MEDICAL RESEARCH COUNCIL

Circulation

Members of the Working Party

Working Party on Factor IX Concentrates


Present:  Dr C R Rizza (Chairman)  
Professor G I C Ingram  
Dr A L Johnson  
Dr W d'A Maycock  
Dr C R H Prentice  
Dr C Prowse (representing Dr J D Cash)  
Miss H Patterson (representing Mr J G Watt)  
Dr C A Ludlam (representing Professor A L Bloom)  
Dr J M Voke and Dr E G D Tuddenham (representing Dr K M Dormandy)  
Dr J Wyke (representing Dr R S Williams)  
Dr Diana M Walford (DHSS)  
Dr E Bidwell (Secretary)  
Dr R Russell (Royal Infirmary, Glasgow) attended by special invitation

In attendance:  Dr A J G Dickens  
Miss B Maxwell

1. Apologies for absence were received from Dr K M Dormandy, Dr J D Cash, Mr J G Watt, Professor A L Bloom, Professor J P M Tizard and Dr R S Williams.

2. Minutes of the sixth meeting (FIXC 76/6)

The minutes of the sixth meeting held on 22nd March, 1976, were accepted as a correct record and signed.

3. Progress report: Trial of rapid anticoagulant reversal with prothrombin complex concentrate versus whole plasma (FIXC 78/2)

An interim meeting of Dr Rizza, Dr Bidwell, Professor Ingram and Dr Johnson had been held on 9th June, 1977, with local co-ordinators of this trial, and the draft minutes (FIXC(0A) 78/3) circulated.

Dr Johnson said that for the patients entered the standard of documentation was good but the entry rate was only 20% of that expected. Since the document FIXC 78/2 had been prepared on 15th January, 1978, three further patients had been entered: one at St. Thomas's (treated with whole plasma) and two at Stobhill Hospital, Glasgow, (one to each group) making a total of 36 patients since the beginning of the trial. Stobhill Hospital, Glasgow, was the only centre which was entering patients at the rate predicted, and there was no clear reason in this trial why the entry rate was so slow. Professor Ingram thought that apart from the natural tendency "not to do work", atypical cases
tended to lead to an interest in starting a trial without full allowance being made for the proportion of patients who would need treatment at times when it was not practicable (because of inconvenient hours) to include them in the trial. Dr Ludlam mentioned the changing of junior staff as also making things difficult.

Professor Ingram was not aware that any need for factor VII had been expressed by local co-ordinators from the "reversal of anticoagulants" trial. Dr Johnson thought that the trial should run for its full two years and then have a review of the data. He was asked whether there was any evidence that local co-ordinators thought that the treatment was doing any harm and he replied that some patients with concentrates had later been treated with whole plasma but that the reverse was also true. Dr Bidwell mentioned that in the draft minutes of the interim meeting of local co-ordinators held on 9th June, 1977, it had been agreed that there should be a meeting convened in about March 1978. It was agreed that in the light of the present meeting, and the report from Professor Ingram and Dr Johnson, such a meeting was not necessary but should be deferred to January 1979 after Dr Johnson had had an opportunity of reviewing the two-year data. Professor Ingram agreed to write to the local co-ordinators to try to increase the effort put into the trial and to mention the decision about the date of the next meeting.

The disproportion between the number of patients entered who had received DEXF and those who had received Type DE(1) factor IX was noted. This was not due to the withdrawal of Dundee but to the slow entry from Royal Infirmary, Edinburgh, and St. Thomas's Hospital, both of which had been allocated DEXF, and to the good entry rate from Stobhill which had been allocated type DE(1) factor IX. Dr Prowse said that Dr Cash's group was concerned only with the "liver biopsy" trial but that he would communicate the difficulty to Dr Davies.

4. **Progress report: Trial of prothrombin complex concentrate for patients prior to liver biopsy (FIXC 78/3)**

An interim meeting of Dr Rizza, Dr Bidwell and Dr Johnson with local co-ordinators of this trial had been held on 14th October, 1977, and the draft minutes (FIXC (LB) 77/3) circulated.

Dr Johnson said that, since that meeting in October, only one further patient had been entered and the trial was now at a standstill. Dr Russell said that of the predicted 11 patients from Glasgow during that period, none had been entered but he agreed with Professor Ingram that abnormal patients had indeed been remembered, thus leading to an over-estimation. He said that they had had local difficulties in the case of the first of these patients; one patient was Australia antigen positive and one patient required treatment at Christmas, so that only three patients had been suitable for the trial during the last year. He emphasised that he thought a close link between the haematologist and the liver unit was essential. Sometimes a patient otherwise suitable would be under the control of another unit, not the liver unit. Dr Voke agreed that there had been a gross over-estimation of the number of patients who might be entered into the trial because they had not excluded private patients or patients who arrived at inconvenient times. She thought that people had found completion of the protocol too much effort. When asked how the patients were in fact treated, she said that they might have extra fresh frozen plasma, or biopsy without correction, or be treated with steroids and a period of waiting. Dr Tuddenham said that the trial appeared formidable to clinicians; he could not get enthusiastic about it, and he asked whether patients less fully "worked up" than in the protocol would be accepted. Dr Johnson said that 'all the
patients who had been entered fell into the group of prothrombin time ratios 1.4 to 1.8. Dr Wyke said that they had been unable to get satisfactory correction with the three-factor concentrate, and with patients whose prothrombin time ratio was in group 1 they went on to biopsy without treatment. If the patients fell in groups 2 or 3, the PTR would not correct with the three-factor concentrate. Professor Ingram felt that for anticoagulant reversal it depended on clinical assessment whether factor VII was required. Dr Johnson thought that there could be no firm evidence on clinical data as the 20 patients in the liver biopsy trial were too few to analyse. Dr Prentice asked what was done at King's College Hospital when the prothrombin time ratio was not corrected. Dr Wyke said that the treatment was with fresh frozen plasma but was not monitored haematologically; some patients with a prothrombin time ratio of 1.7 were biopsied without treatment, and everything depended on how "ill" the patient was. Professor Ingram wondered if the partial thromboplastin time might be better test for the prediction of bleeding. Dr Wyke thought that no evidence could be presented because patients with prolonged PTT were not biopsied; he added that concentrates were not now used for patients with bleeding varices or fulminating hepatic failure. Dr Voke said that during the 1974-5 the factor IX concentrate had been wanted for very disturbed coagulation defects but had not been asked for so much recently - perhaps the clinicians were not prepared to wait. Dr Wyke wondered what was the value of biopsy in these patients since there were only a few clinical situations in which the biopsy results would influence treatment. Dr Russell thought that probably many clinicians might just wait to see what happened to the patient. Dr Prowse said that no more patients had been entered from Edinburgh. The number of available patients with a suitable prothrombin time ratio was low and a few corrected with vitamin K alone; also they were waiting for a decision about factor VII. If factor VII was required, they would prefer to use the four factor concentrate PPSB. Dr Bidwell asked Miss Patterson whether PFC would want to go on making PPSB indefinitely. She replied that since PPSB was made from plasma specially collected into EDTA she did not know how much they could produce, but there were no plans at present to discontinue the production of PPSB. Dr Wyke felt that if a biopsy was required and the reason for doubt was that the prothrombin time ratio was raised, then it followed that the prothrombin time ratio had to be lowered. Dr Russell felt strongly against changing the trial protocol at this point. Professor Ingram wondered whether the failure of the three factor concentrate was really due to the patient's requirement for factor V rather than factor VII. He thought that if the three factor concentrate was given and failed, followed by a factor VII concentrate which still did not correct, then there must be other reasons for failure. Dr Voke felt that even if factor VII were supplied, and even if their local haematology situation improved, it might take several years to get sufficient information. Dr Wyke said that at King's College Hospital they were worried about the use of concentrate in general, and even if factor VII were supplied they could not guarantee to participate in the trial and no patients would be entered on the present protocol. They were concerned about the risk of hepatitis, especially non-A non-B type hepatitis from blood products; the concentrate might have a higher risk than FFP and he confirmed their present reluctance to use concentrates. Dr Russell thought that this was a local view which he did not share. He agreed there was a risk of hepatitis following the use of concentrates but felt it was minimal. Dr Voke thought that at the Royal Free Hospital the liver unit would probably give what the haematologist suggested. Dr Wyke felt that the follow-up might be difficult and could be more trouble than was realised. Dr Maycock asked whether King's College Hospital was satisfied with FFP, and Dr Wyke agreed that the evaluation was not along scientific lines - hence the prothrombin time ratio was not usually checked after FFP. Dr Maycock said that if FFP was satisfactory, why was there any interest in using concentrates? Dr Wyke said that FFP was not always convenient.
Dr Maycock asked if King's College Hospital group would put on paper their evidence for and against the use of concentrates. Dr Wyke said that the investigation was still going on and felt that the final result would be likely to be inconclusive but might leave a high level of suspicion.

Dr Johnson asked if the Working Party was not monitoring clinical procedure and he felt that there was little point in continuing. Dr Veke wondered if some of the tests could be omitted and yet still gain useful information from the trial; she thought that the availability of factor VII concentrate would make a difference to about a quarter of the patients at the Royal Free Hospital and that anything that could be done to simplify the procedure would improve the numbers. Dr Tuddenham thought that if the prothrombin time was corrected, it would help to get patients included in the trial. Dr Prentice emphasised that it was not known whether normalising of the prothrombin time ratio was necessary and that there was no evidence that the factor VII was essential.

Dr Wyke wondered if other centres would consider it ethical to biopsy patients whose prothrombin time ratio was still prolonged but Dr Russell thought it could be unethical not to biopsy. Dr Rizza enquired whether the Working Party should continue as it was doing, hoping that the Royal Free Hospital would introduce more patients. Dr Veke said that the long follow-up was discouraging and also that the hepatitis B antigen samples had to be sent elsewhere while in their centre they were not looking for the non-A non-B types of hepatitis. Dr Bidwell made the point that even if no cases of hepatitis were associated with the use of concentrates in the trial, the information was valid only for the batches used and could not be taken to prove that other batches were free from the risk of transmitting hepatitis. Dr Wyke thought that Professor Zuckerman would think it an advantage to have stored samples in case the possibility of tests for non-A non-B hepatitis virus become a reality in the future.

Dr Johnson thought that with this trial the Working Party should not wait six months before reviewing the progress of the trial and he reminded the members that only one patient had been entered since October. There should be 24 patients entered in the next three months if the trial were to be continued. Dr Tuddenham said that they would try to enter one patient per week.

Dr Johnson said that the quality of the data that had been entered was good. In view of this, many of the members felt that an attempt should be made to keep the trial running along the present lines. It was agreed that there might be more centres willing to co-operate but Dr Bidwell felt that it would take two or three months to get that organised, especially since it would have to be cleared not only with the centres themselves and their ethical committees but also with the Committee of Safety of Medicines. It was agreed that if, after three months, not more than 20 patients had been entered, the data would be analysed and a decision taken whether or not the trial should be continued. It was agreed to defer any decision concerning factor VII. Dr Bidwell said she understood that the Committee on Safety of Medicines would require a new application for a clinical trial certificate if it was desired to include a factor VII concentrate.

5. Any Other Business

Dr Bidwell said she had been asked by Dr Dickens to furnish a brief report on the Working Party to Professor P L Mollison, for incorporation by him in a report to the Council's Physiological Systems and Disorders Board on the work of the Blood Transfusion Research Committee and its associated Working Parties during the last few years. She gave a brief outline of the content of her report, which was endorsed by the Working Party's members.