

IN CONFIDENCE

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Self-Sufficiency

Reports on SNBTS Self-Sufficiency
Payne.

NOTES FOR SCOTTISH HEALTH SERVICE HAEMOPHILIA CENTRE/
TRANSFUSION SERVICE DIRECTORS' MEETING: FEBRUARY 1984

14 January 1984

JDC/SHHD/1/84/1

These notes have been produced to facilitate discussion with regard to future SNBTS planning for the production of blood products required for the management of patients with haemostatic or thrombotic disorders, within the Scottish Health Service. All annual figures contained in these notes refer to years ending 31st March.

FACTOR VIII CONCENTRATESFRESH PLASMA PROCUREMENT

Progress made over the last 5 years has been further consolidated.
A summary is given below (details in Appendix I).

Total Fresh Plasma Processed for Factor VIII Concentrates (Kg)

<u>1979</u>	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u> ^o
20,553	15,059	28,474	35,748	40,739

ISSUES OF FACTOR VIII CONCENTRATES

The figures below include the issue of products from PFC to RTC and the issue of cryoppt. from RTC to Wards or Haematology Departments. The trends since 1979 are summarised below (details in Appendices II & III).

	<u>1979</u>	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>
Cryoppt. (donations) (PFC)	35,199	30,273	26,045	17,855	12,953
Intermediate VIII (million i.u.)	1.66	1.99	3.58	4.70	4.86

COMMERCIAL FACTOR VIII PURCHASES

The information (million i.u.) available to the SNBTS can be summarised as follows (details in Appendix IV):-

<u>1979</u>	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>
0.86	0.98	1.37	1.40	1.04

SUMMARY (Details Appendix V)

	<u>1979</u>	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>
Cryoppt.*	3.52	3.02	2.60	1.78	1.27
PFC	1.66	1.99	3.58	4.70	4.86
Commercial	0.85	1.00	1.37	1.40	1.04
Total	6.03	6.01	7.55	7.88	7.17

* Each donation is assumed to yield 100 i.u. of factor VIII

COMMENTS/

^o Figures do not include Northern Ireland

COMMENTS(a) Current Production targets of Intermediate VIII

Whilst it is recognised (see Appendix V) that some caution is required with regard to concluding that these figures represent the actual use of factor VIII concentrates in the SHS, Haemophilia Centre Directors are invited to comment on the trends over the last 5 years and in particular whether they believe the agreed long term annual production/use target of 13.75 million i.u. (based upon a figure of 2.75 million i.u./annum/million total population) is appropriate.

Clinical colleagues may wish to note that there is increasing evidence (which will be fully analysed in mid-April 1984) that the SNBTS production of factor VIII concentrates may be exceeding clinical demand. Current stocks of intermediate concentrate at RTCs are averaging 6 months useage and appear to be increasing. The existing predicted PFC production figures, with appropriate comments, have been prepared by Dr R J Perry (PFC) and are contained in Appendix VI.

(b) AIDS

The SNBTS has introduced, in common with all UK Transfusion Services, a leaflet directed towards dissuading high risk donors from donating blood or plasma. Further consideration is being given to updating this leaflet and improving its exposure to blood donors.

Clinical colleagues' attention is drawn to a leading article, published in the BMJ (December 10th 1983) by Dr Peter Jones, Haemophilia Centre Director, Newcastle-upon-Tyne, entitled, "AIDS, Hepatitis and Haemophilia" (see Appendix VII). Dr Jones concludes "For the moment, however, it seems sensible to treat very young severely affected children with cryoprecipitate rather than concentrates". The SNBTS Directors would welcome comments on this proposal.

It is noted that cryoprecipitate is no longer issued for haemophilia care at the Inverness and Aberdeen Centres and the size of current intermediate stocks would normally lead to the consideration with the SNBTS of the introduction of similar practices in other regions.

(c) Heat Treated Factor VIII Concentrates

Colleagues' attention is drawn to the potential risk associated with respect to transmitting non-A/non-B hepatitis following the infusion of BPL intermediate concentrate (Appendix VIII). Evidence, currently being collected in/

in the West of Scotland, would suggest that contamination of the PFC product is likely to be similar to that of the BPL product (Dr Charles Forbes, personal communication).

Work at PFC, designed to introduce a heat treated factor VIII concentrate, has progressed satisfactorily so that small batches of material, heated at 60°C for 10 hours, have been infused into volunteer patients in Edinburgh and Glasgow. ^{Appendix X} The in vivo yields and half-life of this material do not appear significantly different from cryoprecipitate or intermediate VIII and extensive in vitro and limited in vivo studies indicate no evidence of heat induced molecular damage. Current work, based upon virocidal studies, is designed to explore the feasibility of a more rigorous heat treatment regime. It is anticipated that batches of VIII concentrate exposed to these higher levels of heat treatment will be available for preliminary clinical studies by April 1984.

At the present time it is not possible to give an accurate estimate on the likely timing of a phased introduction of heat treated VIII concentrates for routine use in the SHS. However, current planning indicates that limited but significant amounts of this material could be available for routine clinical use by September 1984 and full scale production introduced by April 1985 (both subject to available funding). In the meantime it would be of advantage to the SNBTS if Haemophilia Directors were able to indicate where they see the priorities lie and whether it is possible to provide a measure of quantitation (the annual amount of heat treated product for the priority patients). To this end there is also an urgent need to ascertain whether this type of concentrate is efficacious in the management of appropriate patients with Von Willebrand's Syndrome, and particular assistance is requested.

(d) Limitation of batch exposure to individual patients

On the occasions when it has been necessary to follow up reported untoward reactions, presumed to be associated with PFC VIII concentrates, it has been noted that individual patients are often exposed to a large number of batches in any one year. The same may apply for mild/moderate patients.

Whilst it is recognised that a limitation of batch exposure, on the basis of minimising the risk of transmissions of non-A/non-B hepatitis may be largely theoretical it could be of relevance in the context of reducing the exposure to B virus and AIDS. It is suggested to Directors that in view of the current significant national reserves of SNBTS intermediate factor VIII that/

that the time is opportune to direct efforts towards reducing the number of batch exposures per patient per year. It is recognised that this task will not be easy but it is arguable that, within the context of a national BTS working closely with clinical colleagues within an NHS, the potential for success is a real possibility. It is also recognised that such a development will inevitably be gradual and that a significant contribution must be made by the SNBTS, both at PFC and RTC levels.

(e) Commercial Purchases of Human Factor VIII

Subject to the satisfactory clinical acceptability of the SNBTS product range, the current production level of SHS materials is such that there no longer appears to be a need for commercial purchase of human factor VIII concentrates. Clinical colleagues are invited to comment on this topic as our records show that commercial products continue to be bought. It seems probable that these purchases relate to a time when self-sufficiency had not been achieved. On the other hand, in the context of current thinking with regard to the proposed association between AIDS and commercial products, it is essential that the SNBTS is satisfied that this is the case. Thus if there are aspects of the current intermediate VIII product which make it clinically unacceptable, compared to currently licensed commercial products, then comments would be most welcome.

Once again the SNBTS experience of the collection of information on Health Board (District) purchases of factor VIII has been disappointing.

(f) Oxford Returns

We are once again indebted to Dr Charles Rizza and Miss Rosemary Spooner who have provided data from which the following have been extracted.

Factor VIII Use (m. i.u.) Oxford Data

	1980			1981			1982		
	Total Use	Use/m. pop.	% Commercial	Total Use	Use/m. pop.	% Commercial	Total Use	Use/m. pop.	% Commercial
EW/NI	52.3	1.1	67	60.1	1.2	54	67.5	1.4	66
Scotland	5.4	1.1	20	5.7	1.0	22	6.1	1.2	9

It/

It is still somewhat premature to compare in detail the data generated by the Oxford Surveys and those of the SNBTS. However, there is one aspect which may deserve our attention. If the data below is studied there is some cause for concern for it would suggest that the actual use of commercial factor VIII in Scotland may be declining more rapidly than the commercial purchases. If this is substantiated and the trends continue it is conceivable that in the SHS upwards of 500,000 i.u. of commercial factor VIII may outdate (unused) in 1983/84. It is suggested that urgent studies on the stock position of commercial factor VIII be conducted with a view to defining the level, location, outdating and assessing whether there is a need to offer this product to Haemophilia Centres in England and Wales whose access to NHS product is more limited than those served by PFC. It should be emphasised that commercial products are the property of the Health Boards (not the CSA). Nonetheless, if required, the SNBTS will assist in the distribution of any surpluses, if appropriate.

	1979	1980	1981	1982	1983
Total Recorded Purchases of commercial product in Scotland	0.9	1.0	1.4	1.4	1.0
Recorded total use of commercial product in Scotland (Oxford data)	N.K.	1.0	1.3	0.5	N.K.

CONCLUSIONS

Comments by the Haemophilia Directors on the following topics would be welcomed by the SNBTS:-

1. Should the SNBTS continue to plan for an annual total factor VIII concentrate use of 2.75 million i.u./million population?
2. Is it appropriate to commence the phasing out/reducing the production of cryoprecipitate for the management of haemophilia A, subject to the availability of adequate stocks of PFC VIII product(s)?
3. How should the SNBTS approach the phasing in of heat treated factor VIII concentrates for routine clinical use? Can this be quantified?
4. Is it acceptable to initiate programmes designed to reduce the batch exposure of some patients?
5. Given a maintained SNBTS production level of factor VIII concentrates, is there a need to purchase product from commercial organisations? If so, is it acceptable for such purchases to be made, on behalf of and as specified by the Haemophilia Centres, by the Regional Transfusion

Centres in order to facilitate progress towards self-sufficiency?

6. Haemophilia Directors are requested to collaborate on a survey of current commercial factor VIII stocks in Scotland.

FACTOR IX CONCENTRATES

SUPPLY TRENDS

PFC issues to Regional Transfusion Centres since 1979 can be summarised as follows:-

	1979	1980	1981	1982	1983
DEFIX (million i.u. of IX)	0.9	1.0	1.0	0.9	1.0
PPSB (thousand i.u. of IX)	70	44	44	20	35

It is gratifying to note that there has been a sustained decrease in the issue of PPSB since the peak values in 1978 (130,000 i.u. issued). Aside from the high cost of production (donations are collected in EDTA and thus red cells are immediately discarded) this product is regarded as highly icterogenic and in view of the stable DEFIX issues the decline in its (PPSB) issue would suggest that the exposure of non-Christmas Disease patients to factor IX concentrates in Scotland has substantially reduced. Pending the availability of a factor VII concentrate it is the intention of the SNBTS to continue to make PPSB available.

FURTHER COMMENTS

(1) Supernine

This product was developed some years ago on the grounds that its increased purity would lead to a modest reduction in viral contamination. Clinical colleagues in Edinburgh and Glasgow kindly undertook clinical acceptability studies. Reports have been received (Appendix IX) which indicate that the product is acceptable and Dr Ludlam has expressed a desire to see Supernine replace DEFIX for the routine management of Christmas Disease patients.

Subject to the provision of data which satisfies the Licensing Authority it is hoped that Supernine will be introduced for routine use throughout the SHS in 1984/85. This is seen as an interim development pending the arrival of a

a heat treated product (see below). Current provisional targets will be for approximately 1 million i.u./year.

(2) DEFIX

It had been assumed that this product would become obsolete with the introduction of Supernine. However, recent developments have suggested that DEFIX may be of value in the management of haemophilia A patients with inhibitors and a sudden and unexpected increase in clinical demand for this product created serious supply difficulties for PFC in the summer of 1983. The estimated issue of DEFIX for the year ending March 31st 1984 is 1.25 million i.u. (compared to 0.9 - 1.0 over previous 5 years).

We have reason to believe that as a consequence of adjusting production schedules this acute problem has been overcome. It is hoped that the claimed clinical efficacy of DEFIX in these patients will be sustained for it will reduce the need to purchase high cost, commercial activated factor IX concentrates.

As a consequence of this development it is intended to retain, in the medium term, the availability of DEFIX, even when Supernine has replaced it for the routine care of Christmas Disease patients. The current provisional target for DEFIX production once it has been superseded by Supernine is 250,000 i.u./year. This may need to rise to 500,000 i.u./year.

(3) Heat treated Factor IX Concentrates

Work on this product continues at PFC. Colleagues will wish to note that the technology involved raises problems of a much more complex nature than the sister development associated with factor VIII. In the first place there will be a requirement, prior to clinical studies, for extensive animal studies, in order to ensure that the heat treatment does not potentiate the inherent thrombogenicity of these concentrates. There are also other technical considerations: whether to heat treat Supernine or DEFIX. The former is currently a low yielding product and it may not be desirable to suffer further losses associated with heat treatment as the final 'market' for a safer factor IX concentrate may be much larger than is currently envisaged (now involving, in addition to Christmas Disease, patients requiring oral anticoagulant reversal, severe liver disease and perhaps some neonates).

It is not envisaged that a heat treated factor IX concentrate will be available from PFC for preliminary clinical studies until approximately 24 months' time.

FACTOR VII CONCENTRATE

Development of this product has now been given a low priority in favour of the heat treatment work on factor IX concentrates and the decision to continue the availability of PPSB. Clinical colleagues may wish to note that limited supplies of this concentrate may be available from BPU (contact Dr J Smith, Oxford).

ANTITHROMBIN III CONCENTRATE

In view of the availability of what appears to be an excellent heat treated product from BPU (Oxford) and the existing restriction of use to the small number of congenital deficiencies the development of this product at PFC has been given a low priority. However, should there emerge a commitment to study the need for this product in acquired deficiency disorders then this policy will have to be reversed. In the meantime PFC intend to continue (as a low priority) the development of this product.

FACTOR XIII CONCENTRATE

It has been noted that several commercial companies are introducing a heat treated form of this product. The SNBTS would value the advice of the clinical colleagues as to whether there is merit in examining the feasibility of producing such a product.

SNBTS FRESH PLASMA PROCUREMENT FOR FACTOR VIII CONCENTRATE PRODUCTION (Kg.)

	1979		1980		1981		1982		1983	
	Kg.	Kg/ 10 ⁶ pop.	Kg.	Kg/ 10 ⁶ pop.	Kg.	Kg/ 10 ⁶ pop.	Kg.	Kg/ 10 ⁶ pop.	Kg.	Kg/ 10 ⁶ pop.
ABERDEEN	Crypopt.	220	449		333		200		14	
	To PFC	1,188	1,831		1,587		2,221		2,370	
	Total	1,308	2,632	4,588	1,920	3,863	2,421	4,871	2,384	4,796
DUNDEE	Crypopt.	123	57		120		125		22	
	To PFC	1,006	1,572		1,423		2,429		3,048	
	Total	1,129	1,629	3,473	1,543	3,290	2,554	5,446	3,070	6,545
EDINBURGH	Crypopt.	2,720	3,183		3,694		1,946		1,862	
	To PFC	3,982	3,786		3,821		6,256		7,136	
	Total	5,602	6,969	6,178	7,515	6,263	8,202	6,835	8,998	7,977
GLASGOW	Crypopt.	3,678	2,785		1,341		1,068		1,065	
	To PFC	7,322	9,574		14,200		18,965		22,411	
	Total	11,000	12,359	4,320	15,541	5,359	20,033	6,908	23,476	8,205
INVERNESS	Crypopt.	11	3		10		2			
	To PFC	1,503	1,819		1,945		2,536		2,811	
	Total	1,514	1,822	8,098	1,955	8,689	2,538	11,280	2,811	12,493
GRAND TOTALS		20,553	25,059	5,314	28,474	5,476	35,748	6,875	40,739	7,865

Note: Volume of plasma calculated for cryoppt. by multiplying by 0.2 total donations.

PFC ISSUES OF FACTOR VIII TO RTCs (1.u. x 10⁶)

	1979	1980	1981	1982	1983
Aberdeen	0.12 (0.24)	0.10 (0.18)	0.16 (0.33)	0.37 (0.74)	0.46 (0.92)
Dundee	0.10 (0.22)	0.14 (0.32)	0.16 (0.33)	0.37 (0.79)	0.34 (0.73)
Edinburgh	0.31 (0.26)	0.28 (0.23)	1.01 (0.84)	0.87 (0.73)	1.06 (0.94)
Glasgow	0.95 (0.33)	1.33 (0.46)	1.92 (0.66)	2.62 (0.90)	2.48 (0.86)
Inverness	0.18 (0.80)	0.13 (0.61)	0.25 (1.00)	0.47 (2.1)	0.52 (2.31)
TOTALS	1.66 (0.32)	1.99 (0.38)	3.58 (0.69)	4.70 (0.90)	4.86 (0.93)

Figures in brackets per 10⁶ population

SHS PURCHASE OF COMMERCIAL FACTOR VIII CONCENTRATES (i.u. x 10⁶)*

	1979	1980	1981	1982	1983
Aberdeen	0.01	Nil	Nil	Nil	Nil
Dundee	Nil	Nil	Nil	Nil	0.03
Edinburgh	Nil	Nil	0.46	0.73	0.46
Glasgow	0.85	0.98	0.91	0.67	0.55
Inverness	Nil	Nil	Nil	Nil	Nil
TOTALS	0.86	0.98	1.37	1.40	1.04

* Information obtained by SNBTS Directors from Haemophilia
Directors/Pharmacists

SHS: TOTAL "USE" OF FACTOR VIII CONCENTRATES (i.u. $\times 10^6$ / 10^6 POPULATION) *

	1979	1980	1981	1982	1983
Aberdeen	0.52	0.60	0.64	0.95	0.96
Dundee	0.34	0.36	0.45	0.90	0.74
Edinburgh	1.42	1.52	2.66	2.10	2.01
Glasgow	1.32	1.23	1.2	1.38	1.23
Inverness	0.80	0.61	1.00	2.10	2.31
TOTALS	0.88	0.86	1.19	1.49	1.34

* The word "use" is not strictly accurate. The figures are derived from RTC issues of cryoppt., PFC issues of intermediate VIII and commercial purchases of VIII concentrate in each year.

SHS: TOTAL "USE" OF FACTOR VIII CONCENTRATES (i.u. $\times 10^6$ / 10^6 POPULATION) *

	1979	1980	1981	1982	1983
Aberdeen	0.52	0.60	0.64	0.95	0.96
Dundee	0.34	0.36	0.45	0.90	0.74
Edinburgh	1.42	1.52	2.66	2.10	2.01
Glasgow	1.32	1.23	1.2	1.38	1.23
Inverness	0.80	0.61	1.00	2.10	2.31
TOTALS	0.88	0.86	1.19	1.49	1.34

* The word "use" is not strictly accurate. The figures are derived from RTC issues of cryoppt., PFC issues of intermediate VIII and commercial purchases of VIII concentrate in each year.

PFC F VIII PRODUCTION 1975-1985 (EXCLUDING NORTHERN IRELAND)

Year	Plasma Delivered to PFC (kg)	Plasma into process (litres)	Process Yield	F VIII Produced IU x 10 ⁶	F VIII Issued to RTC IU x 10 ⁶	PFC Finished Product Stock IU x 10 ⁶	Plasma Stock (at 31 March) (kg)
1975/76	5 866	8 531	250.6 (1)	1.26	1.07	0.183	116
1976/77	10 824	9 496	229.7 (1)	1.84	1.64	0.374	1 060
1977/78	13 365	12 174	180.1	1.81	1.85	0.336	1 402
1978/79	15 001	13 673	197.2	2.25	2.11	0.419	4 650
1979/80	18 581	17 256	247.3	3.44	2.53	1.396	2 023
1980/81	22 976	20 773	260.1	4.64	4.48	1.558	2 476
1981/82	32 407	28 562	287.2	6.00 (5)	6.35	1.211	5 016
1982/83	38 307	34 163	275.2	8.16 (5)	6.22	3.152	7 647
<u>Forecasts</u>							
1983/84	48 000 (2)	47 191 (2)	300.3 (2)	12.74 (2)	11.35 (3)	4.54 (2)	4 000 (2)
1984/85		45 000	300	12.15	N/A	N/A	
1985/86 (4)		50 000 (4)	225 (4)	11.25 (4)	N/A	N/A	

(1) F VIII Assay calibrated with plasma standard. Concentrate standard introduced in December 1976.

(2) Estimates based on first 9 months of 1983/84.

(3) Assuming F VIII issued according to pro rata input of plasma (current procedure).

(4) Exclusive production of heat-treated F VIII.

(5) High batch rejection in these years. This material is awaiting rework and is equivalent to 1.2×10^6 IU F VIII.

Comments and Conclusions

1. The figures and estimates overleaf (1983 onwards) are based on 1 kg plasma \equiv 270 IU F VIII and one vial \equiv 238 IU. (Data presented on P2 is calculated on 200 IU per kg plasma or per vial).
2. Improvements since 1977 can be summarised:
 - (i) Plasma into process has increased 3.7 fold.
 - (ii) Process yield has improved by 67%.
 - (iii) QA losses have been reduced from 17% to 8.7% per batch.
3. F VIII production levels in 1983/84 are likely to be artificially high as a result of a substantial reduction in the fresh plasma stockpile (7 647 kg — 4 000 kg). It is anticipated that the remaining stock of fresh plasma will be reduced by a further 2 000 kg before April 1984. This will provide an additional 0.5×10^6 IU F VIII.
4. At the current estimated demand of PFC F VIII in Scotland (5.83×10^6 IU) the projected output from PFC in 1984/85 will exceed demand by approximately 6.32×10^6 IU.
5. It can be calculated from the above figures that when added to the present PFC stock of F VIII, total stocks in 1985 will be approximately 10.9×10^6 IU which is equivalent to two years stock at present rates of usage. This forecast does not take account of substantial stocks of F VIII at Regional Transfusion Centres.
6. Work is in progress aimed at the exclusive production of heated treated F VIII by 1985/86. It is anticipated that this process will initially reduce the process yield to 225 IU F VIII/litre providing 11.25×10^6 from an estimated 50 000 kg plasma.