IN CONFIDENCE

MINUTES OF MEETING OF FACTOR VIII STUDY GROUP HELD IN HEADQUARTERS UNIT ON THURSDAY, 14th OCTOBER, 1982

Present:

Dr J D Cash (Chairman)
Dr C V Prowse (Secretary)
Dr F E Boulton
Mr A Farrugia
Dr D S Pepper
Mrs B Griffin
Dr P Foster
Dr R J Perry
Dr G S Gabra
Dr B Cuthbertson (morning only)
Mrs E Porterfield (Notes)
Mr S Keddie (Item 3 (d) onwards)

1. INTRODUCTION AND APOLOGIES FOR ABSENCE

Mr J G Watt had sent his apologies for absence from the meeting as he was on annual leave.

2. MINUTES OF LAST MEETING

The Minutes of the previous meeting held on 3rd June, 1982 were passed as a true record.

3. MATTERS ARISING

(a) FVIII Safety Action Group

Two papers had been circulated prior to the meeting. However, Dr Pepper tabled a third, the notes of a meeting held on 1st July, 1982 of the Safety Action Group. The various topics set out in the paper were studied in detail.

1. INACTIVATION

(a) Heat Treatment was now the first option of the group in view of developments which had occurred since the last meeting. Dr Alex McLeod (PFC) would continue studies of heat process using high purity product. Edinburgh BTS to assist if necessary.

(b) Radiation

Porcine VIII had been obtained (from Speywood) and irradiated with 2.5M rads which produced solubility problems and, in view of this, radiation, at this stage, was not thought to be a practical proposition.

(c) Adsorption

Dr Cuthbertson introduced this item and outlined his work on CUNO filters, which had not produced satisfactory results. It was not considered worthwhile to pursue this aspect further.

Various other aspects for study were discussed: hydrophobic columns developed by Kabi were not suitable for FVIII:C although would be suitable for FIX; horse antisera had been obtained from BPL and monoclonal antibodies, it was hoped, would soon be available from the Edinburgh Centre for HBsAg, but antibody

treatment is currently a research proposition and not immediately adaptable to clinical products.

Dr Pepper thought it might be possible to carry out studies to identify HBsAg binding receptor sites using polymerised albumin. Theoretically it was possible to make albumin from plasma obtained from primate species and polymerise using a process described in a recent publication.* Unfortunately, he was unable to carry out this work at the present time, but he was of the opinion that this could be a viable route to animal model selection for infectivity studies.

Dr Cash pointed out that if, in fact, a range of binding sites was demonstrated then it would be necessary to proceed to infectivity studies, in which case animals would be essential.

It was decided that Dr Cuthbertson/Dr Pepper would pursue this possible line of work.

* Milich, T.R., et al
Gastroenterology (1981) 81, 218-225.

(d) Purification

Dr Milan Bier had started work on zinc fractionation and it would therefore be worthwhile to await his results before continuing with this aspect of study.

(e) Detergents

Much information had been collected since the last meeting. Practically all of the detergents tested so far had proved quite successful, with a good survival rate of FVIII:C, although there was a possible problem with toxicity. All in all, detergents were thought to be a worthwhile proposition, but should not be pursued at the expense of heat treatment, which was considered a better option.

2. INFECTIVITY

(a) Owl Monkeys

No real progress to report, however, this would be pursued as quickly as possible with Major le Duc.

(b) Marmosets

The offer of help from PHLS at Colindale was still open. This involved injecting two different types of NANB implicated material into two different species of animal. Dr Cash was of the opinion that it might be worthwhile to send Dr Gabra and Dr Hopkins (Edinburgh) a small amount of the infected material for separate testing. He thought it should also be tested for B virus before injection.

Interest had been expressed by Dr Sharn Evans of Stirling University. She might be prepared to send animals to BTS or co-operate with experiments.

3. RAW MATERIALS

There was no real problem at the moment. As well as 3 ~~virals~~ mab of Armour Factorate concentrate Dr Pepper had received a gift (from BPL) of a hepatitis B implicated FVIII. He would also try to obtain samples of agent 'H' from BOB, which had previously been offered.

It was agreed that the Armour Factorate concentrate should be tested by Dr Hopkins (Edinburgh) and, if possible, by Professor Dane's laboratory (Professor Dane had now retired).

Dr Cuthbertson, Dr Perry and Dr Foster would collaborate on working out a method for albumin polymers. Dr Joan Dawes would be approached to see if she had any primate sera which could be made available to send to Dr Cuthbertson.

3. (d) Quality of Plasma Working Party

Dr Cash invited Dr Gabra to speak next as he wished to devote some time to the document which had been circulated, "Quality of Fresh Frozen Plasma: Current Practice in Scotland: Comments and Recommendations". Mr Sam Keddie (PFC) was invited to join the meeting at this point as he was a member of this Working Party and had helped in the production of the report. Dr Gabra wished to put on record that he had found the visits to Regional Centres while preparing this document extremely helpful and also felt that Regional Centre staff had appreciated many of the points emphasised during these visits with regard to working practices, etc.

The various sections of the report were considered individually.

1.1 Bags and Anticoagulants

All Centres used CPD, as this was considered superior to ACD. There had been a proposal to move to CPD-Adenine but Mr Watt had pointed out that this would not be appropriate until a test batch of plasma collected into CPD-A bags had been fractionated to check problems, if any. The West of Scotland Centre had supplied plasma collected in CPD-A which had been fractionated. Work was still in progress, but it was not anticipated that any major problems would arise.

It had been noted that source plasma from plasmapheresis was collected into ACD rather than CPD, the reason for which was not known. Dr Gabra would investigate and report back. (N.B.: PFC produces anticoagulant for use on Haemonetics machine).

It was not thought that different manufacture or type of bag affected FVIII yield and a study to this effect had been described by the Groningen Centre staff at the ISBT Congress in Budapest.

It was recommended that different procedures employed in Centres would be worth recording, e.g. if a significant amount of material was collected for platelet supernatant, this should be quantified. The percentages of 5 litre, 2 litre and "single wafer" batches sent to PFC might also be helpful.

1.2 Venesection Time

This was not recorded at all.

1.3 Mixing

This was achieved manually except at the Edinburgh Centre, where bags were inverted. It might be worthwhile to study this to ascertain if there was a difference in the quality of plasma collected.

1.4 Volume

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1.4 Volume

The Working Party recommended that SNBTS Directors should consider asking all Centres to use 450 ml. bag (2 currently use 420 ml.).

1.5 Method of Weighing

Dr Cash asked Dr Gabra to prepare a paper comparing different weighing systems employed at Centres (manual vs. automatic).

1.6 Type of Session/
1.7 Ferrying of Blood

Since between 80% to 100% of collection was conducted outside the Centre this had a marked effect on the practices employed for ferrying of blood, as did the geography of each Region. The Group considered that a study should be carried out (in one Centre only) of practices involved, temperature of storage etc., to see if it could be ascertained at what point/ temperature after collection FVIII yield was affected. Dr Gabra, Dr Boulton and Dr Prowse would liaise on this study.

2.3 Centrifugation

Dr Gabra was not aware of the comprehensive study which had been carried out by the Technical Evaluation Group (previously known as Working Group on Refrigerated Centrifuges). He would ask Mr Muir for copies of the Reports prepared by this Group.

2.4 Volume of Plasma/
2.5 Type of Plasma

The machine developed for automated plasma expression was drawn to the attention of the meeting.

Plasma volume did affect freeze rate of bigger packs. Plastic of the bigger Nusac packs shattered at -50°C, and it was therefore necessary to blast freeze single packs. Dr Prowse was asked if he would send to Dr Gabra results of a comparison study which had been carried out on samples from packs prior to freezing and on core samples after freezing which had shown a 7% reduction in FVIII content.

Samples taken from 5 litre and single packs had shown no difference in VIII content.

Discussion followed on the development of the tear-down bag system at PFC, which would inevitably lead to changes in practice with regard to pooling etc. Dr Perry would keep Dr Gabra informed of progress. The current SAGM evaluation would also have to be taken into consideration.

3. Freezing

Practices varied considerably throughout the Regions. Dr Cash reminded the group that the Medicines Inspectorate was active in this area and, in view of the fact that the majority of Centres would require some rebuilding, to a greater or lesser degree, to comply with MI recommendations, perhaps the Group's views would be sought by the Regional Directors when assessing requirements for freezers etc. The most important factor to be taken into consideration was to ensure that freezers could cope with the throughput of material to prevent a backlog building up.

3.6 Age of Plasma when Frozen

70% of plasma is frozen within 2-8 hours of collection, the other 30% is frozen within 8-18 hours. The time to be recorded in this section is the total time from collection to end of freezing. Two unknown components were involved in this total time. None of the Centres could estimate the time lapse between collection and centrifugation or the unknown time between centrifugation and freezing. A wide-ranging discussion ensued: could these unknown quantities contributed to the undoubted drop in yield over the last year? Was the Group concluding that quicker cooling to, and storage at, 4°C was advisable? Dr Pepper suggested carrying out a pilot study of temperature control at the point of donation on, say, 10 bags, 5 immersed in iced water immediately and 5 kept at ambient temperature and then compare yields. Dr Foster was aware of temperature studies which had been carried out by Dr Jim Smith at BPL, which showed a 20% additional loss of factor VIII in whole blood (but not plasma) stored at 4°C rather than 20°C. In view of this the effects of transport from donor to centrifuge at different temperatures on blood temperature and factor VIII should be investigated. The possible effects of cell contamination of source plasma were mentioned. Previous work had shown no correlation of VIII content with BTG or particle count. PFC occasionally sees 'pink' packs, presumably due to red cell contamination, but this was not thought to be a problem due to its low frequency, although it reflects poor technique at Regional Centres.

3.7 Storage Temperature

This is validated at Centres: records are kept. The quoted figure appeared a nominal one and Dr Gabra and Mr Keddie undertook to obtain the actual records for July 1982 from each Centre as a sample.

3.8 Time spent in storage at Centres

This varies from less than 7 days (55%) to 4-11 days (21%) and less than one month (24%).

3.9 Boxing and Volume of Plasma available for Despatch

76% of plasma despatched originates from the two large Centres (55% from Glasgow). Most is now prepared as single units and 55% of this is repacked in bags prior to despatch, a very labour intensive process.

4. DESPATCH TO PFC

Discussion of this topic centred mainly on the monthly round trips of the PFC refrigerated vehicle to outlying Regions. It was obvious from the data quoted on p.16 of the document that the plasma is subjected to marked fluctuations in temperature throughout the journey to PFC. Mr Keddie explained the current practices involved in these trips in detail, which helped to clarify the figures. In summary, the total journey is as follows:-

1. Vehicle delivers blood products etc. to (1) Dundee, (2) Aberdeen and (3) Inverness. During this journey van kept at ambient temperature.

2. After unloading at Inverness, refrigeration unit switched on to cool van. If sufficient time van is loaded that evening (therefore van not cooled properly). If not, van is left to cool overnight and plasma loaded in morning.

3. Drives to Aberdeen with cooling unit on. Loads plasma at Aberdeen, therefore temperature drop incurred during loading.

4. Drives to Dundee with cooling unit on. Loads plasma at Dundee, therefore, further temperature drop incurred during loading.

5. Drives to PFC. Usually arrives late evening, therefore unloading not carried out until following morning - van left with cooling unit on overnight.

6. Unloading in morning. Plasma subject to further temperature fluctuation during unloading, documentation and stacking in freezer.

It was recommended that Dr Perry should investigate this area as a matter of urgency with a view to introducing a SOP as soon as possible. The temperature of the van at the start of loading in Glasgow was apparently rather high.

Dr Gabra asked the group to consider this first draft in detail and to let him have written comments/recommendations, if any.

(b) Assays and Standards Working Party

Dr Prowse summarised the progress to date, as outlined in the paper which had been circulated. There were no subsequent developments to report and none of the Group had any comments to offer. The Workshop for staff would be organised as soon as practicable.

(c) Factor VIII Yield Working Party

Dr Foster briefly summarised the points made in his Progress Report. He also tabled two further documents, (1) FVIII Content of FFP (SNBTS) Processed at PFC during 1982; (2) History of 9 Fresh Frozen Plasma Pools Processed at PFC.

Progress Report

2.1 Calcium Addition

The Group's views were sought on the acceptability of adding calcium to FVIII concentrates: the general opinion was that calcium addition in the small quantities envisaged would be quite acceptable.

2.2. Solubility

Since the last meeting Dr Foster had become aware that patent applications had been filed by some commercial companies on the use of dextrose. He therefore thought it worthwhile to study the effects of this sugar on solubility.

2.3 Stability

Licensing Authorities had advised, verbally, that any alteration in manufacturing method would require a change in product licence and, therefore, new stability data would require to be submitted to prove there were no adverse effects on the final product. Dr Foster and Dr Perry were advised to write to the Licensing Authority giving brief details.

3.2 FIX Removal and Zn Precipitation

Dr Pepper was still working on an antigen assay. Dr Boulton's paper on zinc

(which had been tabled) should prove helpful in this work.

Dr Cash thanked Dr Foster for his update. Discussion followed on Mr Farrugia's paper "Work Carried Out at Edinburgh BTS on FActor VIII Fractionation" which he had tabled.

This paper summarised the results which had been obtained on studies of possible FVIII precipitating agents. These results excited much interest and discussion, particularly those obtained using albumin and hydroxyethyl starch (HES). Mr Farrugia was asked to continue his work and also try studies with cryoprecipitate and intermediate purity concentrate, and report to the next meeting.

4. DATE OF NEXT MEETING

Friday, 3rd December, 1982 at 10.00 a.m. in HQ Unit.