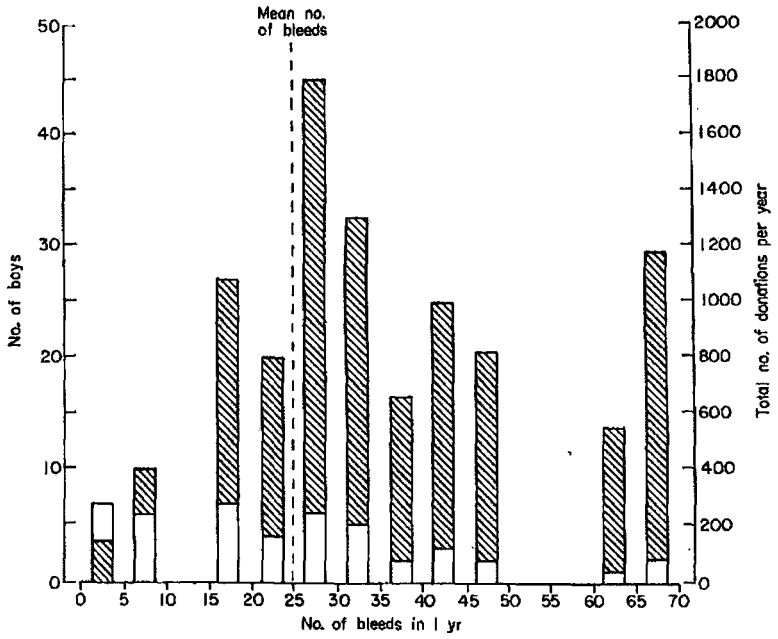

FIG 2. The number of bleeds per year for 45 boys severely affected with haemophilia (open columns). The amount of therapeutic material used for the same boys per year expressed as the number of equivalent single blood donations (hatched columns).

data for 45 boys during the spring term of 1971 at Lord Mayor Treloar College. It will be seen that the number of bleeds per boy varies from 0 to 70 with a mean of 25. In general it is a characteristic of those patients who bleed frequently that they continue to bleed frequently but the boys who approximate more closely to the mean may have spells of frequent bleeds

interspersed with periods of freedom from trouble. The material that would be required to treat these boys according to the above calculations is also shown in Fig 2. It will be seen that the boys with above average number of bleeds (56% of the total) consume 75% of the material.

From these calculations the total amount of material considered desirable to treat these Treloar boys for 1 yr is the amount derived from 9690 blood donations or approximately 678 300 factor-VIII units. In 1971 cryoprecipitate derived from 7270 blood donations was used for the 9 mth treatment while the boys were at school. For a whole year the amount would be derived from 9700 blood donations. Thus the calculation agrees well with the observations for the boys at Treloar College. The amount per boy is the product from 194 blood donations or about 13 500 factor-VIII units.

Taken over the country as a whole, the estimated 2434–3000 patients would require treatment from 7–8 × 2434–3000 × 30 blood donations a year, which is the product of 511 140–720 000 blood donations a year. The lower figure is likely to be an underestimate since the number of haemophiliacs probably exceeds 2434. In terms of factor-VIII units the calculated amounts are approximately 35 779 800–50 000 000 factor-VIII units.

It may be thought that the boys at Treloar College are not representative; selection to attend the school could indicate particular severity of bleeding. In fact the boys attend the college for a wide variety of reasons and some of the boys bleed infrequently.

Major Surgery

When calculating the requirements for operations, patients who are mildly affected must be included as well as those who are severely affected. An additional 1000 patients have been added to make this allowance. It is assumed that each patient has a life expectancy of 50 yr and that each patient will require one major surgical operation in his life. According to these assumptions the number of operations per year would be:

$$4000/50 = 80 \text{ operations}$$

In fact, during 1969, 44 operations were carried out at Haemophilia Centres but many patients still remain on waiting lists. If each operation requires the level of factor VIII to be raised to 100% daily for 10 days then the amount of material required for each operation will be the product from:

$$35 \times 10 = 350 \text{ blood donations}$$

(the product from 35 donations being the amount required per day); and for 80 operations the total amount would be derived from:

$$350 \times 80 = 28\,000 \text{ donations per year}$$

or 1 960 000 factor-VIII units.

Dental Extractions

For dental extractions it is assumed that each patient will require three such operations in his life giving a total of 240 per year as an estimate (in fact 173 patients underwent dental extractions at Haemophilia Centres during 1969). Each operation should require 2330 factor

VIII units (Walsh *et al*, 1971) or the material from 35 donors. Thus the total material should be that derived from:

$$35 \times 240 \text{ blood donations a year} = 8400$$

This is approximately 600 000 factor-VIII units.

Total Requirements of Factor VIII

Thus for all types of bleeding (spontaneous, at operation and for dentistry) the total material required is likely to be that derived from 547 540–750 000 blood donations per annum. This estimate includes 'on demand' treatment and the upper figures assumes the present best yield of factor VIII. It implies the use of concentrate derived from 222–230 blood donations per severely affected patient per year. Expressed as factor-VIII units the range is likely to lie between 38 327 800 and 53 000 000 factor-VIII units. The estimate is of the same order as that of the American survey, which suggests that a minimum number of 3 million blood donations would be needed in the U.S.A., or the product from 270 blood donations per severely affected patient per year. Our figure also agrees well with the estimate of Lazerson (1972) that each well-treated patient requires cryoprecipitate derived from 222 blood donations per year and with a Spanish estimate giving a figure of the product 181 donations per patient per year.

Home Treatment

Home treatment involves the administration of therapeutic material in the home by a relative, by the patient to himself, or by the general practitioner. This form of treatment is becoming accepted and experience shows that it does not involve the use of more material than does good hospital care (Lazerson, 1972). There is no doubt that the freeze-dried concentrate is the best material to use for home care (C. R. Rizza & J. M. Matthews, personal communication, 1972). Were the most severely affected 1000 patients in the United Kingdom allocated to home treatment this would require material derived from about 250 000 blood donations of freeze-dried concentrate or 17 500 000 units of factor-VIII activity but this would be instead of, not in addition to, the doses given on demand in hospital.

Prophylactic Treatment

As far as we are aware, there has been no properly controlled trial of prophylactic treatment in haemophiliacs. Prophylactic treatment for haemophilic patients would require much more material since this treatment envisages regular administration of factor VIII once or twice a week to the patient regardless of whether or not bleeding has occurred. The estimate of the amount required for such treatment in the U.S.A. is the product from 13 million blood donations (Stengle, 1972). For Great Britain, a corresponding estimate would be about 3 million donations, but Lazerson (1972) estimates that 636 blood donations per patient would be needed for prophylaxis, which would give a maximum figure for Great Britain of the product from 2 million donations. It is not at present certain that this prophylactic treatment is desirable for even the most severely affected patients. It is certainly at present impracticable. In the U.S.A. about 4% of patients receive prophylactic treatment. Should it eventually be shown that such treatment is effective in preventing haemorrhage and without serious

complications and should transfusion practice alter sufficiently to make this treatment feasible then allowance would have to be made for this when calculating the amount of material required to provide treatment for haemophiliacs in this country.

DISCUSSION

The present study has been made from the point of view of the Haemophilia Centre Director, whose primary responsibility is the day-to-day care of haemophilic patients. In fact about 1.7 million blood donations are collected annually by the Blood Transfusion Service in the United Kingdom and traditionally the bulk of this blood is supplied as citrated whole blood for the treatment of acute haemorrhage, surgical operations and anaemia.

The idea that one third to one half of the donations should be collected in plastic containers and have a proportion of the plasma removed for fractionation to provide factor VIII seems at first sight unreasonable when viewed from the point of view of the transfusion service. But several developments in recent years have tended to alter the traditional image of the transfusion service as a purveyor of whole blood. For many patients packed cells may be equally as effective as whole blood. Fractions other than factor VIII are also very valuable—for example, platelets, concentrates containing factor II, IX and X, immunoglobulin and albumin. In the present communication the needs of the haemophilic population have been highlighted but in the future the rational use of all human blood products may become the most important priority of the transfusion service.

The cost of haemophilia treatment is mainly the cost of producing suitable and sufficient amounts of concentrates. Viewed in an integrated service it is difficult to separate the cost of haemophilic treatment from the cost of supplying other components. One cost which can be calculated with certainty is the price of commercial factor-VIII concentrates and this is 10 pence per clotting factor unit. Using this commercial material the treatment of each patient is likely to cost £1800 per annum. Undoubtedly United Kingdom material would be equally effective and very substantially cheaper than the commercial material in the long run. It should perhaps be noted that poorly treated haemophilic patients who spend a lot of their time in hospital at a cost of more than £100 a week are not cheaply maintained by the State.

CONCLUSIONS

1. Calculations suggest that the amount of material required for optimum treatment of all the haemophilic patients in Great Britain would be derived from 547 540–750 000 blood donations a year. This material would be used for 'on demand' treatment of all patients, including 'home treatment' of the 1000 or so patients who might benefit from it. The present supply is that derived from approximately 300 000 blood donations per year, of which most is in the form of cryoprecipitate.

2. Comparison of cryoprecipitate and freeze-dried concentrate made in Oxford suggest that from the point of view of conservation of the factor-VIII activity of the donor plasma and of recovery of infused activity in the patient the two preparations are equally efficient. It should be noted that the Oxford cryoprecipitate is among the best cryoprecipitate preparations tested.

3. Cryoprecipitate is more difficult to make up for administration to the patient than freeze-dried factor-VIII concentrate. Cryoprecipitate also varies very much in potency from batch to batch and from centre to centre and thus standardized dosage schemes cannot be established using cryoprecipitate.

4. For home treatment it is our opinion that a freeze-dried concentrate is the therapeutic material of choice. The gradual introduction to home treatment of the most severely affected patients who have the most frequent bleeding would reduce hospital management of haemophilia by half. To give this proportion of patients (approximately 1000) home treatment would involve the use of factor-VIII concentrate from about 250 000 blood donations a year. The present (1973) total of factor-VIII concentrate is derived from 40 000–45 000 donations a year.

5. The number of donations contributing to pools of plasma used to make concentrates does affect the probability that a particular pool may contain hepatitis virus. However, the incidence of jaundice in multi-transfused patients seems to be, to some extent at least, dose related. In practice the incidence of jaundice in multi-transfused haemophilic patients does not rise very greatly with the use of freeze-dried concentrates. In any case, with universal screening of donors for hepatitis B antigen now in operation the danger of infection will decrease to some extent in the future. The incidence of anti-factor VIII antibodies is not affected by the type of human material used to treat the patients.

6. We think that within the next few years a great effort should be made to increase the amount of plasma which is fractionated in the United Kingdom to produce both cryoprecipitate and freeze-dried preparations of factor VIII. From the point of view of patients with haemophilia present estimates suggest a need for 547 540–750 000 donations to be fractionated annually to produce factor VIII. Within the next few years it is hoped that most of this material may be provided in the form of freeze-dried concentrate rather than as cryoprecipitate. On a national scale this need for factor VIII must be co-ordinated with other demands on the Transfusion Service, for example the need for albumin fraction. Clearly a 20-fold increase in the production of freeze-dried factor VIII cannot be achieved overnight but it is to be hoped that very substantial increase may occur without too much delay. The present estimate of the need for factor VIII is based on data now available and as time passes and more concentrates become available the true amounts of factor VIII required will be defined more certainly. Our present opinion is that the provision of freeze-dried material from 500 000 blood donations annually will do as much to improve the lives of haemophilic patients as was achieved several years ago by the provision of cryoprecipitate.

7. Freeze-dried factor-VIII concentrate of good quality is now available commercially. At present, treatment of patients at many of the Haemophilia Centres in this country involves a dangerous policy of balancing the needs of one patient against those of another and of delaying reconstructive orthopaedic surgery which would greatly improve the lives of many patients. We believe it very important that the material made in the United Kingdom, which is second to none in quality, should be substantially increased in amount.

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