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A PROPOSAL TO INCREASE THE PRODUCTION OF FACTOR VIII CONCENTRATE IN ORDER TO ACHIEVE SELF-SUFFICIENCY IN SCOTLAND FOR THE NEXT DECADE

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INTRODUCTION

1.01 Over the last 5 years there have been, world-wide, dramatic improvements in the care of haemophilia A patients, by virtue of the increased availability of factor VIII concentrate preparations, primarily from commercial sources. Thus at the present time there are an increasing number of patients living a life-style which has much in common with the diabetic: replacement therapy is available in the home environment and is conducted on a prophylactic basis. As a consequence there has been a significant reduction in hospital admissions and a gradual decline in the demand for major reconstructive (orthopaedic) surgery. The socio-economic life-style of both patients and their relatives has changed dramatically. The former can now look forward to a normal life-span and be a productive (from an employment point of view) member of the community.

1.02 In a country with limited resources for health care, it is inevitable that access to this desirable therapeutic approach is restricted. Nevertheless, significant progress has been made over the last 5 years, primarily, in the U.K. setting, by the purchases of factor VIII concentrates from foreign commercial concerns (approximately 70% of the factor VIII used is purchased from commercial sources). In Scotland the overall trend is similar but the reliance on commercial products has been less marked due to the activities of the SNBTS (see figure below).

Fig. 1: Use of Factor VIII Concentrate in Scotland for 12 months, year ending 31st March, 1981

Product	Factor VIII (i.u.) issued in 12 months	
	Total	per 10^6 pop.
Cryoppt.	2,604,492	500,864 (200,000)
P.F.C. Product	3,900,000	750,000 (300,000)
Commercial	1,300,000	250,000 (700,000)
TOTAL	7,804,492	1,500,864 (1,200,000)

NOTE: Figures in parenthesis are comparable figures for NBTS.

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1.03 In December 1980 the Under-Secretary of State for Health & Social Security, Sir George Young, announced in the House of Commons that it was the intention of Her Majesty's Government to take all necessary steps to see that the U.K. became self-sufficient in blood and blood products. As a consequence substantial investment is planned (some is already being implemented) for the NBTS. No such agreed plans yet exist for the SNBTS, primarily because the Directors of the Scottish Transfusion Service felt that in view of the enhanced position of the SHS with regard to the availability of blood and blood products, it would be appropriate to delay the submission of such plans until such times as detailed alternatives had been studied, which might be more cost-effective than the proposed developments South of the border.

1.04 Nevertheless, recent events related to the financial management of the SNBTS have led the Directors to conclude that it would be appropriate at this time to outline their current thinking, primarily in order that consideration can be given to bids for additional funds over the next 5 years. In doing so the Sub-Committee will wish to know that the SNBTS is not in a position, at the present time, to make available detailed rolling costs, partly due to present difficulties with regard to access to skills in the area of cost accounting, but also because the Directors are of the opinion that initial funding should be guided primarily towards research and development.

THE NEED

2.01 Less than 5 years ago a Committee, created by the DHSS, advised that the basic needs of the haemophilia A population in the U.K. would be met by the production of 1×10^6 i.u. factor VIII/10^6 total population/year. SNBTS representation on the Committee was of the opinion that the figure advised was more closely related to what was believed to be possible with regard to plasma procurement and the fractionation facilities of the NBTS, rather than a true estimate of what was required. In any event, it should be stressed that this Committee referred itself to basic needs and did not take into consideration the extensive introduction of Home Therapy and in particular, the concept of prophylaxis.

2.02 Studies carried out in the last 6 months in Scotland, in association with the Scottish Haemophilia Centre Directors under the aegis of the SHHD, have revealed, when examining world-wide trends, that it would be more appropriate to plan towards the production of 2.75×10^6 i.u. factor VIII/ 10^6 total population/year. This dramatic increase takes cognisance of the

introduction of prophylactic therapy, the increased life expectancy of the haemophilia A population with the concomitant increases in surgery for cardiovascular disease, orthopaedic surgery of the elderly and surgery required to manage malignant disease. In addition it is believed that the proposed target may go some way to meeting the potential needs for bleeding associated with chronic liver disease, which is likely to appear in this patient group within the next 10 years.

2.03 It is significant that the use in Scotland in the year ending 31st March, 1981 was of the order of 1.5×10^6 i.u./10^6 total population and this is likely to have risen further to 1.7 for the year ending 31st March, 1982.

THE PROBLEMS

A. RAW MATERIAL SHORTAGES

3.01 Factor VIII can only be obtained from plasma which is harvested within 18 hours of donation - such plasma is called fresh plasma. Due to prodigous efforts over the last 5 years by staff in the Regional Centres, the SNBTS is processing almost 60% of all the donations collected for transfusion purposes within 18 hours of donation. This performance is remarkable and in sharp contrast to most other parts of the U.K. It amounted in the year ending 31st March, 1981 to approximately 30,000 litres of fresh plasma per annum, of which approximately 23,000 litres was sent to PFC. Thus, in overall terms, the SNBTS collected 5,800 litres of fresh plasma/10^6 total population in the year ending 31st March, 1981.

3.02 Assuming that cryoprecipitate will eventually be largely abandoned in favour of the PFC product, and assuming that the PFC yields remain at 220 i.u./litre of fresh plasma processed (see below), then the fresh plasma requirement to meet the target of 2.75×10^6 i.u./10^6 tot. pop./yr. will have to be raised from 5,800 litres/10^6 tot. pop./yr. to 12,500 - an increase of approximately 50%. In simple terms the SNBTS would be looking to increase its fresh plasma procurement by approximately 35,000 litres per annum.

3.03 It is the opinion of the Transfusion Directors, along with most leading world authorities, that without substantial changes in technology, management of staff and equipment resources and, most importantly, clinical practice (see below) it is not possible for this increased plasma volume to be obtained from the existing donation input of the SNBTS. Subject to a continued commitment to self-sufficiency, alternative solutions must be sought.

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B. FRACTIONATION YIELDS

3.04 It is well recognised in all commercial and non-commercial fractionation centres that there are very substantial losses incurred during the production of factor VIII concentrates from fresh plasma. For the high purity type of product this can be almost 90% (10% yield); for the intermediate purity type of product it is approximately 70% (30% yield). The losses are cumulative and begin immediately after donation.

3.05 The importance of this problem, which is exceedingly complex and difficult to resolve, can be assessed by reminding Sub-Committee members that if PFC could double its yield then this alone would create a situation in which there would be no requirement for an increase in plasma to meet the new targets. Unfortunately, future developments, designed to reduce or eliminate the hepatitis risk of factor VIII concentrates, may negate any immediate advantage gained. However, these new developments can only re-emphasise the urgent need for improving fractionation yields.

3.06 Over the last 5 years significant developments have taken place in this area as a result of work within PFC and following collaboration between PFC R & D staff and other colleagues within the SNBTS. Some of the fruits of their labours have already proved beneficial, for during this period PFC fractionation yields have risen from 180 to 260 i.u./litre of plasma processed. Of no less importance has been the growth of knowledge on the likely sources of factor VIII loss and the gradual emergence of ideas which, when fully explored, could lead to a significant further reduction in losses and therefore increases in yield (see below).

C. IMBALANCE OF PRODUCTS

3.07 If it is assumed that by 1990 the SNBTS has reached the target of 2.75×10^6 i.u./10^6 tot. pop./yr. and that at that time the current fractionation yields still pertain, then, as a result of the increased plasma fractionated the availability of albumin will rise from the current 180 Kg./10^6 pop./yr. to approximately 300 Kg./10^6 pop./yr. It is not really known what the genuine market needs are for albuminoid preparations. (The author is currently involved in international studies of this problem). Recent (within the last 5 years) estimates from the Council of Europe and the DHSS have suggested a minimum of 200 Kg./10^6 pop./yr., but in some countries the use is now already in excess of 300 Kg./10^6 pop./yr. However, it should be emphasised that one of the consequences of increasing factor VIII production could be an excess of albumin. This adds extra weight to the need to study ways of improving factor VIII fractionation yields.

CONSIDERATION OF OPTIONS

A. PLASMA PROCUREMENT STUDIES

4.01 The Transfusion Directors have agreed that there is a need to examine the options available for increasing the procurement of fresh plasma. At the present time these options can be summarised as follows:-

4.02 (i) Increase in routine donation input

This approach has been rejected on the grounds that it would lead to an inevitable and substantial increase in the waste of red cells. Studies by colleagues in the NBTS have also indicated that this is the most expensive approach to fresh plasma procurement and they have calculated a figure of approximately £80.00 per litre.

4.03 (ii) Plasmapheresis

This is a procedure, developed in 1916, in which a donation is obtained, it is centrifuged and the red cells returned to the donor and plasma retained. The maximum annual amount of plasma available from a donor giving routine donations (in which the red cells are retained by BTS) is approximately 1 litre (4 donations per year). Plasmapheresis permits this to rise to 15 litres because the red cells are returned (WHO recommendation).

4.04 Plasmapheresis is performed daily throughout the SNBTS on a relatively small scale at Regional Centres for the procurement of plasma which contains specific antibodies (hyperimmune plasma). There is no doubt that one option available to us is to introduce a major plasmapheresis programme for routine fresh plasma. This option has been taken up in Belgium and an SNBTS group spent 3 days studying this programme. It is the option currently favoured by the NBTS. For the SNBTS it would mean a shift from the current plasmapheresis programme which yields a total plasma volume of 4,000 litres per annum to one of approximately 35,000 litres per annum. It should be remembered that plasmapheresis cannot be performed in mobile donor sessions; permanent accommodation is required and thus the physical burden of this development would fall within the Regional Centres.

4.05 Industry has anticipated these developments in the demand for fresh plasma and over the last 2 years a machine has been introduced which will automatically plasmaphrese a donor. Machine plasmapheresis is claimed to be safer and quicker than the traditional method of plasmapheresis (known as manual plasmapheresis). At the present time, however, the revenue costs are probably about 20% more expensive than manual plasmapheresis. This cost differential is controversial and requires detailed studies based on working practice within the U.K.; the machine was designed and is built in the U.S.A. Moreover, it is possible that the machine approach could

could lend itself more readily to certain technical maneouvres which could enhance the final yield of factor VIII. Such a development might well elminiate existing concern in the area of cost differentials between manual and machine plasmapheresis, and indeed there may be substantial cost savings.

4.06 NBTS colleagues have calculated that the likely revenue cost of producing fresh plasma by manual plasmaphresis is in the area of £50 per litre. Both SNBTS and NBTS Directors agree that there will be no insurmountable problems in securing the support of the voluntary donors for a plasmapheresis programme designed to procure an extra 35,000 litres/year.

4.07 (iii) Improved Use of Existing Donation Input

This option has been the one preferred by the Transfusion Directors in the past and has been implemented on the grounds that it is both morally most acceptable and most cost-effective. It has been outstandingly successful as can be seen by examination of Table I, below.

Table I: SNBTS: Plasma procurement from Routine Donations

	1975	1976	1977	1978	1979	1980	1981
Useable donations	233,485	247,685	256,359	272,066	270,575	266,995	282,312
Total fresh Plasma (Kg.)	10,639	14,687	17,044	20,762	23,172	26,738	30,430
Fresh plasma per donation (ml)	46	59	66	76	86	100	108
Total plasma (Kg.)	28,684	36,597	37,068	38,965	38,689	42,483	46,290
Total plasma per donation (ml)	123	148	145	143	143	159	164

4.08 This remarkable performance by both laboratory and medical staff has been achieved by increasing the number of donations which are processed within 18 hours of donation. Processing involves centrifugation and the removal of approximately 200 ml. from each donation. In 1981 approximately 60% of all useable donations collected were processed in this way.

4.09 Two questions now arise: why only 60%, and why only 200 ml. from the 60%? The answer to the first question is complex but the primary reason is the ready availability required by many clinicians (particularly anaesthetists) of a product which will run into the patient rapidly when massive bleeding occurs. Those donations which have had 200 ml. of plasma removed (called red cell concentrates) have a high viscosity and do not transfuse rapidly with ease. The answer to the second question is primarily one related to the potential danger of removing all the vital constituents in the anti-

coagulant

anticoagulant mixture which ensured red cell viability during storage in the Blood Bank.

4.10 Recent technical developments, which have been under intense study in Sweden, Finland and Australia in particular, have sought to achieve two separate but related ends: the removal of up to 300 ml. of plasma from all donations and the partial replacement of the plasma, immediately after it has been removed, by a special (and additional) volume of anticoagulant to the red cells. The anticoagulant(s) is currently named SAG (Saline Adenine Glucose) but there are now emerging a variety of variants on this basic formula. Dr Boulton (Edinburgh Centre) and Mr Ian Gordon (Inverness Centre) will be visiting Uppsala and Helsinki Transfusion Centres and associated hospitals with a view to studying their SAG programmes. Dr McClelland will be visiting the Sydney Transfusion Centre during his forthcoming visit to Australia, where the Australian work in this field is in progress.

4.11 The potential benefits of this type of approach are substantial and can be summarised as follows: if 300 ml. of fresh plasma could be obtained from all the donations currently collected by the SNBTS then the gross yield would be 280,000 x 300 ml. = 84,000 Kg./p.a. This volume, assuming current PFC yields of 260 i.u./Kg., would then be equivalent to 22×10^6 i.u. or 4.2×10^6 i.u./10^6 pop./year. It should be emphasised at this point that formidable difficulties are envisaged in the development of this approach which will be technical, administrative, managerial and clinical. Nevertheless, the Transfusion Directors are of the opinion that this option should be actively explored, for although it is possible that a conversion to a 100% SAG programme (all donations processed) may not be clinically acceptable it is clear that a conversion to 60% (the existing red cell concentrate programme) might yield an additional 15,000 Kg. of fresh plasma. This alone would provide the SNBTS with access to a total source plasma potential equivalent to 2.2×10^6 i.u./10^6 pop./yr.

4.12 Although the SAG programme looks extremely attractive - revenue costs may be as low as £20 per litre - it is the opinion of the Transfusion Directors that the likely long term solution, with regard to fresh plasma procurement, for the SNBTS will be a combination of plasmapheresis and SAG. In any event, there is a likelihood that a requirement for increased plasmapheresis facilities for hyperimmune plasma will emerge in the foreseeable future and this feature provides additional weight to the broadly based proposals outlined below.

PROPOSED ACTIONS

5.01 The Directors are of the opinion that it would be appropriate to spend a period of time (probably 18-24 months) studying the options prior to establishing a definitive routine rolling programme designed to achieve self-sufficiency for the next decade.

5.02 Full details have yet to be worked out but the following scenario seems reasonable at the present time:-

	1982/ 83	1984/ 85	1985/ 86	1986/ 87	1987/ 88	1988/ 89	1989/ 90
Option Studies	Yes	Yes	Possible (Residual)	Possible (Residual)	-	-	-
Rolling (Total) Routine Programme	No	No	5,000Kg	10,000Kg	20,000Kg	27,000Kg	35,000Kg.
Estimated Extra Revenue costs at RTCs for Rolling Programme	?	?	+£250,000	+£250,000	+£500,000	+£350,000	+£350,000

5.03 It should be emphasised that the estimated costs of the Rolling Programme are based upon a current (plasmapheresis) figure of £50.00/litre from the DHSS. Both this figure and the shape of the rolling programme (approx. 7,500 Kg. increment per year for 5 years) may be radically altered by the results of the "Option Studies".

5.04 The proposed Option Studies can be summarised as follows:-

5.05 A. SNBTS FACTOR VIII STUDY GROUP

A group of SNBTS staff has been formed, comprising of Mr Watt (PFC), Dr Foster (PFC), Dr Prowse (Edinburgh Centre), Dr Boulton (Edinburgh Centre), Dr Pepper (HQ Laboratory), Dr Gabra (Glasgow Centre), under the Chairmanship of Dr Cash (NMD). The primary purpose of this group will be to keep under regular review the whole area of factor VIII concentrates.

5.06 The Study Group met on Thursday, 28th January, 1982 and agreed to create Action Groups in the following areas:-

1. Assays and Standards (Dr Prowse/Mrs Griffin/Dr Gabra)
2. Plasma Quality (Dr Gabra/Dr Boulton/Mr Keddie)
3. PFC Yield Studies (Dr Foster/Mr Watt/Dr Prowse)
4. Viral Contamination (Dr Pepper/Dr Somerville/Dr Foster)

5.07 The BTS Sub-Committee members will wish to know that each Action Group has been asked to produce a review of their particular area of responsibility for/

for the main Study Group, and to make proposals for further studies, if required. It is envisaged that some of these applied research proposals, if approved, will have financial consequences.

B. PLASMAPHERESIS STUDY

5.08 The West of Scotland Regional Transfusion Service has agreed to undertake this study in collaboration with PFC. It is hoped to be designed with the following questions in mind:-

(i) What are the donor attitudes (acceptability) to manual versus machine plasmapheresis?

(ii) Can plasmapheresis (manual or machine) be used to facilitate 'on-line' addition of "factor VIII protective substances" during the process of plasma procurement, and do these maneouvres enhance the ultimate fractionation yield?

(iii) Does a plasmapheresis programme (manual or machine) facilitate in a practical way, efforts designed to reduce the interval of time between plasma procurement, freezing and fractionation and, if so, does this improve the final fractionation yield?

(iv) What is the comparative cost-effectiveness of manual versus machine plasmapheresis?

At the present time studies are currently underway in the West with a view to the detailed design of the research programme and to delineate the annual cost. It is hoped that the project will begin in late 1982/early 1983 and be completed within 18-24 months.

C. SAG STUDY

5.09 The Inverness and Edinburgh Centres have agreed to develop this research project on behalf of the SNBTS. It is anticipated that the following questions will be answered:-

(i) Do the SAG solutions produce significant effects on red cells, with particular respect to haemolysis and red cell survival, in vivo?

(ii) What changes in equipment and staffing numbers and management etc. would be required to introduce an effective SAG programme?

(iii) Is the SAG suspended red cell concentrate (RCC) an acceptable clinical product?

(iv) To what extent does the introduction of a SAG/RCC programme influence the clinical use of fresh frozen plasma (clinical units)?

(v) What are the comparative unit costs of fresh plasma (per litre) produced by the existing and SAG approaches?

The time scales for these studies are likely to be close to those proposed in the West of Scotland.

ACTION REQUIRED

5.10 1. The BTS Sub-Committee are requested to accept the advice of the Transfusion Directors that major expenditure on an overall routine policy of self-sufficiency (with respect to factor VIII and albumin) for the next decade is not considered until sufficient results from a set of experiments designed to examine future options are to hand.

2. The BTS Sub-Committee are further requested to agree that the 3 sets of proposals (A-C) outlined above cover the appropriate areas for study and recommend that the Transfusion Directors forward for their consideration, as soon as possible, full details of each project with the appropriate costing.

3. Significant partial support from industry may be available for the plasmapheresis and SAG projects. This would be in the form of making available, at no charge, some of the machines and plastic blood bags. Guidance is sought from the BTS Sub-Committee on whether this support should be encouraged.