

MINUTES OF MEETING OF FACTOR VIII STUDY GROUP HELD IN THE
HEADQUARTERS UNIT, ELLEN'S GLEN ROAD ON 30th MARCH, 1982

Present:

Dr J D Cash (in the Chair)
Dr F E Boulton (morning only)
Dr C V Prowse (Secretary)
Dr D S Pepper
Mrs B Griffin
Mr A Farrugia
Dr G S Gabra
Mr A Barr (morning only)
Mr J G Watt
Dr R J Perry
Mrs E Porterfield (notes)

1. APOLOGIES FOR ABSENCE

An apology had been received from Dr P Foster who had a previous appointment in London.

2. MINUTES OF PREVIOUS MEETING:

Agreed as accurate.

3. MATTERS ARISING:

(a) FVIII ASSAYS & STANDARDS WORKING PARTY

A paper had been circulated to members of the Study Group concerning a pilot study being carried out using the reagent from artificially produced FVIII deficient plasma to assess its suitability for manual and automated assay. Preliminary results were now available and Mrs Griffin passed round a paper showing these to members of the Group.

Dr Cash wondered if it would be worthwhile, at this stage, involving the West in the testing of artificially and congenitally produced substrate as a supplement to the study, although he was aware of the previous decision to confine the study to the Edinburgh group. It was agreed that it might be feasible to involve the West in a small way and sufficient material for 3 assay runs would be sent to Dr Gabra and Mr Barr.

At this point Dr Prowse informed the group that the supply of congenitally deficient plasma was almost depleted and that it would prove necessary to purchase from commercial sources to continue the comparison study with artificially produced mate. In view of Dr Boulton's close contact with the Haemophilia Society it was agreed that he would communicate with the Secretary of the Society regarding the possibility of volunteers willing to undergo plasmapheresis in order to maintain supplies.

The pilot study would continue for a further six weeks and, if successful, the idea would be, if possible, to freeze dry a 5 litre batch of substrate together with a similar size batch of plasma as a standard. However, Mr Watt raised doubts as to the capacity of PFC freeze drying facilities to cope with any further demands at

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at the present time. However, it was thought that, given careful planning, it might be possible to meet the Group's request.

The question of utilising the Law freeze drying plant was raised, but it was agreed that, given the different types of machine etc., it would be difficult to achieve such definitive results as could be obtained using PFC equipment.

Assuming that suitable results are obtained in stages described above Dr Prowse had prepared a SOP for circulation to RTCs, but this would not be done until assay etc. was standardised. However, in view of the fact that Law was to assay some material it was agreed that Dr Gabra could be sent a copy.

Dr Cash then asked the Group for thoughts on how Regions could be involved once all relevant factors were standardised. There was general discussion on this aspect and the consensus of opinion was that a "Wet" Workshop should be organised to which all staff concerned in the RTCs would be invited. Dr Prowse would organise this when appropriate.

Regarding the question of possible computer programme to assess national results etc. for QC purposes, it was agreed that Dr Prowse would liaise with NIBSC and Mr Ian Mann of ISD.

The work on phospholipid coated beads continues. Mrs Griffin had conducted experiments which showed that the lipid coat was easily washed off the beads and studies were now being carried out to see how this could be rectified. The Group would be kept informed of developments.

(b) FVIII YIELD WORKING PARTY

Because of Dr Foster's absence it was agreed that no meaningful discussion of his paper was possible and it was therefore agreed that this would be carried forward to the next meeting of the Group with the recommendation that in the meantime Dr Foster should delineate the priorities of his group.

(d) RTC QUALITY OF PLASMA WORKING GROUP

Information had been obtained from 4 Centres on the framework which might be adopted for the evaluation of plasma handling. Any comments on and amendments to the proposed format which the Group felt necessary were invited.

Mr Watt felt that it might be helpful at this stage to outline the problems etc. of different temperature levels for storage of plasma and the effects this could have on yield etc. of FVIII, which would be relevant when deciding a format for completion of studies. These were outlined as follows:-

Refrigeration/

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Refrigeration costs were:-

<u>Desired temperature</u>	<u>Cost</u>
- 20°C	£ X
- 30°C	£ 1.2X
- 40°C	£ 1.6X
- 50°C	£ 4.5X

Studies up to the present time had shown that the pre-freezing age of plasma did not seem to be a relevant factor to yield, but that with the current improved yield of the order of 300 iu/l., 18 hour plasma yield was 15% lower. Studies currently being carried out in PFC suggested that temperature was an important factor in consideration of the yield problem.

Dr Gabra then introduced his Group's ideas so far on how best to record the information required from Centres to evaluate the handling of plasma from donation to delivery to PFC. The Group had quite a few recommendations to make and a typed draft, including changes recommended by the Group is attached at Appendix I. It was pointed out that the title of the Group heading the pro forma should in fact be "Action Team on Quality of Recovered Plasma", not "..... Source Plasma".

Dr Pepper asked if it would be possible to correlate the information obtained with quality of plasma, but this was not a viable proposition at the moment. There was much discussion on the question of times involved in bleeding donors and getting whole blood to centrifuges etc. and it was generally agreed that this area would be very difficult to evaluate. Dr Perry felt that as it was inevitable that the format would become quite complicated it might be necessary to produce guidance notes for staff at Centres. However, Dr Gabra and Dr Boulton felt that as they would be visiting individual Centres to discuss and help where required, this would not be necessary.

Dr Cash thought that plasmapheresis should not be included in the study but left Drs Gabra and Boulton to make the final decision. The attitude of Regional Centre staff to the study was discussed. Dr Gabra was of the opinion that a neutral attitude on his and Dr Boulton's part should be maintained. Dr Pepper suggested that perhaps a member of staff from each of the Regional Centres should be invited to a future meeting of the Group in order to keep them fully informed. He also thought that it should be possible to develop, within the Group, a means of record temperature/time profiles of plasma in transit.

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So far as page 3 of the framework was concerned it was thought this should possibly be titled "Process Validation" and that the temperature validation aspect could more effectively be added to this section. Possible instrumentation etc. could be checked with Mr Grant at PFC. Mr Barr said that Mr Muir at Law was currently carrying out a study of this kind although he did not have the exact details, although he knew the study involved following one donation from collection to storage and time involved to reach temperature of $+4^{\circ}\text{C}$. Mr Muir had now extended this to follow processing of concentrated red cells. Mr Muir should be invited to a future Study Group meeting to talk on his studies when completed.

Dr Cash expressed the view that pH measurement might not be necessary but, after some discussion, it was agreed that, for the moment, this item would remain.

(c) FVIII SAFETY ACTION GROUP

Dr Pepper spoke on the first report of this Group which had been circulated. He outlined the points made in the paper's introductory paragraph and commented as follows:-

- (i) The option of doing nothing at this time might be most appropriate if NANB screening was to become available in the near future.
- (ii) If haemophiliacs being treated for the first time were studied this would show that the incidence of B markers was dropping but liver dysfunction remained high. Only indirect evidence to support this was available. It was not possible to obtain a product which had been implicated in infection. At this point the problem of haemophiliacs receiving IX concentrates showing raised LFTs was raised and provoked a great deal of interest and discussion. There was evidence to support the theory that the problem of infection exists on a UK basis rather than in Scotland only.
- (iii) The proposals to achieve a hepatitis reduced VIII product would take time and considerable investment. It was thought this could not be achieved in less than 2 years and it was possible that in the interim other current developments throughout the world might render this study less viable.

The relevant factors to be taken into consideration were:

Hepatitis B is still a risk although reducing now that screening was available. Available data indicated that the properties of NANB were similar to those of hepatitis B although this was by no means certain.

There is an existing review showing that there are separate classes of B virus:

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one of the problems is that the pathology of hepatitis B virus is still not well defined. Because of this it would not be worth pursuing unless there was a commitment to prove that treatment is effective.

The use of animal models for infectivity study purposes was discussed. Chimpanzees would cost £10,000 per animal test per 6 months. If humans were used it would not be possible to have a "known positive" control. The methods of inactivation available were heat treatment; irradiation or absorption.

The proposals of the Safety Action Group were:

Bruce Cuthbertson would continue to look at filters and the work started by Alex McLeod on heat treatment would be pursued.

Dr Pepper would investigate the variable factors of irradiation (temperature, additives and fibrinogen content).

Mr Watt pointed out that possibly Dr Foster's work on precipitating out fibrinogen should be included in this section.

It was agreed that infectivity was the crucial question and the dilemma over the use of chimps (an endangered species), owl monkeys (information to be supplied by Dr Sommerville when available) and humans formed the basis of a long discussion

Dr Cash took up the question of laboratory accommodation which would be required for irradiation and heat treatment work on the separation of virus(es) from VIII. Because this would involve using both infected and uninfected material separate facilities would be necessary. The work currently underway only involves uninfected material. Neither Phase I nor PFC Microbiology building would be available in the time scale envisaged. It was possible that the Law Laboratory might be available and of sufficient size to carry out the work, but it was doubtful if any ancillary equipment necessary could also be sited there.

It was possible that the filtration work could be done in the West and the irradiation work in Edinburgh. Dr Robert Hopkins would be asked if he would do the RIA/antigen assays. Ideally, 20 to 30 vials of infected material from a single batch was required.

Mr Watt spoke on the practicalities involved in using chimpanzees. Because they are an endangered species this would make it arguable that they were a viable proposition for study because of the problems involved in maintaining a supply of animals. The cost of using owl monkeys would be approximately the same as that of chimpanzees. However, it was not known if this would be an available option because of the time factor involved. Mr Watt had ascertained that owl monkey colonies did exist in the UK and he would circulate details when they became available.

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It was stressed that access to animal models was required immediately.

It was suggested that Dr Pepper should contact Dr John Craske (Virologist) in Manchester for details of reactions (Hepatitis B) to FVIII in order that he might possibly obtain some of the contaminated product. However, it was doubtful that this would produce results in view of the long incubation period, by which time the batch concerned would probably be exhausted.

Dr Prowse pointed out that PFC would have samples of infected material, although this would not, obviously, include commercially produced VIII.

Dr Cash offered to contact Dr P Mannucci and Dr Prowse would contact Dr Ludlam in the Royal Infirmary to see if they could help.

It was agreed that Dr Pepper and his group would continue the active exploration of this area.

An opinion was sought on whether this Group should be encouraged to submit a grant application for their work. Mr Watt was of the opinion that this work should be funded by BTS development monies although Dr Cash and Dr Pepper thought a grant application was probably more feasible. Dr Pepper said work could continue in the short term, with existing resources but in the long term extra staff and infectivity assays would be required. It was recommended that the Group should look at this area and decide if work should be carried out and, if so, consider the costs involved in doing so.

DATE OF NEXT MEETING:

Thursday, 3rd June, 1982 at 9.30 a.m. in the Conference Room, Headquarters Unit.

- AGENDA:
- ASSAYS & STANDARDS WORKING PARTY
Report on Finalised Pilot Study
 - FVIII YIELD WORKING PARTY
Dr Foster's report - deferred from 30th March.
Proposals for Action.
 - QUALITY OF PLASMA WORKING PARTY
Information obtained from Centres: Report.
 - FVIII SAFETY ACTION GROUP
Report on progress.