The Management of Haemophilia in the United Kingdom*

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Although haemophilia is the commonest of the hereditary haemorrhagic diseases, it is a rare condition. Its importance stems from the fact that when inadequately treated it is associated with repeated bleeding episodes. These episodes occur mainly into joints and muscles but also into other sites. They are painful, and distressing to the sufferer and his family. They are sometimes dangerous. They produce temporary disability and ultimate crippling.

Adequate treatment controls bleeding early, minimises pain and disability and allows near normal life. Such treatment is costly and requires expertise which may place considerable strain on the medical and economic resources of the community.

The Organization of Treatment

The very special needs of the haemophiliac patient have been recognised for some time in the United Kingdom. More than 20 years ago, in 1954, the Haemophilia Committee of the Medical Research Council proposed the creation of Haemophilia Reference Centres to ensure uniformity of diagnostic standards and to co-ordinate information. The Committee also introduced the provision of special medical cards for haemophilic patients and the organization of a registry of haemophiliacs. Since 1964, the Ministry of Health and Social Security has had sole responsibility for the Reference Centres and the Medical Research Council has ceased to be involved in treatment. During the past 20 years the number of Reference and Treatment Centres has gradually increased until today there are 45 such centres throughout the country (Fig. 1). The number of patients attending the different centres varies considerably. Some centres treat fewer than five patients per year whereas others treat more than 200 different patients each year. In addition the staffing at the different centres varies a great deal. In the majority of instances the director of the centre is a haematologist and the patients are looked after by him and his junior staff in collaboration with physicians and surgeons where necessary. In these centres the director's main responsibility is to provide general haematological service and the care of haemophiliacs is only a small part of his practice.

In a very few centres extra staff have been appointed whose whole commitment is to the care of haemophilia and other bleeding disorders. This extra staff may consists of a nursing sister trained in venepuncture and transfusion techniques and a doctor of registrar or senior registrar grade who has a special interest in this aspect of haematology. The clinical department at the Oxford Haemophilia Centre is staffed by a consultant physician, a medical assistant, two senior house officers and a transfusion sister. The clinical laboratory is staffed by a chief technician and three junior technicians. This number of staff is in our experience the number required for the care of 250 haemophiliacs who regularly attend this centre each year.

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Another major step forward in organizing and improving the management of haemophiliacs in the United Kingdom was achieved in 1968 when the directors of haemophilia centres in the United Kingdom held their first joint meeting to sxchange information and ideas. The meeting was a great success and it was decided that such meetings should be held every year. This conference of haemophilia centre directors has proved useful not only because it provides an opportunity to exchange views on specific problems, but also because within the framework of such meetings it is possible to collect information, not otherwise easily obtained, concerning many aspects of haemophilia and its management. By pooling such information it then becomes possible to make recommendations and plans for the management of haemophilia on a national scale. The haemophilia centre directors of the United Kingdom are now involved in a very active programme of research, including a review of the incidence of hepatitis and factor VIII antibodies in haemophiliacs, a trial of prophylactic treatment, and a survey of home therapy.

Fig. 1 Haemophilia centres in the U.K.

Incidence of Haemophilia in the United Kingdom

One of the first tasks undertaken by the haemophilia centre directors was to try to find out exactly how many haemophiliacs there are in the United Kingdom requiring treatment. It is obviously very important to know this figure so that estimates of factor VIII requirements for the whole country may be calculated, for inclusion in any proposals submitted to central government.

The estimates of the number of haemophiliacs in various populations has varied considerably from 2–3/100,000 for Spain (Martin-Villar et al. 1971) to 9/100,000 in U.S.A. (NHLI Study 1972). Recent estimates based on the number of known haemophiliacs attending haemophilia centres for treatment in the United Kingdom suggest that the figure for this country is between 3 and 6 patients per 100,000 of the population. It should be stressed that this figure is an estimate and at present we do not know with certainty the total number of haemophiliacs but presumably with the passage of time and as more patients attend haemophilia centres for treatment the estimates of the total number of patients will become more precise.

Age Distribution of Haemophiliacs in the United Kingdom

A survey (MRC Working Party Report 1974) of the 1,625 haemophiliacs treated at haemophilia centres during 1969, 1970 and 1971 showed that a high proportion of patients were in the 5–30 year age group (Table 1). These are presumably the physically active years most likely to be associated with bleeding episodes. The age distribution indicates that improved treatment has increased the likelihood of haemophiliacs surviving through childhood and suggests that one can expect an increase in the number of haemophiliacs in the future. On the other hand the age distribution observed in this survey may be subject to error due to the fact that some of the older haemophiliacs still prefer not to come to hospital for treatment but treat themselves at home with bed-rest, ice packs, analgesics etc.

Table 1 Age distribution on 31 December 1971 of haemophiliacs included in the 1969–71 survey carried out in U.K. by haemophilia centre directors.

Age group (years)	General male population 1971 (%)	Haemophiliacs No. of patients	%
0–4	8.4	91	5.6
5–9	8.4	227	14.0
10–19	15.0	408	25.2
20–29	14.8	333	20.5
30–39	12.2	231	14.2
40–49	12.6	132	8.1
50–59	12.0	83	5.1
60–69	10.0	43	2.6
70+	5.7	19	1.2
Unknown	–	41	2.5
Dead	–	17	1.0
Total		1625	

Incidence of Antibodies to Factor VIII

In the above mentioned survey 6% of haemophiliacs were found to have antibodies to factor VIII. The number of patients with antibodies seems to have remained constant during the period of the survey. Table 2 shows the age distribution of patients with antibodies to factor VIII.

Table 2 Age distribution of haemophiliacs with factor VIII antibodies included in the 1969–71 survey carried out in the U.K. by haemophilia centre directors.

Age group (years)	No. of patients	*With antibodies* No. of patients	Expressed as % of total	Expressed as % of those with antibodies
0–4	91	3	3.3	3
5–9	227	10	4.4	10
10–19	408	28	6.9	28
20–29	333	25	7.5	25
30–39	231	13	5.6	13
40–49	132	4	3.0	4
50–59	83	7	8.4	7
60–69	43	4	9.3	4
70+	19	1	5.2	1
Unknown	41	1	2.4	1
Dead	17	4	2.3	4
Total	1625	100	6.15	

Delivery of Care to the Patient

Having been diagnosed the patient is given a "Haemophilia Card", by the haemophilia centre. This contains details of the patient's haemophilia, including his blood group, the level of factor VIII in his blood, whether or not he has antibodies to factor VIII and whether he has any allergies. In addition he is given a booklet which gives some basic information about haemophilia and simple advice on its management. It also contains a list of the haemophilia centres of the United Kingdom along with their telephone numbers. The patients are advised to ring for advice when necessary and to go to hospital as soon as possible after the onset of bleeding to obtain replacement therapy. Most general practitioners agree to their patients seeking hospital admission on their own initiative, and most ambulance services are prepared to accept requests for an ambulance direct from the patient. In this way delay in getting to hospital is greatly reduced. The current policy in the United Kingdom is for the haemophiliac to be looked after by his nearest haemophilia centre and receive "on demand treatment" at the centre whenever he bleeds. Many patients however, live some distance from the haemophilia centre and it is obviously undesirable and difficult for them to have to travel a long way to receive treatment. In order to help such patients it has been proposed that 'Satellite Centres' be set up in the area served by a haemophilia centre and that these Satellite Centres in collaboration with the main centre should treat the more minor haemorrhages. Severe haemorrhages and major surgery are still to be managed at the main haemophilia centres. The main centre also provides assay and other diagnostic facilities as well as an advisory service to the Satellite Centres in its area.

Home Therapy

Home therapy for the management of haemorrhages into joints and muscles is provided by only some centres in the United Kingdom. It is not possible at present to say how many patients are receiving this form of treatment. Probably the most important reason for this form of treatment not being used more widely is the non-availability of freeze-dried concentrates.

Cryoprecipitate has been used sucessfully for the management of haemophilia at home but it is very difficult to store and handle and in the opinion of most doctors and patients, freeze-dried concentrates are preferable. There are conflicting views as to whether or not home therapy results in a greater usage of factor VIII compared with hospital on-demand therapy. In our experience home treatment results in an increase in the amount of factor VIII used. Of the 33 patients at Oxford who were on home therapy in May 1974, 10 patients used more than twice the amount of factor VIII than they had used before home therapy, 10 showed an increase of less than twice the amount, 10 showed a decrease in the amount and 3 showed little change in usage. Before home therapy these 33 patients had received on average 1,638 units of factor VIII per month, while on home therapy they received on average 2,109 units per month.

Materials Available for the Treatment of Haemophilia

The types of material available in the United Kingdom for treatment are shown in Table 3. This table also shows the recovery of factor VIII activity following transfusion of those materials into haemophiliacs. Plasma is now very rarely used for the management of haemophilic bleeding but is included in Table 3 as a comparison with the other therapeutic materials.

Table 3 Recovery of factor VIII activity in the plasma of haemophilic patients after transfusion of different therapeutic materials.

Type of material	Number of doses	Mean dose u/kg.	Mean rise of factor VIII. (%/unit/kg)	% Theoretical.
Plasma	90	9.29	2.01	96[1])
Cryoprecipitate	28	28.04	1.68	69
AHF concentrate (intermediate purity)	22	5.98	1.65	69
Commercial AHF concentrate (1)	34	30.10	1.82	76
Commercial AHF concentrate (2)	14	9.06	1.73	72
Porcine AHF[2])	59	66.80	1.00	41

[1]) Allowance was made in the calculation for the patient's increased plasma volume after transfusion.

[2]) Animal preparations are at present not freely available but may be obtained in cases of emergency and for specific named patients from Speywood Laboratories Limited, Nottingham, England.

Cryoprecipitate. Cryoprecipitate is the mainstay of therapy in most centres in the United Kingdom and in most centres is the only material which is available. It is prepared by the Regional Blood Transfusion Centres and is usually dispensed in plastic bags, each bag containing the product of 1 blood donation. The factor VIII content of each bag varies from bag to bag and from centre to centre, but on average is probably about 70 units. In spite of this variability in factor VIII activity and other well known disavantages of cryoprecipitate, its introduction in 1964 was a major step forward in the management of haemophilia. The most recently published national figures (MRC Working Party Report 1974) show that in 1971, 220,000 blood donations were used to make cryoprecipitate in England, Wales and Northern Ireland. Since those figures were obtained there has been a further increase in the amount of cryoprecipitate prepared and used. Despite this the majority of haemophilia centre directors still feel that the supply is inadequate.

Freeze-Dried AHF Concentrate

The freeze-dried preparations of factor VIII available in the United Kingdom are made either in the National Health Service establishments in London, Edinburgh and Oxford, or by commercial companies. In all three National Health Fractionation Centres, the method of manufacture is roughly the same and is based on a first step cryoprecipitation, followed by washing or extracting with tris buffer and then freeze-drying. Our own experience has been almost entirely with material made at the Plasma Fractionation Laboratory, Elstree, and the Plasma Fractionation Laboratory at the Oxford Haemophilia Centre. These materials are easy to reconstitute and to administer and are clinically effective. All of the materials made at Oxford are used at the Oxford Haemophilia Centre and the material made at Elstree is distributed to other Centres in England and Wales. The material made in Edinburgh has up until now been used principally in Scotland.

It is unfortunate that the total amount of freeze-dried AHF prepared in the United Kingdom falls far short of the patients' needs. During 1974, a total of approximately 3.5 million units of factor VIII activity were prepared at the Fractionation Centres in London and Oxford. 1.5 million units of that were prepared and used at Oxford. The other 2 million units were prepared at Elstree and were distributed to other haemophilia centres in England and Wales. Both cryoprecipitate and the freeze-dried AHG preparations are provided to the patient free, within the National Health Service.

Factor VIII Requirements for the Management of Haemophilia in the United Kingdom

Various estimates have been made of the amount of material required for optimum treatment of all haemophiliacs in the United Kingdom. During 1974, 219 different haemophiliacs received a total of 2,464,285 units of factor VIII at Oxford, each patient receiving on average 11,252 units of factor VIII during the year. These figures include factor VIII given at the centre and in the home therapy programme. Comparison with previous years suggests that the rate of increase of the annual requirement of factor VIII at least in Oxford is slowing down and is probably "levelling off".

Assuming that there are 3,000 haemophiliacs in the country requiring treatment and that they require treatment at the same level as that given in Oxford, the 3,000 patients would require a total of 3,000 × 12,000 units of factor VIII i. e. 36,000,000 units. Allowing a yield of 70 units of factor VIII from each blood donation either in the form of cryoprecipitate or intermediate purity freeze-dried concentrate, 500,000 blood donations would be required. This is the lowest estimate which can be made based on the Oxford figures, since the yield of factor VIII from each donation of blood is likely to be less than 70 u and not more, if fractionation procedures are scaled up and especially if high purity factor VIII concentrates are made. Also more blood donations than this would be required if the annual need for each patient "levelled off" at more than 12,000 units of factor VIII. Slightly higher estimates of the annual need per patient have been arrived at by the MRC Working Party on Cryoprecipitate. The latter group concluded that 40,000,000–50,000,000 units of factor VIII would be required for the management of all forms of bleeding in haemophilia. Slightly higher figures still have been published by Cash (1975) who has calculated that more than 1 million blood donations might be required each year if enough factor VIII is to be provided in the form of freeze-dried factor VIII.

At present no more than 20–25,000,000 units of factor VIII activity in the form of freeze-dried concentrates or cryoprecipitates are produced within National Health Service establishments each year. In other words, only ½ of the minimum estimated requirement is being

met by material produced within the National Health Service. The introduction of commercially prepared AHF has to a limited extent helped to bridge the gap between what is needed and what is available. The commercial materials at present available are potent, easily reconstituted, easy to use and clinically effective. They are unfortunately expensive, costing 10–12 p per unit of factor VIII activity and this has greatly limited their use. Table 4 shows the trend in the usage of different factor VIII preparations at Oxford over the past few years. During 1974 approximately one third of all the factor VIII used at Oxford was of commercial origin. More than 900,000 units were used at a cost of approximately £ 100,000. The money to pay for this material has to come from the money allocated each year to the Region in which

Table 4 Material (expressed as units of factor VIII activity) used for treatment of haemophiliacs at Oxford – 1969–1974.

Year	No. of patients treated	Plasma	Cryo	NHS VIII	Commercial VIII	Total
1969	190	193,760	227,640	475,400	–	896,840
1970	176	260,190	378,840	560,000	–	1,199,100
1971	198	114,800	606,550	692,370	–	1,413,720
1972	207	9,750	624,270	1,350,765	–	1,984,785
1973	217	Nil	371,630	1,471,215	393,750	2,240,195
1974	219	Nil	95,000	1,500,480	868,805	2,464,285

the Centre is situated since there is no Central source of money to meet the cost. Fortunately in Oxford and in several other centres, the Regional Administrators understand the problem and are doing all they can to make funds available to meet this extra cost. Central Government is also aware of the needs of haemophiliacs and has recently given £ ½ million to be distributed amongst the blood transfusion centres to enable them to separate more plasma for processing into cryoprecipitate and freeze-dried a AHF concentrates.

References

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