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CONFIDENTIAL

REPORT ON THE ACTIVITIES OF THE SNBTS HQ

FACTOR VIII STUDY GROUP

INTRODUCTION

The SNBTS HQ Factor VIII Study Group held its first meeting on 28th January, 1982. The Group had been invited by the author to join him in examining certain strategic and operational concerns with regard to the future production of factor VIII concentrates at PFC.

The Group consisted of the following colleagues (with the author in the Chair):-

Dr P Foster (PFC)
Dr F E Boulton (SEBTS)
Dr G S Gabra (WBTS)
Dr C V Prowse (SEBTS)
Dr D S Pepper (HQL)
Mr J Watt (PFC)
Dr R J Perry (PFC)

The following acted as occasional observers: Mrs B Griffin (HQL), Mr A Farrugia (SEBTS), Mr A Barr (WBTS) and Dr B Cuthbertson (PFC).

It was agreed at the first meeting that the Group should sub-divide into small working sections to cover the following areas:-

1. Quality of recovered fresh frozen plasma produced at RTCs.
(Dr Gabra, Dr Boulton, Dr Cash and Mr Keddle (PFC)).
2. Methods of improving fractionation yields.
(Dr Foster, Dr Pepper and Dr Prowse).
3. Methods of reducing viral contamination by in-process (PFC) manipulation.
(Dr Pepper with Dr Cuthbertson (PFC) and Dr Sommerville (Belvidere Hospital) co-opted).
4. Factor VIII:C assays systems suitable for RTCs quality assurance programmes.
(Dr Prowse, Dr Gabra, Mrs Griffin, Mr Blue (WBTS), Mr Mackay (SEBTS), Mr McQuillan (PFC)).

The main Study Group met on 6 occasions and there were a total of 19 Working Section meetings. Each section produced a progress report for every Study Group meeting. The author wishes to convey his sincere thanks to all members, observers and co-opted members of the Group. The amount of extra work these colleagues have done has been prodigious and the standard of a high order. It has been a pleasure to co-ordinate their activities and note the level of active genuine collaboration between staff of different

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Centres. This latter feature has set new standards for the SNBTS and has revealed the potential for soundly based research and operational advancement.

For the sake of clarity and brevity this Report summarises the activities of the Study Group on a Sectional (topic) basis.

QUALITY OF RECOVERED FRESH FROZEN PLASMA

The primary task of this Section's work was to produce recommendations for a workable SNBTS specification for recovered fresh frozen plasma destined for PFC.

In reviewing the literature (bibliography prepared by Dr Prowse and Mr Farrugia: see Appendix I) it became apparent that it was essential to study the current practice in each RTC. Accordingly Drs Gabra and Boulton were asked to visit all Centres and discuss in detail, with the appropriate staff, those matters which were believed to be relevant to the quality of fresh plasma for factor VIII production, to record and report their findings and make appropriate recommendations. This exercise was a substantial one and it was discovered that more than one visit was necessary to several Centres. The final Report, compiled by Dr Gabra, was examined by the Study Group on 12th January, 1984 (Appendix II).

Whilst this Report is perhaps now of historical interest only it provided an essential factual database upon which the Study Group were able to approach realistically the examination of a draft specification prepared by Drs Gabra and Boulton. This draft was modified by the Study Group and forms the basis of a formal proposal for the consideration of the SNBTS Directors (Appendix III).

This Section, in collaboration with other members of the Study Group, conducted a useful inter-Centre research exercise on the fibrinopeptide A content of plasma (Appendix IV). There is little doubt that it would be opportune for further studies to be conducted in this area within the SNBTS for many important questions still remain unanswered.

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METHODS OF IMPROVING FACTOR VIII FRACTIONATION YIELDS

The Group was especially pleased to discover at its first meeting that Dr Foster's PFC team were well advanced in their thinking with regard to improving fractionation yields. It is doubtful whether the Group had much influence on subsequent progress, which has been substantial, but members would like to feel that, at the very least, Dr Foster's team received their active support and perhaps they may have influenced more recent developments.

There can be no doubt that Dr Foster eventually succeeded in convincing colleagues of the need for high quality stable fresh plasma from RTCs and this has had, and should continue to have, a profound influence on subsequent developments. It should be noted that the link between the WBTS plasma-pheresis study and PFC, which may prove of considerable interest in this area, was conceived within the Study Group. It should also be noted that during the period the Group has been active PFC yields have risen from 260 to 300 i.u./Kg. Moreover it has witnessed the introduction of a new (zinc) precipitation technology which has contributed to the development of a heat treatment process (see below).

METHODS OF REDUCING VIRAL CONTAMINATION

The Section advised the Study Group that there were three broad options: physical and chemical treatment of the final product and in-process affinity techniques. All were examined in detail and as a consequence the following decisions were made:-

- (a) Wet heat treatment was considered to be the most appropriate immediate target area. This decision has been implemented and Directors are aware of subsequent progress. It should be emphasised that Dr Bruce Cuthbertson's team have been able to respond to a request by the Study Group that appropriate in vitro virus models should be established to monitor this work. This decision may prove to be a crucial factor in subsequent studies.

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- (b) Radiation has been investigated in Dr Pepper's laboratory. It has been shown that the levels required to achieve virocidal effects give rise to an insoluble product. This work will be further pursued when more highly purified products are available.
- (c) Chemical and affinity treatments (currently favoured by several commercial companies) have been rated a low priority option, pending examination of the results of (a) and (b) above in view of potential long-term toxicity. However, Dr Pepper has been invited to retain an active interest in this option and he is currently monitoring the activities of those pursuing this type of development.

FACTOR VIII:C ASSAY SYSTEMS SUITABLE FOR RTC QUALITY ASSURANCE PROGRAMMES

The Study Group invited Dr Prowse's group to explore the possibility of producing SNBTS plasma VIII standards for routine work at RTCs and to examine ways of validating existing RTC technology and encouraging those Centres not currently involved. To this latter end a Wet Workshop was held in March 1983 at which representatives of all SNBTS Centres attended.

The Section's work has been particularly successful and the following points arise:-

- (a) A readily available SNBTS freeze-dried plasma factor VIII:C standard is now to hand. It has been calibrated against the UK (NIBSC) plasma VIII:C standard. Stocks are currently located at the SEBTS (Dr C V Prowse).
- (b) A quarterly SNBTS Quality Control System has been established in which all Centres can participate. The results of the first two studies have been especially gratifying (Appendix V).
- (c) An artificial substrate deficient plasma has been prepared and validated for the QA work at RTCs. Stocks of this material can be made available from SEBTS, if required.

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- (d) The Section is currently studying a new (chromogenic) factor VIII:C assay system. Preliminary studies (Appendix VI) are encouraging and if successful this technology may represent an important advance towards simplification and automation.

FUTURE ACTIVITIES OF FACTOR VIII STUDY GROUP

It is the view of the Group that its major work, the establishment of actively collaborating scientific and operational groupings within the SNBTS, has been successfully completed and that it will meet, for the time being, no more than 1/year to review further progress and report to the TDs. In the meantime the established Sections will continue their work and provide the Study Group with an annual report of their activities. It is intended to use this forum (Study Group) for the maintenance of advice to the Directors with regard to the SNBTS specification for recovered fresh frozen plasma and in due course for the establishment of a specification for source fresh frozen plasma (for factor VIII production).

RECOMMENDATIONS TO THE TRANSFUSION DIRECTORS

The Study Group wishes to make the following recommendations to the SNBTS Directors:-

1. That the Directors agree to proceed to formulate an SNBTS specification for Recovered Fresh Frozen Plasma destined for factor VIII production at PFC. To this end the Study Group recommends to the Directors its proposals contained in Appendix III.
2. That the Directors agree to the continuation of the SNBTS quarterly Centre factor VIII:C assay quality control programme and that this programme should be supervised by Dr Prowse and Dr Gabra. *? NBQATS*
3. That the Directors agree that Dr Prowse and Dr Gabra supervise the continued supply of an SNBTS factor VIII:C plasma standard, and an artificial substrate plasma (if required) but that these products should in future be issued from PFC. *if acceptable to the PFC assays*

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4. That the Directors agree that high priority should be given at PFC to development work designed to improve both yields and purity.
5. That the Directors encourage, where appropriate, development work designed to improve the quality of fresh frozen plasma.

APPENDIX 1FROM DONOR TO FRACTIONATOR:

(C.V.P.)

HOW IS FACTOR VIII LOST?A Literature Survey

A short review of the literature is given under the following headings:

1. Donation Time and Mixing

2. Anticoagulant

3. Centrifugation and Cellular Contamination

4. Temperature and Time from Donation to Freezing

5. Freezing Rate

6. Frozen Temperature and Storage Time

7. Factor VIII in Feedstock

References

C Prowse
A Farrugia
F E Boulton

22 February 1983Revised 1 July 1983Appendix - 14 December 1983