

## Contemporary Themes

### Haemophilia A and the blood transfusion service: a Scottish study

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#### Summary

The demand for blood products containing factor VIII for treating patients with haemophilia A in south-east Scotland was reviewed. From 1961 to 1975 the demand for fresh frozen plasma (FFP), cryoprecipitate (CP), and antihaemophilic factor (AHF) increased by seven and a half times, while total donations increased by only a third. Patients with severe haemophilia A treated at the regional haemophilia centre used about 85% of the factor VIII issued in 1971-4, most of which was used on demand. A patient with severe haemophilia A on unlimited on-demand home treatment would need about 500 units of factor VIII/kg body weight/year, and a regional haemophilia centre, treating moderate and mild cases as well as severe ones, would use 15 000 units/patient/year. Altogether about 50 million units of factor VIII will be needed each year in the UK.

Although cryoprecipitate is much harder to store and administer than AHF, its yield from plasma may be far greater and its cost far smaller. Unless the blood transfusion services receive increased amounts of money and reappraise their functions and operation, it seems likely that they will have to rely increasingly on commercial (and costly) sources for the major plasma fractions.

#### Introduction

The demands made on the blood transfusion services in the UK for the wide range of blood products available increase annually, and the problem of planning to meet them has to be resolved. Perhaps the best example of this difficulty is the shortage of coagulation factor VIII concentrates for managing patients with haemophilia A; this complex issue has become a matter of national and local concern, ventilated in Parliament, the press, and scientific journals. One of the major difficulties has been the lack of information on the requirements of people with haemophilia, which has denied the transfusion services the opportunity of defining targets and preparing detailed plans for staff, equipment, and accommodation. The information has been difficult to obtain partly because of the dramatic changes in the

way factor VIII concentrates have been used since the introduction of on-demand and prophylactic treatment. The findings of the Medical Research Council's blood transfusion research committee working party in 1974<sup>1</sup> were an important step forward. Information was obtained by questionnaire from regional haemophilia and blood transfusion centres on the preparation and use of factor VIII concentrates made in the United Kingdom in 1969-72. From these data the likely demand for the optimal treatment of all patients with haemophilia A was estimated. It ranged from 550 000 to 750 000 donations each year. The wide range in the estimated requirements and the knowledge that the upper figure (750 000 donations) represented a demand for fresh plasma from as much as half the then total national intake of blood caused some concern and raised doubts about the accuracy of the figures.

We report here an analysis of the blood products and donations used in managing patients with haemophilia A in south-east Scotland in 1961-75.

#### Methods

Since 1961 patients with haemophilia A in this region have been managed with various products, including fresh frozen plasma (FFP), cryoprecipitate (CP), and antihaemophilic fraction (AHF). The amounts of FFP, CP, and AHF administered can be expressed in donation equivalents—that is, the number of donations of whole blood required to produce one dispensing unit of each product: 1 unit of CP (20 ml) needs one donation, 1 unit of FFP (400 ml) needs two, and 1 unit of AHF (400 U) needs six. The FFP and CP are prepared in the regional transfusion centre, whereas AHF is produced by the Scottish National Protein Fractionation Centre, Edinburgh.

The regional population has been relatively static since 1961 and in 1973-4 was 1.2 million. Seventy-five people had haemophilia A during this period; in 40 the condition was severe, in 16 it was moderate, and in 19 it was mild. About 95% of the patients were managed by the staff of the regional haemophilia centre. Details of the amounts of blood products issued for managing these patients were available from two sources: the clinical notes of the haemophilia centre and the records held in the transfusion centre, where copies of requests and issues for all patients are retained. In 1970 the blood transfusion service records showed that 2629 donations had been issued and the clinical case notes showed 2786—a difference of 0.05%. The figures for 1971 were 4790 and 4629 respectively—a difference of 0.05% in the opposite direction. These figures agreed so closely that we could use either source of data with equal confidence. We used the blood transfusion centre's data because of ease of access and because they included patients not managed in the haemophilia centre.

#### Results

Fig 1 shows the total yearly issues of donation equivalents for managing patients with haemophilia A who were permanently residing in the region in 1961-75. There was a substantial increase from 1326

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donations in 1961 to a peak of 10 835 in 1973. From 1961 to 1963 about 1300 donations were required each year, but in 1964 demand increased abruptly with the introduction of major reconstructive surgery and reached a new plateau by 1970, at about 2750 donations. Subsequent sharp increases were due to the gradual introduction of on-demand treatment. Particularly important, however, was the fact that by 1973 this programme was available to all patients, and since that time no further increases in demand have occurred. This suggests that a saturation level may have been reached. Thus demand increased by seven and a half times between 1961 and 1975, but total donations increased by only a third over the same period, indicating a substantial change towards more efficient use of blood donations. No commercial preparations of factor VIII were used to supplement this programme.

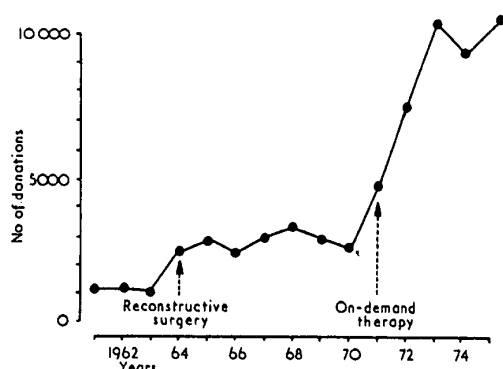


FIG 1—Total number of donations processed and used in south-east Scotland in 1961-75 for managing patients with haemophilia A.

Fig 2 shows the changes in the products prepared and issued in 1961-75. Both AHF and FFP consumption showed wide annual fluctuations, but the use of FFP increased up to 1970, and then fell dramatically. This fall was more than balanced by a substantial increase in CP and, to a lesser extent, AHF. Cryoprecipitate was used almost exclusively to service the on-demand programme.

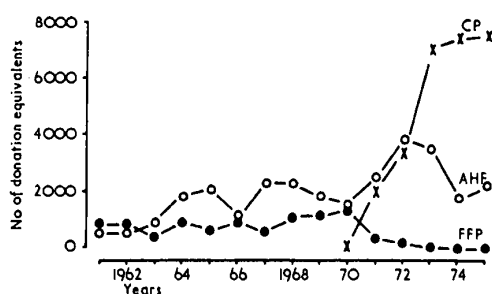


FIG 2—Different factor VIII-containing preparations used in south-east Scotland in 1961-75. CP—Cryoprecipitate. FFP—Fresh frozen plasma. AHF—Antihaemophilic fraction.

A more detailed analysis of the factor VIII concentrates issued to local patients with severe haemophilia A treated at the regional haemophilia centre over the four years 1971-4 showed that this group consumed about 85% of the total number of donation equivalents used by 1974. Over 80% of this material was issued to outpatients and represented the contribution made to on-demand treatment. Further calculations using body weight estimates, based on age,<sup>2</sup> showed that in 1974 a patient with severe haemophilia A on unlimited on-demand treatment in this region required about 500 U factor VIII/kg body weight/year.

## Discussion

Perhaps the most important aspect of these data is not the dramatic changes in the demands of patients with haemophilia A for blood products since 1961 but the clear indication that after the introduction of on-demand treatment for all patients a plateau seems to have been reached. This enables us to explore several important features of the complex problem associated with the availability of factor VIII concentrates.

### CONCENTRATE SPECIFICATIONS

For the patients and physicians the best type of factor VIII concentrate is undoubtedly that supplied by national fractionation centres or commercial companies—namely, AHF. It is stable at ordinary refrigerator temperatures, readily soluble, potentially more concentrated than cryoprecipitate, and can be dispensed in standard doses; it is particularly ideal for home treatment. Set alongside this is cryoprecipitate, a product that is unstable (needs to be stored at  $-30^{\circ}\text{C}$ ), has variable yields (making accurate doses impossible), and is much less convenient to administer (particularly by the patient himself) than AHF.

For the blood transfusion service the selection of these alternatives (which may not be mutually exclusive) is of considerable importance. The present techniques of large pool collection, transporting, and thawing of fresh frozen plasma in fractionation centres results in an average loss of as much as 40% of the original factor VIII. Thus the quality of the starting material for the protein chemists working in these centres is likely to be around 0.6 U/ml. Despite this serious disadvantage, the final absolute yields during the preparation of such concentrates as intermediate (New York) factor VIII<sup>3</sup> may be as high as 40%. In many parts of the world, however, yields are likely to be much nearer 30%, and during the preparation of even more potent concentrates are certainly less than 20%. The corresponding yields for the production of cryoprecipitate may be as high as 60%. Moreover, this product has an extra attraction to the regional blood transfusion centre: the interval from donation to receipt by the patient may be less than 24 hours compared with about 12 weeks for AHF. Finally, the present system of AHF distribution from the NHS fractionation centres to the regions is such that there are considerable attractions in a factor VIII concentrate, such as cryoprecipitate, than can be produced locally, so that those responsible for its production (with its financial as well as logistic implications) know that it will be given to patients in their own area.

We recognise that the preparation of cryoprecipitate with an average of 60% yield may be unusual,<sup>1</sup> but this can be achieved provided the centre's staff regard it as a high priority and appreciate that it is extremely cost effective. The average factor VIII content of single-donation cryoprecipitate prepared in this centre is 120 U/bag. This experience closely agrees with that of others,<sup>4-8</sup> and we have used this figure for calculating the annual factor VIII requirements/kg body weight for our severe haemophiliacs. We appreciate that many colleagues in haemophilia centres consider that the modern developments surrounding on-demand treatment, in particular its implementation in the home, make the ready availability of AHF essential. Although we recognise that ideally such a policy is admirable, enough evidence shows that cryoprecipitate can be used successfully for home treatment.<sup>9-12</sup> Should this be wholly unacceptable for certain patients then recourse to hospitals and health centres, peripheral to the regional haemophilia centres, may prove satisfactory temporary alternatives. Certainly what supplies of AHF there are, whether from NHS fractionation centres or commercial sources, should be reserved for outpatient use, while cryoprecipitate is used for inpatients.

The cost of different concentrates must also be considered. Studies carried out in early 1975 showed that, so long as it was assumed that the major cost of obtaining the blood was dominated by the use of red cells and the provision of plasma for

albumin production, then the *extra* cost of cryoprecipitate production was equivalent to 1.5p/factor VIII unit. This figure is close to one reported (1.69p) from another centre.<sup>13</sup> Commercially available AHF costs at least 10p/unit and nationally fractionated AHF probably 5p/unit.<sup>14</sup> Moreover, haemophiliacs do not demand an open-ended financial commitment, and even if a severe case were managed entirely with commercial factor VIII concentrates the total yearly cost would probably be no more than that required for managing patients with end-stage renal failure.<sup>14</sup>

#### RAW MATERIAL REQUIREMENTS

We have found the figures reported here valuable in planning our own activities. Extrapolation to national figures, and also to other regions, however, must be approached with some caution, with respect to both the absolute number of donations required and the specific factor VIII consumption (units/kg body weight/year). Firstly, although our figure of 6 haemophiliacs/100 000 population is likely to be similar in other regions, the proportion of patients with severe haemophilia in south-east Scotland may be higher than in other parts of the country. Secondly, the average dose of cryoprecipitate administered to these patients attending each on-demand outpatient visit was eight donation equivalents (about 960 units of factor VIII), and this amount of factor VIII may be higher than that used in some haemophilia centres. On the other hand, during 1973-5 there were no demands for major reconstructive surgery, no other elective or emergency general surgical procedures, and no patients with inhibitors treated with large amounts of factor VIII.

Hence we have concluded that the blood transfusion services should consider a production target of an average of 15 000 units of factor VIII/patient/year with a total UK annual requirement of around 50 million units. Regionally we should aim to process at least 12 000 fresh donations/million people/year. Those regions with a smaller proportion of patients with severe haemophilia than our own should find that this will cover all contingencies. If nearly half the haemophiliacs have severe or moderate disease or much reconstruction has yet to be done, or both, then 15 000 donations may be more realistic. These calculations are based on the assumption that 70% of the concentrate used is cryoprecipitate, which is by most standards a high yielding product. Any movement towards completely replacing cryoprecipitate by AHF, unless counterbalanced by reducing the dose of factor VIII at treatment, will, because of diminishing yields, necessitate a substantial increase in donations. A more appropriate figure in these circumstances would be 20 000 donations/million population/year. This figure would rise further if the volume of fresh plasma obtained from each donation was reduced, something that is already occurring with the increasing introduction of red cell concentrates (which yield on average 160 ml plasma) instead of packed cells (which yield 220 ml plasma) as a replacement for whole blood. It is difficult not to conclude that a programme designed to switch completely from cryoprecipitate to AHF will prove to be too costly and wasteful of raw material for the next decade. Consideration should instead be given to striking a balance between both products and perhaps even rethinking the cost-effectiveness of freeze-dried cryoprecipitate.

The real difficulties seem to lie in developing a strategy aimed at making the blood transfusion services more responsible for all aspects of blood component treatment. Clearly the amount of plasma currently available falls short of what is required, and we shall see the emergence of albumin as the blood product that dominates the raw material requirements. Thus factor VIII concentrates should become a plentiful byproduct of modern fraction techniques. This complex problem will have to be considered carefully, for more money is urgently required over the next five years. This should be seen by government departments as an important long-term investment in an organisation

closely allied to the pharmaceutical industry. The return on this investment over the next 20 years will be so great that undue delay now may be a serious error of judgment. In the meantime the blood transfusion services ought to look towards improving the quality of cryoprecipitate production and procedures for the procuring of bulk fresh plasma. The plasma fractionators should look towards technical developments that will lead to improved yields, the general hospital medical staff towards a dramatic increase in the use of red cell concentrates and packed red cells in preference to whole blood, and the staff of regional haemophilia centres to the more economical and critical use of factor VIII concentrates. There is no evidence to suggest that the voluntary blood donor will not respond; indeed those in the regional blood transfusion centres know that quite the reverse is true.

We want to express our thanks and appreciation to the staff of the Regional Haemophilia Centre and in particular to Doctor Howard Davies for his continued support and encouragement.

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*What is the shortest interval that may elapse between a patient being stabilised on lithium and the recurrence of an attack of depression or mania or both?*

Provided the usually accepted therapeutic serum lithium concentration has been established when the patient is free of either depression or mania, recurrence of either may be evident within a short interval, even within a week. Although, if correctly used, lithium prevents recurrence in most sufferers from recurrent depression or manic-depressive illness, total prevention from the start is comparatively uncommon. The usual pattern is for attacks to become less severe or less frequent, or both, until they are no longer manifest. A "latent interval" before lithium has this effect may deceive the doctor into assuming that it is ineffective. This interval is often several months and may be as long as three years. During this interval attacks may occur as before. If an episode is about to develop while the patient's appropriate lithium dose is being found the usual symptoms will reappear soon after this has been achieved.

*When should erythromycin estolate be used and what are its possible side effects?*

There are no compelling reasons for using erythromycin estolate in preference to other oral forms, although it is less susceptible to acid and is absorbed to a greater degree. The principal disadvantage of erythromycin estolate is the rare association with cholestatic hepatitis, probably resulting from a hypersensitivity reaction. It is not related to dose and usually appears in people who have received the drug before. Patients with liver damage should not receive erythromycin estolate. The other possible adverse reactions are similar to those described for other erythromycin preparations.