Minutes of Haemophilia Centre Directors' Meeting 27.10.72

Present: Professor E.K. Blackburn (Chairman), Dr. P.G. Arblaster, Dr. A. Aronstam, Dr. P. Barkhan, Dr. Bruce Bennett, Dr. Enid Bennett (representing Professor Prankerd), Dr. E. Bidwell, Dr. R. Biggs, Dr. A.L. Bloom, Dr. T.H. Boon, Dr. Clark (representing Professor Davidson), Dr. G.P. Clein (representing Professor Hayhoe), Dr. A. Dawson, Dr. S.H. Davies, Dr. I.W. Delamore, Dr. H. Dodsworth (representing Professor Mollison), Dr. K.M. Dormandy, Dr. J.O.P. Edgcumbe, Dr. D.I.K. Evans, Dr. M. Fisher (representing Dr. Jean Grant), Dr. P.T. Flute, Dr. C. Forbes, Professor R. Hardisty, Dr. R. Ibbotson (representing Dr. G.C. Jenkins), Dr. G.I.C. Ingram, Dr. P. Jones, Dr. J. Leslie, Dr. J.M. Matthews, Dr. W. d'A. Maycock, Dr. M.J. Meynell, Dr. R.S. Mibashan, Professor M.G. Nelson, Dr. J.R. O'Brien, Dr. C.R.M. Prentice, Dr. S.G. Rainsford, Dr. A.B. Raper, Dr. C.R. Rizza, Dr. D. Stern, Dr. H. Sterndale, Dr. J. Stewart (MRC), Professor J.W. Stewart, Dr. J. Stuart, Dr. L.M. Swinburne, Dr. D.N. Whitmore (representing Dr. C.A. Holman), Dr. C.R.R. Wylie.

Apologies received from: Professor Hayhoe, Dr. Inglis, Dr. Tudhope, Professor Girdwood, Dr. Cook, Dr. Black, Professor Mollison, Dr. Jenkins, Professor Davidson, Dr. Holman, Professor Prankerd, Dr. Humble, Department of Health.

Professor Blackburn thanked Dr. Biggs for arranging for the meeting to take place and Dr. Jean Grant for the use of the room. He reported the death of Dr. Obank (Department of Health) and expressed appreciation for the interest Dr. Obank had shown in the work of the Haemophilia Centres and the help he had given over administrative matters. Directors stood in silence for one minute. Dr. Blackburn welcomed the Directors of the new Haemophilia Centres (Dr. Stern, Bournemouth; Dr. Evans, Manchester Children's Hospital; Drs. Arblaster and Aronstam, Alton; Dr. Leslie, Southampton). Also welcomed Dr. Bruce Bennett, who had recently been working with Dr. Ratnoff and was now with Professor Douglas in Aberdeen.

The discussions which took place were informal and the various subject matters were referred to in different contexts throughout the day. In the summary which follows an attempt has been made to collect together the various views under the subject headings.

1. Matters Arising from the Minutes of the Last Meeting

A. Survey of the amounts of therapeutic materials used at the Centres in relation to the incidence of jaundice and antibodies to factors VIII and IX. (Appendix A)

Dr. Biggs summarised the data presented as Appendix A. She thanked the Directors for their hard work over the last three years in collecting data. She suggested that the present survey should be terminated and the results published as from the Haemophilia Centre Directors. The information provided during the three years had not shown an increase in jaundice or of antibodies directed against blood clotting factors VIII and IX.

Dr. Biggs suggested that future information to be collected should be:-

a) The names and dates of birth and diagnosis of patients treated each year. Cumulatively this information should give an estimate of the total number of patients in the United Kingdom.

b) The names of patients who develop jaundice or antibodies to factors VIII or IX.

c) The names and dates of birth of patients who die.

Discussion

Dr. Bidwell thought it a pity to stop collecting data about materials used as this was very useful to those who had to manufacture the materials.

Dr. Biggs said that three things had made her feel that the future collection of detailed data was unrewarding. One was that apparently at many Transfusion Centres (confirmed by Dr. Maycock) only about half of the cryoprecipitate made was issued for use at the Haemophilia Centres. The second point was that estimates based on various sources of data suggested that severely affected patients should ideally receive 200-250 donor units per annum of concentrate. At present patients at the Centres received on average 120 donor units a year. The material used at the Centres merely reflected supply. As more was made available more would be used. Thirdly, the very great amount of work involved prevented a number of Directors from participating in the trial when full returns were required.

ACTION

It was agreed that Dr. Biggs should prepare the report for publication and that new forms should be prepared so that Directors could make returns for 1972 onwards.

B. Report on the progress with survey of Au Antigen in house contacts and relatives of haemophiliacs.

Dr. Ingram reported on the progress with his study on the Au Antigen in house contacts and relatives of haemophiliacs. The purpose of the study was to find out if house contacts can become Au Antigen positive from contact with multi-transfused patients. He had written to all Haemophilia Centre Directors to see how many would be willing to participate in the study. Any Directors who had not received the letter and would like to participate were asked to contact Dr. Ingram. Not many Centres had more than one or two patients who were Au Antigen positive. At some Centres patients had not yet been tested for Au Antigen. There was a long way to go with the study but it was under way now.

Dr. Davies (Edinburgh) and Professor Stewart (Middlesex) had collected information about patients at their Centres. Professor Stewart raised the question of the frequency and duration of tests for relatives. One patient at his Centre had been Au Antigen positive for six months. Dr. Davies raised the problem of choosing the best technique for measuring Au Antigen and Dr. Ingram said

that Dr. Banatrala was studying the question of the best testing methods. Dr. Ingram said that so far he had not found any positive contacts.

C. Protocol for a trial of prophylactic therapy in haemophiliacs

Dr. Biggs said she had been asked at the last meeting to prepare a protocol. She had had a great deal of trouble with it. She had sent it to a number of important persons to see what they thought of it and they all objected to it for one reason or another. She concluded that it would be very difficult to organise a prophylactic trial from a Haemophilia Centre and that perhaps the only place where it could be done would be at Lord Mayor Treloar College. She had sent the protocol to Drs. Arblaster, Aronstam and Rainsford (at their request) and they were now planning to organise a trial along lines similar to those in the circulated protocol. Although there were difficulties in organising a trial and in the setting up of the control groups, Dr. Biggs felt that it was very important for a trial to be undertaken because we really want to know whether the patients are better having prophylactic therapy or just receiving treatment "on demand". There were sharp differences between these two modes of treatment:-

On Demand Treatment means giving treatment at home or at hospital whenever a bleed occurred. Prophylaxis involves treatment at regular intervals regardless of whether or not bleeding occurs. Dr. Biggs suggested that the Directors should support the conduct of this trial at the Lord Mayor Treloar College.

Discussion on this topic was lengthy and recurring and centred around three main topics:-

(i) The placebo group.

(ii) The material to be used.

(iii) Details of the trial organisation.

The discussion about the Placebo Group centred around the desirability of using an inactive placebo. Some thought that an inactive placebo should be used and some preferred a low-dosage of factor VIII. Some thought it very important that the placebo be indistinguishable from the treatment material since it was essential that the boys should not know to which group they belonged. It was however pointed out that the boys could be told that they were receiving two different treatments.

The choice of material to be used was discussed at length. It was decided that the trial material would have to be provided in addition to the material supplied for routine use at Lord Mayor Treloar College. The conclusion was that a freeze dried concentrate should be used. Drs. Arblaster and Aronstam had decided to use the Immuno material from Vienna if this was possible and had applied to the Ministry of Health and Social Security for £15,000 to buy enough material.

It was pointed out that the Hyland concentrate was also of good quality. Also, Drs. Maycock and Bidwell thought that they could supply enough material were they asked. Dr. Biggs said that she had felt that any

material which could be made in England was too urgently needed for treatment of serious bleeding for it to be allocated to a clinical trial of prophylactic therapy.

About the organisation of the trial, questions were asked about the treatment of boys during holidays. The trial treatment would have to lapse during holidays and this was a pity. The frequency of dosage was discussed and Dr. Matthews said that previous workers had advocated dosage varying in frequency from twice daily to once every three to four weeks. It was decided that once weekly was the most frequently that dosage could be given in practice and that trial treatment must be allowed to lapse during holidays.

It was stated that 10-15 boys could be included in the trial at Lord Mayor Treloar College. Some wondered if any significant results could be obtained with so few boys. It was pointed out by Dr. Aronstam that each boy had many bleeds and that it was bleeding frequency which was to be used as a criterion of treatment effectiveness. Moreover the boys would all have periods in the treatment group and in the control group. It was pointed out that since prophylactic treatment might treble the usage of factor VIII only a highly significant result was of interest.

Co-operation of Haemophilia Centre Directors would be required wherever possible to obtain parents' consent for boys in the trial and to supervise boys in the holiday.

ACTION

In conclusion it was pointed out that details of this particular trial, including the choice of therapeutic materials and questions of ethics, were the responsibility of the Alton Centre and it was proposed and agreed with one dissenting vote (Professor Stewart, Middlesex) that the Chairman should write to the Ministry of Health and Social Security supporting the conduct of the trial of prophylactic treatment at the Lord Mayor Treloar College. It was also agreed that the Haemophilia Society be asked to make a contribution toward the cost of the trial.

2. Home Treatment

Dr. Antony Britten's film on Home Treatment was shown and formed the basis of discussion. Dr. Matthews outlined the policy at Oxford using freeze dried concentrate and Dr. Dormandy that at the Royal Free Hospital using cryo-precipitate.

It was stated that the supply position in some areas was so poor that Directors could not allow any material to be kept in patients' homes as this policy would deplete stocks. It was suggested that since freeze dried material was preferable Regional and Hospital Boards should be asked to buy material to support a home treatment programme.

Details of organisation of home treatment were discussed. Topics included were those of possible loss of personal contact with patients. It was pointed out that these patients

attended hospital regularly to collect material and could always phone for advice. Dr. Rainsford pointed out that there was more to treating haemophilia than giving injections of factor VIII and close contact with the treatment Centre should always be maintained. It was emphasized that this close supervision was the means by which the Doctor's responsibility for the patient could be maintained.

ACTION

There was discussion about the possible legal implications of home treatment and it was decided that the Chairman be asked to write to the Department of Health and Social Security to see what their opinion was.

3. Supplies of Therapeutic Material

A. Factor VIII.

Dr. Biggs described a recent attempt she had been making to assess the amount of factor VIII likely to be needed. This showed that freeze dried concentrate was unlikely to be more wasteful of plasma than cryoprecipitate. The amount needed was dependent on the number of patients in the country and the amount required per patient. The conclusion was that we were likely to need freeze dried material from 250,000 donor units annually and the total material required was likely to be of the order of 500,000 donor units annually. The desirability of increasing home treatment and the availability of good commercial material make the question of increased British Supply very urgent.

The cost of preparing concentrate was discussed and it was emphasized that material made by the NHS was unlikely to be more expensive than the present commercial material.

Dr. Maycock said that about 300,000 donor units of blood were used for cryoprecipitate or concentrate and that about 25,000 donor units of concentrate were made. There were large regional differences, for example, in Oxford 40/1,000 donations were used for concentrates whereas elsewhere as little as 1-2/1,000 donations was used. The cost was about £4 per 100 ml dried concentrate.

Two main topics were discussed. One concerned the purchase of commercially available factor VIII preparations and the other was the more long term problem of increasing the supply of a good quality soluble British Product. Many Directors were pressing for permission to purchase the good commercial products manufactured overseas.

ACTION

1. It was agreed that the Chairman should ask the Ministry of Health and Social Security to set up an Expert Committee to consider and advise on the supply of factor VIII in this country, taking into consideration the fact that Directors prefer freeze dried factor VIII to cryoprecipitate.
2. Dr. Bidwell asked that Directors complete a questionnaire about their factor VIII requirements for the future.

B. Factor IX.

Dr. Bidwell gave a short address. She had asked Directors to tell her how much material they would need to treat all their Christmas disease patients with concentrate instead of plasma and from the replies she estimated that she could meet the annual demands from the Directors to keep the patients treated at the present level of treatment. She had also asked Directors to forecast what their needs would be in the future and there were wide differences in the estimates from Centre to Centre. She was looking into this further. She emphasized that although it is quite safe when properly used, any preparation containing a high concentration of prothrombin is potentially lethal and this must be impressed on inexperienced medical staff and nurses and must especially be borne in mind with the inevitable move towards home treatment. The prospects of satisfying the Directors' demands for factor IX for the treatment of Christmas disease patients are excellent. The use of the concentrate for the treatment of patients with liver disease was another matter and Dr. Maycock would deal with this.

Dr. Maycock said that information from the USA suggested that the administration of some preparations of factor IX might give rise to disseminated intravascular clotting. Dr. Bidwell's material had been used almost exclusively for the treatment of Christmas disease patients. Physicians who wished to use Dr. Bidwell's

material for liver disease patients should do so at their own responsibility. He was trying to get further information from the USA but so far this was not available.

Several Directors had used factor IX preparations for the treatment of liver disease, for new born premature babies and reversal of anticoagulant overdosage. None had any complications in these patients.

There was some discussion about the restriction of supplies of factor VIII and IX to Haemophilia Centres. It was pointed out that acute shortage of material at the Centre could derive from the misguided use of valuable material at other hospitals (Dr. Nelson). Dr. Biggs said that she thought that both factors VIII and IX were still classed as materials on clinical trial and that there was thus good reason to restrict their use. Dr. Maycock said that it would be difficult for a Transfusion Director to refuse to supply material to a hospital. If a recommendation came from the meeting to the Department of Health, this might be helpful.

4. Staffing and Organisation of Haemophilia Centres

A. Staffing

Professor Blackburn referred to his correspondence with Dr. Obank and said that Dr. Obank had done his best to impress the needs of the Haemophilia Centres on the Regional Boards and Boards of Governors.

It was pointed out that staffing is a local matter and the needs of the different Centres very variable

and it was the responsibility of the Directors to put the case for the staff they needed to the local Committees.

B. Organisation (Appendix C).

The document Appendix C had been drawn up by Drs. Biggs and Rizza because they had become aware that some Directors were having difficulty in providing adequate treatment for their patients. The difficulties, which have given rise to very sad results in at least two cases, arose from failure to provide an adequate administrative structure for the Haemophilia Centres in some areas.

The Directors commented on the document and made many suggestions for its improvement and there was some general discussion about the organisation of Centres.

ACTION

Drs. Biggs and Rizza undertook to rewrite Appendix C and circulate to Directors for detailed corrections. It was decided to ask the Chairman to forward the corrected document to the Department of Health and Social Security with the request that the Department should circulate it to Regional Hospital Boards asking them to review the administration of the Haemophilia Centre (or Centres) in their Region.

5. Diagnosis of Carriers of Haemophilia

Dr. Rizza gave a talk about the use of immunological methods in the diagnosis of carriers of haemophilia. Dr. Bruce Bennett showed some slides illustrating similar results from the United States.

Dr. Rizza offered to carry out tests at the request of Haemophilia Centre Directors or to teach the technique to staff.

6. Memorandum from the Haemophilia Society

Dr. Biggs suggested that a letter should be sent to the Society thanking them for the Memo and saying that all the questions raised had been discussed. She suggested that the Society should be asked to write directly to the Directors concerned about individual complaints. This was agreed.

7. Any Other Business

There was a short discussion about laboratory precautions to be taken to protect the staff against infection with hepatitis. Dr. Mibashan raised the question of drug addiction and warned against the use of hard drugs to relieve pain which should be cured by specific treatment.

It was agreed that the next meeting should take place in 18 months' time.