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Chapter 4. The Amount of Blood Required Annually to make Concentrates to Treat Patients with Haemophilia A and B

ROSEMARY BIGGS

During the first 25 years of this century the effectiveness of blood transfusions in the treatment of haemophilia was established. During the next 25 years whole blood, and towards the end of this time, plasma in small amounts became available to treat the patients. Large scale fractionation of human blood before 1950 was considered quite impracticable. Blood collection was concerned with the provision of whole blood for the saving of lives of war casualties, to treat severe anaemia of various sorts and to prevent exsanguination following or during major surgical operations.

Improvements in transfusion techniques, particularly the use of plastic bags for collecting blood, have made it possible to consider the more effective use of plasma and red cells. The plasma can be removed from fresh whole blood in plastic containers without exposing the contents of the containers to contamination. A simple method (cryoprecipitation) to separate factor VIII from plasma was discovered (Pool & Shannon, 1965) which could be carried out in any blood bank. The discovery of cryoprecipitate has provided a widely available effective haemophilia treatment based on close co-operation between local physicians and Blood Bank organisers. In addition laboratories for protein fractionation have developed methods for preparing freeze dried clotting factors from plasma on a large scale. Such freeze dried products are now also made commercially from plasma collected by plasmapheresis.

It is now clear (NILH Survey, 1972) that very substantial amounts of blood are already being fractionated in the USA and other countries to produce factor VIII concentrates. For example it seems that 1·5 million litres of plasma were fractionated annually in the United States by commercial firms alone during 1970 and 1971. Most of this plasma was derived from plasmapheresis but if it were derived from single whole blood donations it would require at least 7·5 million single donations. In the United Kingdom between 1·5 and 2 million donations is the total amount collected annually by the Blood Transfusion Service.

The time seems appropriate to try and assess the amounts of factor VIII required in the U[illegible]d Kingdom and to make some decision about the best type

of material to make. Viewed on a National scale there are many things which need to be taken into account. There is no need to consider the problem of supply of blood to make factor IX separately since sufficient factor IX to meet the needs of Haemophilia B patients can be derived from the same plasma which is processed to give factor VIII and other valuable plasma derivatives.

The main considerations which affect an assessment of the amounts of factor VIII required are:

1 the total number of patients in the population;
2 the average amounts given to each patient annually;
3 what type of material is it best to use?
4 how can the material be provided?

The number of patients with haemophilia A in the population

The prevalence of haemophilia in the population depends on the number of patients born with the disease and the number who survive into adult life. The number born with the disease (the incidence) depends on the number of families in which the abnormal gene is inherited and on the number of cases contributed by mutations. In 1935, when Haldane considered the inheritance of haemophilia, it was rare for haemophilic patients to reach adult life and the prevalence of haemophilia was estimated by Haldane to be about 2 per 100,000 of the population of London.

Estimates of the prevalence of haemophilia in different countries are given in Table 4.1. In most of these estimates of frequency it seems a little unlikely that all of the patients were known to the doctors making reports. The NILH Study is exceptional in that great care was taken to detect all of the patients in the United States. First of all a postcard was sent to all haematologists, all members of the American Medical Association thought to treat haemophilia and to selected populations of internists, paediatricians, pathologists, etc. The postcard served simply to identify those doctors who treated haemophilic patients in the years 1970 and 1971. The identified 'treaters' were then asked to complete much more detailed questionnaires and the answers were clarified by telephone if necessary. This is the most ambitious and comprehensive attempt to identify all of the patients in a very large population. This survey gives the highest present estimate for the incidence of the disease but it is not much higher than two other recent estimates for localities inside the USA.

In the United Kingdom the Directors of the Haemophilia Centres in the country were asked to make returns of the numbers of patients treated during the years 1969, 1970 and 1971 and a report of this work was published in 1974

Table 4.1. Prevalence of haemophilia in various populations.

Author	Country or city	Year	Prevalence per 100,000 of population
Haldane	London	1935	2·0
Andreassen	Denmark	1943	2·2
Sjolin	Denmark	1960	3·6
Ramgren	Sweden	1962	3·35
Nilsson	Sweden	1972	5·5
Nilsson	Sweden	1976	6·9
Ikkala	Finland	1960	3·7
Martin-Villar *et al*	Spain	1971	2·3
Martin-Villar *et al*	Spain	1976	3·3
Larrain *et al*	Chile	1972	3·5
Rosenberg	Brazil	1972	7–10
NHLI Study	U.S.A.	1972	9·0
Sulz	New York	1972	7·3
Hemophilia Foundation	Michigan	1971	7·3
Biggs	Great Britain	1974	6·0
Cash	Edinburgh	1975	6·3
Mandalaki	Greece	1976	6·25
Mannucci & Ruggeri	Italy	1976	9·8
Brackmann *et al*	West Germany	1976	9·2
Allain	France	1976	5·3
Soulier	France	1976	6·6
Davey	Australia	1976	5·9
Masure	Belgium	1976	4·6

(Biggs, 1974). During this time about 1700 haemophilia A patients are known to have been treated at these Centres. During these years no attempt was made to sample hospitals outside the haemophilia centres and in fact about half of the cryoprecipitate made in the Transfusion Service for the treatment of haemophilic patients was apparently not used at the Haemophilia Centres. It seems therefore that only about half of the patients were treated at the Haemophilia Centres. The 1700 patients represents about 3 per 100,000 of the population. Since this report, the survey has continued and the number of haemophilia A patients known at the U.K. Centres had increased to 2,600 in 1975 and there may still be patients who are not known at the Centres. Thus 3,300 haemophilia A patients, about 6 per 100,000 of the population, is unlikely to be an over estimate of the number of patients in the United Kingdom.

From Table 4.1 it will be seen that the prevalence of haemophilic patients has increased since the middle of the present century. This increase may be due to two causes:

1 As treatment has improved more patients may have presented for treatment at specialist centres where statistics are kept. There may not actually be more patients but more of the existing patients may be known.

2 The patients born with the condition may live longer than they did before infusion therapy was available. This is certainly a factor since the average age of death of haemophilia A patients is now probably about 40 whereas it was 16–20 years earlier in the century (Ramgren, 1962; Andreassen, 1943).

The increase attributable to longer survival in the United Kingdom is almost certainly not complete since the average age of patients known at the Haemophilia Centres is below that of the whole population. In comparison with the general population there is an excess of haemophilia A patients in the age group 10 to 30 (Biggs, 1974).

We must, therefore, expect a further increase in the number of haemophilic patients who require treatment. In addition, seen in the long term, a further increase will result from mutation. Haldane (1935) pointed out that any gene resulting from mutation must die out if it caused malfunction sufficient to cause death before puberty. Such a gene could not be passed to future generations since the affected persons would have no children. If contrary to expectation such a harmful trait is found to survive then its incidence must be maintained by mutation. The incidence will represent a balance between loss of genes through early death of patients and the formation of new genes by mutation. For a sex-linked condition like haemophilia, Haldane (1947) represented this balance by the equation:

$$I = \frac{3m}{1\text{-}f}$$

where I is the incidence of the condition at birth before selection due to early death has occurred and m is the mutation rate per generation, a generation being taken to be about 30 years.

f = fitness of haemophiliacs. The fitness refers to the number of children born to haemophiliac fathers in comparison to those born to normal males at the same era of time. Thus if 1 child is on average born to a haemophiliac where 2 are born to normal males then the fitness of the haemophiliac would be ½ or 0·5.

Haldane (1947) applied this equation to figures then available from Denmark (Andreassen, 1943). From these figures $I = 13{\cdot}3 \times 10^{-5}$ live male births. Haldane calculated $m = 3{\cdot}2 \times 10^{-5}$ per generation and $f = 0{\cdot}280$. Subsequent estimates (Table 4.2) have given similar results with the exception of those of Barrai *et al* (1968). The calculations of Barrai *et al* are based on very low figures for the incidence of Haemophilia A which were derived from questionnaires to selected doctors. There is every reason to believe that the incidence of Haemophilia A was much higher than they supposed at the time.

Haldane took the incidence of Haemophilia A to be $13{\cdot}3 \times 10^{-5}$ males which is identical to the modern estimate of the prevalence of haemophilia which

Table 4.2. Genetic data about haemophilia.

Author	Incidence at birth $\times 10^{-5}$	Prevalence $\times 10^{-5}$	Mutation rate $\times 10^{-5}$ males per generation	Fitness
Andreassen** (1943)	13·3	4·5	1·9	0·570
Haldane** (1947)	(13·3)*	(4·5)*	3·16	0·280
Ikkala (1960)	15·4	5·9	3·2	0·236
Ramgren (1962)	12·9	6·6	—	—
Vogel (1955)			2·7	0·386
Bitter (1964)	16·0		4·1	0·240
Barrai *et al* (1968)	(5·5)		(1·31)	(0·280)
Means	14·1		3·01	0·342

( ) not included in means
* copied from Andreassen
** Haemophilia A and B included.

is 6–7 $\times 10^{-5}$ in relation to the whole population both male and female. The improved survival of haemophiliac patients as a result of infusion therapy must improve the fitness of haemophiliacs. Using the above formula improved fitness of haemophiliacs to 0·50 or 0·80 from Haldane's figure of 0·28 would lead to an increased incidence of haemophiliacs from Haldane's figure of $13{\cdot}3 \times 10^{-5}$ to 19·2 or 48×10^{-5}. It is in fact difficult to predict the extent to which improved survival will affect the fitness of haemophiliacs. The improved survival will be accompanied by pressure towards family limitation from the general trend in the population during the next 200 years and through genetic counselling. It can, however, confidently be predicted that any increase in the number of haemophiliacs from increased fitness will be slow. For one generation all the abnormal sex-linked genes transmitted by surviving haemophiliacs will pass to their daughters. Thus the increased incidence will await the birth of grandsons. After two generations the incidence will show an irregular tendency to increase for several centuries till the new equilibrium is reached.

For the present an estimate of 6 haemophilia A patients per 100,000 of the population will be assumed to give a fair estimate of the number of haemophilia A patients requiring treatment.

The amount of factor VIII expressed as units of activity required on average by each haemophiliac

The amount of factor VIII used for each haemophiliac in the United Kingdom has increased steadily year by year as more material has become available. In 1974 the average usage in the United Kingdom was about 12,500 units per patient per year. This is rather less than the amount of that used in the U.S. as

recorded by the NILH study for 1790-1971 which was about 14,000 units. In 1975 the amount of factor VIII used per patient in the United Kingdom was 14,800 units.

The haemophilic patient receives factor VIII treatment for the control of spontaneous bleeding into muscles and joints, for the control of bleeding after accidents, dental extraction and operations. Ten years ago the main use was to protect patients after dental extraction, surgery and accidents but now 80% of the material used is for the control of spontaneous bleeding into joints and muscles. Current practice after dental extraction and surgery can readily be defined and the amounts of material likely to be needed for the safety of the patient is easily predictable.

In the case of so-called spontaneous bleeding the amounts needed are not so easily to be foreseen. The patients are treated for spontaneous bleeding either at hospital as out-patients or at home. The patients who attend as out-patients may have to be driven by car or ambulance for long distances to reach the special centre. This makes them hesitate to come to hospital especially in the case of a small child for whom a visit to hospital may be frightening. Older patients are also often hesitant to bother the doctor. Thus there are reasons to suppose that patients who are treated as hospital out-patients receive less than optimum treatment because they hesitate for various reasons to avail themselves of treatment. There may also be some reluctance on the part of some doctors to treat patients on a purely 'on demand' basis. It may be thought that if there is no obvious physical indication of bleeding, treatment should be withheld. The treatment given in the past to patients for spontaneous bleeding may also have been limited by the amounts of cryoprecipitate and NHS concentrate available at the haemophilia centres and by the prohibitive cost of commercial factor VIII concentrates.

There is thus reason to suppose that the present usage of factor VIII averaging about 12,500 units of factor VIII activity per patient annually is not the optimum amount required to treat haemophilia A patients.

The number of doses given per year to haemophilia A patients in Oxford

A concept which should be mentioned at this stage is the record of the amount of material given to haemophilia A patients in terms of the number of doses of material received by each patient every year. The number of doses given per year gives an idea of the work done at a centre and the number of units of activity per dose will reflect to some extent the amount of activity dispensed in each bottle or ampoule. The amount per dose will also reflect experience in the management of patients and is likely to be influenced by the predictability of the activity of a particular preparation.

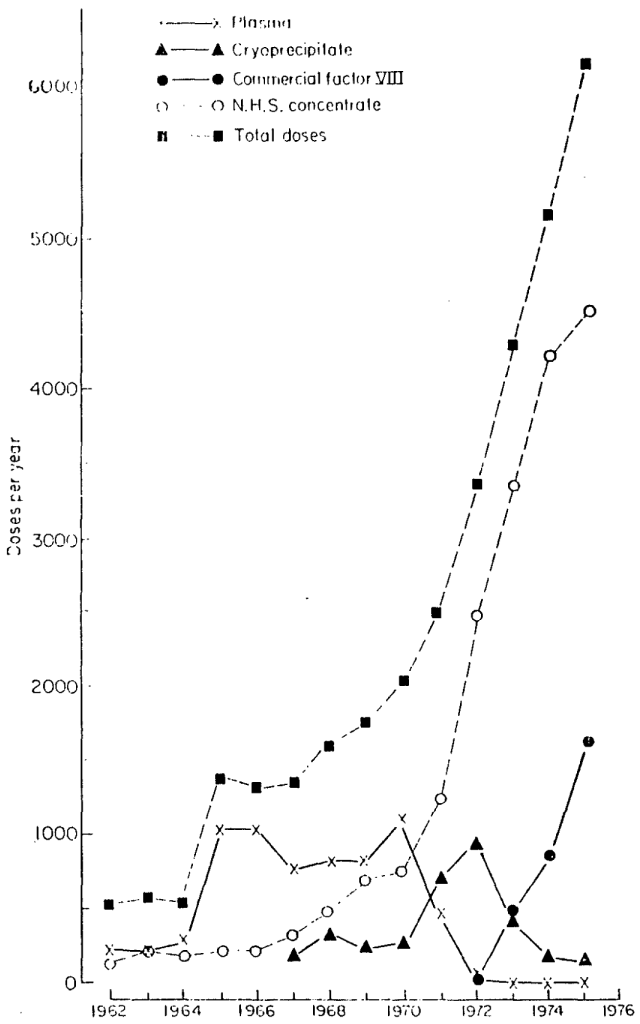

Figure 4.1. The numbers of doses of various sorts of factor VIII given to haemophilia A patients at the Oxford Haemophilia Centre from 1962 to 1975.

Since 1962 data have been collected about the number of doses of factor VIII given to haemophilic patients in Oxford. The information is summarised in Table 10.1, Figures 4.1 and 4.2. In Figure 4.1 the information is related to the different sc of material used. It will be seen that from 1962 to 1964 small

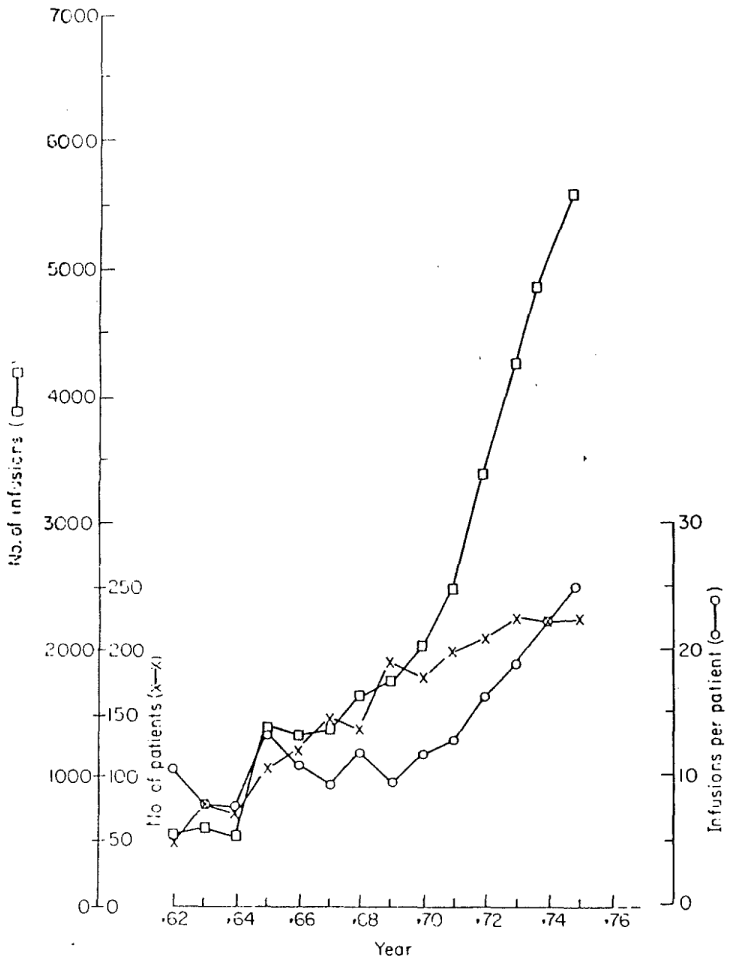

Figure 4.2. The total number of infusions given to haemophilia A patients at the Oxford Haemophilia Centre (□). The numbers of patients treated each year (×) and the number of infusions per patient (○) are also shown.

amounts of human factor VIII and concentrate were used. During this time and until cryoprecipitate was introduced in 1967, small amounts of animal factor VIII were also used for patients who did not have inhibitors. From 1964 to 1965 there was a large increase in the production of plasma by the Oxford Transfusion

Service. In 1967 there was an increase in the use of human concentrates associated with the start of production of freeze dried concentrate in Oxford and with the introduction of cryoprecipitate. The use of plasma was phased out in 1971 and in 1973 the freeze dried concentrate had largely taken over from cryoprecipitate.

In Figure 4.2 are shown the doses of factor VIII given in relation to the numbers of patients treated. There was an increase in the number of patients treated during the decade 1960 to 1970. Since 1969 there has also been an increase in the number of doses given per patient per year.

As would be expected this dual increase has been associated with a very marked increase in the total number of doses given annually. In 1975 the average number of doses per patient per year for haemophilia A patients was 24·4 (Table 10.1). Inspection of Figure 4.2 suggests that there is likely to be an increase in the future if enough therapeutic material is made available. Since 1972 there has been a rapid increase in home therapy for Oxford patients. By 1975 nearly all of the very severely affected patients who live in the Oxford Region were on home therapy and thus the number of doses given at the Centre have decreased slightly.

Information can also be derived from the treatment of 60 haemophilic boys at the Lord Mayor Treloar College in 1973 (Table 4.3 and Rainsford & Hall, 1973). Each boy had on average 26.4 observed bleeds per year and these required 32.5 doses of factor VIII. Once again it could be claimed that these boys also must have been very severely affected. In fact 7 were mildly affected and had measurable levels of factor VIII and only 17 were classed as severely affected. Information is also available from the NILH (1972) survey of haemophilic patients in the United States (Table 4.3). In this survey the average number of treatments per year per patient for severe and moderately affected patients works out at 34 per patient per year. This is not very different from the number of treatments given to the boys at the Treloar College.

Table 4.3. Amounts of factor VIII used to treat haemophilic patients.

	Average values		
	Treloar College 1973	Oxford 1973	NILH 1970–1971
u/kg/dose	9·21*	9·6	12
doses/year	32·5	19	34
wt of patient	—	55·7	34·6
units/patient/year	15,073	10,160	14,117
u/dose			

* assuming an average weight of 50 kg.

The average units of factor VIII given per infusion

The size of the dose in u/kg varies greatly with the reason for giving the infusion. Since more than 80% of infusions are given for the spontaneous type of bleeding the dosage schedule for this type of bleeding will predominate. The aim of therapy for spontaneous bleeding in Oxford is to raise the plasma concentration of factor VIII between 15 and 20% of normal. Study of modern therapeutic materials suggest that a dose of 1 unit/kg produces a rise of about 1·6 to 2% (Chapter 5) in the level of factor VIII. Thus a dose of 10 u/kg should on average have the desired effect. In 1971 in Oxford the average dose given was 9·6 u/kg. The NILH Survey did not collect exactly this data but the calculations assume a dose of about 12 u/kg. For the boys at Treloar College an approximate idea of the units/patient/year can be derived from the total amounts of material used. About 9·2 u/kg may have been used per dose. The relevant data is given in Table 4.3.

The data outlined above may be used to calculate the probable factor VIII needs of haemophilic patients. The average weight of haemophilic patients is taken to be 50 kg and the average dose 10 u/kg. The number of doses per patient per annum may be assumed to lie between 25 and 30. The number of patients is assumed to be 6 per 100,000 of the population giving a total of 3,300 for the United Kingdom. The total factor VIII required, based on these data, would lie between 41,250,000 and 49,500,000 units.

There is now some evidence that the size of the single dose needed by patients having spontaneous bleeding may depend on the promptness with which the dose can be given after the episode of bleeding is first detected. A dose as low as 5 u/kg may be sufficient as a single dose for the immediate treatment of a spontaneous bleed. Thus more frequent treatment of bleeding episodes will not necessarily increase the total amount of factor VIII used.

The types of therapeutic material available to treat haemophilia A patients

The types of therapeutic material at present available to treat haemophilia A patients are:

(a) fresh frozen plasma;
(b) cryoprecipitate;
(c) intermediate potency NIIS factor VIII;
(d) commercial human factor VIII concentrate;
(e) commercial animal factor VIII concentrate.

Before considering the comparative values of the various preparations certain general principles may be considered. One is the yield of factor VIII from the starting blood, the second is the purification of the factor VIII activity and the third concerns clinical considerations of safety for the patient and the recovery of administered activity in the patient's circulation.

THE YIELD OF FACTOR VIII

The yield of factor VIII from the starting material concerns the amount of activity which is lost during handling. Factor VIII is a very labile substance and if much time elapses between collection of blood and separation and processing of the plasma, activity may be lost. Similarly during storage of frozen plasma prior to fractionation activity may be lost. During fractionation and freeze drying further activity may be lost. In the case of cryoprecipitate, activity may be left inside the plastic bags if these are not carefully washed out when making up the dose. The yield is expressed as a percentage and is:

$$\frac{\text{Volume of concentrate} \times \text{activity of concentrate} \times 100}{\text{Volume of starting plasma} \times 0{\cdot}9}$$

0·9 is a factor which makes allowance for the fact that the starting plasma contains a larger volume of citrate than the standard of laboratory plasma used for assay. This factor is for blood collected into plastic bags. For bottles in which 120 ml acid citrate dextrose is mixed with 420 ml blood the factor would be 0·8.

The concept of yield is of the utmost importance since the yield will determine the amount of blood from which a given amount of activity can be obtained.

PURIFICATION

The purification of factor VIII concerns the extent to which the protein carrying the factor VIII activity is separated from other irrelevant proteins. Purification is expressed as a ratio:

$$\frac{\text{Activity units per mg of protein in the preparation}}{\text{Activity units per mg of protein in the starting plasma}}$$

It is clear that this concept has nothing to do with yield and in general so far as factor VIII is concerned the higher the purification the less the yield. Purification affects clinical practice in several ways. Impure preparations may produce dangerous immunisation of the patient to proteins other than factor VIII and cause severe and even dangerous reactions. The greater the purification the less the volume [illegible]h the material must be dissolved. Thus plasma and large

doses of cryoprecipitate must be given by slow intravenous infusion whereas the more concentrated preparations can always be given by syringe. In general the higher the purification the greater the convenience of the material in use. However, high purification as at present carried out for factor VIII, greatly reduces the yield on preparation and the best high purity preparations would require at least twice as much blood for their manufacture as cryoprecipitate or the intermediate purity factor VIII.

RESPONSE TO TREATMENT

The patient's response to treatment is expressed as percentage rise in factor VIII in the plasma per u/kg dose. Biggs, 1966 calculated that the maximum rise that could occur was about 2·44%/u/kg assuming a relation between plasma volume and weight of 41 ml/kg (see also Chapter 5). The various modern concentrates differ from each other very little in respect of their recovery in the patient's plasma; 75–85% of the activity is recovered.

With these few preliminary concepts it is possible to consider the relative merits of the three most usual varieties of factor VIII used in the United Kingdom which are cryoprecipitate, intermediate potency NHS factor VIII and commercial human factor VIII. General properties of the preparations discussed are given in Table 4.4.

Table 4.4. Recovery of factor VIII activity.

Preparation	Factor VIII u/ml	Purification ratio	Yield on preparation %	Overall yield in patient %
Plasma	0·6	nil	80	64
Cryoprecipitate	3–10	6–16	20–45	16–36
Intermediate purity Oxford factor VIII	7–8	15–20	35–40	28–32
Hemofil	25	65	15–20	12–16
High purity Oxford	15	130	20	16
Factor IX Oxford	33–50	300	60	17

Fresh frozen plasma

An essential requirement for a factor VIII preparation is that it shall be able to be given to the patient in small volume and shall cause a large enough rise in plasma factor VIII concentration. Fresh frozen plasma is plasma collected following centrifugation of whole blood within 6 hours of collection and then immediately frozen at −40°C and stored at −30°C. Such plasma has an average factor VIII content of 0·6 u/ml (Table 4.4). The low potency of this preparation means that it can never be used to raise the plasma factor VIII above 20% of average normal and must always be used at the maximum dose compatible with safety. Plasma is not now often used to treat haemophilia A patients in the United Kingdom. Eighty per cent of the original activity is retained in fresh frozen plasma.

Cryoprecipitate

When plasma is frozen at −40°C and then thawed at a temperature below 8°C a residue of gelatinous material amounting to 3% of the plasma proteins remains undissolved and can be separated by centrifuging in the cold (Bidwell, Dike & Snape, 1976). Pool & Shannon, 1965 realised that this cryoprecipitate contained much factor VIII activity. They devised a method for its separation from whole blood collected into plastic bags which allows the red cells to be used for anaemic patients and those suffering from acute haemorrhage. The plasma separated from the cryoprecipitate may be returned to the red cells or may be used in a comprehensive fractionation procedure to give other valuable therapeutic materials such as factors II, VII, IX and X, albumin, and gamma globulin.

From the point of view of yield of activity from the starting material cryoprecipitate cannot easily be assessed since small changes in technique will alter the results. In fact in a study of 5 different centres the value in units of factor VIII per donation of blood varied from 12 to 130 (Biggs *et al*, 1974). Moreover, the average value varied very much from one centre to another. Under carefully controlled conditions 45–50% of the activity of the starting plasma may be recovered in cryoprecipitate. But even under ideal conditions the value of individual cryoprecipitates must vary greatly since the normal level of factor VIII varies from 50–200%. Some differences between centres may be due to the removal of different amounts of plasma from each unit of whole blood and some is due to relaxation of the attention to detail required to get the best yield. For example if plasma is thawed at too high a temperature some activity may go into solution or if the separation of plasma from whole blood is delayed a proportion of activity is lost. In general preparation the yield is seldom more than 35%. Also of course, the least deviation from the ideal in making up a dose of cryoprecipitate will lead to mechanical loss of activity which is left behind in the bags.

The degree of purification of cryoprecipitate is such that large enough doses can always be given. The circulation is never overloaded. Patients very seldom have reactions to cryoprecipitate. The preparation cannot easily be used for home therapy

The recovery of factor VIII activity from cryoprecipitate in the patient is usually about 80% of that administered which gives an overall recovery in the patient from 16 to 36% (Table 4.4). The major difficulty in the use of cryoprecipitate is that the exact value of a particular dose cannot be known before it is given. Since there is very much variation it is wise always to assume that the dose is low and to give higher amounts than would be safe for a more predictable preparation. This fact means that even if calculations suggest that the average yield of factor VIII is 70 units of factor VIII activity per donation this average cannot be used to calculate the dose for any particular patient. The dose must be calculated from previous experience of the *least* amount of factor VIII that the cryoprecipitate is likely to contain. Although cryoprecipitate may seem to give a better yield of factor VIII than is customary in many fractionation procedures the material may be wasteful in clinical use.

In addition to these basic features of cryoprecipitate it must be noted that the material is very inconvenient to use. A single dose may require the doctor to pool the contents of 20–30 plastic bags each one of which must be washed out and the washings added to the dose. If trained staff carry out this work the yield of factor VIII will be best but in many hospitals the doses are made up by staff with little experience of this particular work. This is likely to be the case for example, in hospitals where relatively few patients attend.

When cryoprecipitate was introduced it made it possible for all blood banks to provide some of this factor VIII concentrate and thus the total amount of available concentrate was quite rapidly increased and this increase not only made possible safe operations and dental extractions but opened up the possibility of much wider use of concentrates. It was really never envisaged that very large numbers of blood donations (e.g. 500,000) should be fractionated annually in the United Kingdom by this method.

Cryoprecipitate must be stored at a temperature not higher than −30°C.

The intermediate purity NHS factor VIII

The method used in Oxford is described in detail by Bidwell, Dike & Snape (1976). The properties of the preparation are given in Table 4.4. The yield on preparation tested over the year 1971–72 in Oxford was almost the same as that of cryoprecipitate made during the same time (Biggs *et al*, 1974). The results of this experiment should be emphasised because it is often thought that the yield of factor VIII in cryoprecipitate is always higher than in freeze-dried concentrates. The belief rests on experiments at centres of exceptional excellence for the preparation of cryoprecipitate. Were such centres to supply plasma for the preparation of intermediate potency factor VIII the product would be found to be correspondingly better than average.

The obvious difference between the freeze-dried preparation and cryoprecipitate from the point of view of yield and purification is the much greater reliability of the freeze dried preparation from one batch to another and from one time to another. The material is a white dried powder easily soluble in sterile pyrogen free distilled water and each bottle contains 250 or 500 units of factor VIII. The material is stable and may be stored for over a year at 4°C without loss of activity.

The material is best made on a large scale and is not well adapted for preparation in any blood bank. Thus the making of this material envisages adequate centralised large scale fractionation plants and the transport of fresh frozen plasma in refrigerated containers from the blood banks to the fractionation laboratories. The setting up of fractionation laboratories and the degree of co-ordination required to transport plasma to the fractionation laboratories means considerable initial cost.

In clinical use the freeze-dried intermediate purity factor VIII is very satisfactory both at hospital and for home therapy. Intermediate potency factor VIII is not quite so convenient in use as the commercial factor VIII since it is at present made up for administration in a larger volume than is the commercial factor VIII.

Commercial human factor VIII

There are now several sources of commercial human factor VIII in addition to hemophil which is listed in Table 4.4. All of these preparations are more purified than the intermediate potency NHS factor VIII. They are very convenient to use since a dose can be dissolved in a small volume. Commercial human factor VIII is very expensive to buy.

Animal factor VIII

Animal factor VIII is available as freeze dried commercial preparation. In the past it was used to protect patients requiring major surgical operations. Now it is seldom used for this purpose but may be needed for patients having antibodies directed against factor VIII activity. A proportion of such antibodies have higher potency against human than animal factor VIII activity. Thus the animal preparations given to these patients may have more chance of giving a detectable factor VIII [illegible] the plasma than human preparations.

The total amount of factor VIII required annually for all haemophilia A patients in the United Kingdom and the number of blood donations required to provide this amount

If it is assumed that there are 6 haemophilia A patients per 100,000 of the population. Then there will be 6 × 550 = 3300 patients in the United Kingdom. The 1974 usage of factor VIII in the United Kingdom was about 12,500 units per year. Thus the known need is for:

$$3300 \times 12{,}500 = 41{,}250{,}000 \text{ units of factor VIII}$$

The 1975 figures for use of factor VIII per patient give:

$$14{,}800 \times 3{,}300 = 48{,}840{,}000 \text{ units}$$

These calculations agree well with that given earlier which were based on the average number of doses per patient per annum and the average dose value in u/kg.

The number of factor VIII units derived from each blood donation will depend on the amount of plasma removed from each donation of whole blood and on the skill in preserving this activity during the preparation of the concentrate. In the United Kingdom it is commonly assumed that each donation used for the preparation of cryoprecipitate or NHS concentrate, yields 70 units of factor VIII. This assumption is based on the yield in Oxford between 1970 and 1972. In Oxford 220 ml of plasma was removed from each donation. In 1975 it is much more usual to remove 180 ml thus it is probable that the present average yield of factor VIII is about 54 units per donation. The approximate number of donations needed to supply factor VIII is thus:

$$\frac{41{,}250{,}000}{54} = 764{,}000 \text{ donations} \quad \text{or} \quad \frac{481{,}840{,}000}{54} = 904{,}444 \text{ donations}$$

The above calculations make no allowance for batches withdrawn from use for various reasons such as testing for pyrogenicity and sterility and for estimates of potency which could require the withdrawal of 10% of each batch. The calculation also takes no account of the high dosage often used when the factor VIII is presented as cryoprecipitate.

What is the best form in which the factor VIII should be presented?

From Figure 4.1 it will be seen that the first big increase in treatment given to haemophilic patients in Oxford from 1964 to 196[illegible] was associated with an increased supply of fresh frozen plasma, the second spurt in treatment was provided by cryoprecipitate but that the tendency from 1971 has been to rely increasingly on freeze dried concentrate and by 1975 it nearly replaced all other forms of therapy in Oxford. Choice between the various kinds of concentrate for use nationally lies between cryoprecipitate, intermediate potency NHS freeze dried factor VIII and various commercial preparations. In 1975, 80% of all NHS factor VIII in the United Kingdom was in the form of cryoprecipitate. All users of factor VIII in the United Kingdom agree that the NHS freeze-dried preparation is much preferable to cryoprecipitate and it is to be hoped that before long plasma now used to provide cryoprecipitate will be used to make intermediate potency freeze-dried concentrate. There is no doubt that the higher potency commercial factor VIII is very convenient to use and particularly convenient for home therapy. A certain amount of high potency material is essential for the treatment of patients having anti-factor VIII antibodies for whom large doses of factor VIII are often used. If all the NHS factor VIII were provided in a form similar in purification to the commercial factor VIII then nearly twice as much blood would need to be fractionated to provide this factor VIII. It seems unlikely that such amounts of plasma could be made available except by plasmapheresis. It would seem that the most economic and reasonable plan at present should concern the provision of adequate amounts of NHS freeze-dried concentrate of intermediate potency.

Is it possible to provide the factor VIII from a wholly voluntary blood transfusion service?

This question has been considered in an International Forum organised by *Vox Sanguinis* (1976). The conclusion of all of those experts consulted was that it should be possible to provide the material. This optimism is based on estimates of the number of donations required to supply the factor VIII. In the United Kingdom plasma derived from one-third to half of all donations would require to be fractionated. Experience suggests that one-third to half of red cell transfusion may be acceptable as packed cells. Jeffrey (1976) has made definite estimates of the amounts of blood needed to supply various products in a population of 1 million based on studies in Scotland. Jeffrey calculates the need for 21,000 units of red cells, either as whole blood or as concentrated red cells. He states that in Scotland 35% of all red cell transfusions are at present given as red cell concentrates and that 200 ml of plasma is removed from each donation used to make the red cell concentrates. If 40% of red cell transfusions were given as concentrated red cells, Jeffrey estimates that 672,000 units of factor VIII activity could be provided. This calculation is based on an assumed recovery of

40% of the factor VIII present in the initial plasma. In a population of 1 million we calculate that there might be 60 haemophilia A patients and 672,000 units of factor VIII would provide on average 11,200 units of factor VIII per patient which approaches the present calculated need. Even if the recovery of factor VIII were 30–35% and if 180 ml of plasma were removed from each donation instead of 200 ml, a very large amount of factor VIII would be provided. Jeffrey points out that the number of donations needed to make albuminoid fractions is at least twice the number needed to supply factor VIII. Thus if the objective of supplying albuminoid fractions within the NHS were met there would be no shortage of factor VIII.

Thus it is possible to provide the plasma. The next essential provision concerns staff equipment and accomodation for fractionation. The supply of these facilities depends on priority judgements for the expenditure of public money both nationally and locally. In the provision of fractionation facilities it is absurd to think of factor VIII alone. Fractionation will provide many other valuable plasma components such as albumin and various immune gamma globulins as well as fibrinogen and other coagulation factors. In the future it is very probable that many new components will be found to be useful.

The production of plasma components to meet the needs of various groups of patients (including the haemophiliacs) is possible but it is difficult to know exactly when and how this may be achieved. At present much factor VIII made by commercial companies supplements the National supplies made from volunteer donors in Western Europe. Soon albuminoid fractions will be available commercially. The question of supply and demand in a National organisation is not a simple question of a market place with buyers and sellers of blood. It is a problem for which no entirely satisfactory pattern has as yet been found. This subject is discussed in Chapter 11.

The treatment of patients with factor IX deficiency

Factor IX deficiency is less common than haemophilia. In the United Kingdom 373 were identified between 1969 and 1974. By 1976 493 patients had been identified. It would seem that on average Christmas disease is one fifth to one tenth as common as haemophilia.

Using figures for patients treated in Oxford and the NILH Survey figures fewer doses were given each year to Christmas disease patients than to haemophiliacs. The data is summarised in Table 4.5. The amounts of blood product required to treat patients with factor IX deficiency can be estimated in a way similar to the calculations for haemophilia. The recovery of activity in the patient is given in Table 4.4, where it will be seen that the yield on fractionation is much

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Table 4.5. Treatment of factor IX deficient patients in 1973.

	Average values	
	NILH	Oxford
Patients	5,202	42
doses/year/patient	23	11
wt patient	36·6	55·7
units/year/patient	7,136	15,230
units/dose/patient	310	1,384
u/kg/dose	8·46	24·8

higher for factor IX than for factor VIII but that the recovery of activity in the patient is lower. Thus the overall recovery of activity in factor IX deficiency patients given concentrate is about the same as for recovery of high potency factor VIII in haemophilic patients.

The average number of units per dose given to each Oxford patient was about 3 times that given to each haemophilic patient but since only about a third as much of the activity was recovered in the circulation the effective doses were about equivalent in the two conditions. By effective dose is meant the dose required to produce the same plasma concentration of the relevant clotting factor. The NILH figures given in Table 4.5 have not taken into account the low recovery of factor IX activity in the patient's circulation.

Since the factor IX concentrate is made from the same plasma that is fractionated to make factor VIII it is unlikely that there will ever be a shortage of supply of factor IX for the treatment of haemophilia B patients if the need for factor VIII is met.

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