

CORRECTED 21st June, 1976

Minutes of the Meeting of Haemophilia Centre Directors held
in Glasgow on 18. 9. 1975, with Professor E.K. Blackburn in the Chair

Those present at the meeting were :-

Dr A. Aronstam,
Treloar Haemophilia Centre, Alton.

Dr T.W. Barrowcliffe,
Institute of Biological Standards.

Dr A.J. Bellingham,
Liverpool.

Dr E. Bidwell,
Plasma Fractionation Laboratory, Oxford.

Dr Rosemary Biggs,
Oxford Haemophilia Centre.

Dr T. Black,
Liverpool.

Professor E.K. Blackburn,
Sheffield.

Dr T. E. Blecher,
Nottingham.

Dr A. L. Bloom,
Cardiff.

Dr F. E. Boulton,
Department of Haematology, Liverpool.

Dr M. Bridges,
Belfast.

Dr J. Cash,
Edinburgh.

Dr D.G. Chalmers,
Cambridge.

Dr Morag Chisholm,
Southampton.

Dr I. A. Cook,
Raigmore Hospital, Inverness.

Dr J. Craske,
Poole Public Health Laboratory.

Dr S. H. Davies,
Edinburgh.

Dr A. A. Dawson,
Aberdeen.

Dr I. W. Delamore,
Manchester.

Dr K. M. Dormandy,
The Royal Free Hospital, London.

Dr J. O. P. Edgcumbe,
Exeter.

Dr O. Eliamin,
Westminster Hospital, London.

Dr D. Ellis,
Elstree.

Dr D. I. K. Evans,
Manchester.

Professor P. J. Flute,
St George's Hospital, London.

Dr C. Forbes,
Glasgow.

Dr Hugh Geoffrey,
Edinburgh.

Professor R. M. Hardisty,
Hospital for Sick Children, London.

Dr N. E. Hawker,
Middlesbrough.

Dr A. Inglis,
Carlisle.

Professor G. I. C. Ingram,
St Thomas' Hospital, London.

Dr G. Jenkins,
The London Hospital.

Dr Peter Jones,
Newcastle.

Dr M. Joyner
Kings College Hospital, London
(Representing Professor White).

Dr Peter Kirk,
Treloar Haemophilia Centre, Alton.

Dr John Leslie,
Southampton.

Dr M. L. Lewis,
Kings College Hospital, London.

Dr J. S. Lillyman,
The Children's Hospital, Sheffield.

Dr W. d'A Maycock,
Blood Products Laboratory, Elstree.

Dr R.S. Mibashan,
Hammersmith Hospital, London.

Dr G. A. Mc Donald,
Glasgow.

Dr A. Mc Intyre,
Department of Health Scotland.

Dr J.R. O'Brien,
Portsmouth.

Dr C.R.M. Prentice,
Glasgow.

Dr F.E. Preston,
The Royal Infirmary, Sheffield.

Mr J.L. Prothero,
Haemophilia Society.

Dr S.G. Rainsford,
Lord Mayor Treloar College, Alton.

Dr W.H. Richmond,
Bradford (Representing Professor R.L. Turner).

Dr C.R. Rizza,
Oxford.

Dr G.L. Scott,
Bristol.

Dr T. Snape,
Plasma Fractionation Laboratory, Oxford.

Dr David Stern,
Bournemouth.

Dr J. Stuart,
Birmingham.

Professor J.W. Stewart,
Middlesex Hospital, London.

Dr L.M. Swinburne,
Leeds.

Alan Tanner, Esq. ,
Haemophilia Society.

Dr G.R. Tudhope,
Dundee.

Dr Sheila Waiter,
DHSS, London.

Dr J. Wallace,
Blood Transfusion Centre, Edinburgh.

Dr P.J. Whitehead,
West Cumberland Hospital.

Dr D. Whitmore,
Lewisham Hospital, London.

Professor Blackburn welcomed those present and thanked the Royal College of Physicians and Surgeons of Glasgow and Drs. Forbes and Prentice for organising the meeting.

MATTERS ARISING FROM THE MINUTES

(a) Progress of the Directors study of Jaundice and Factor VIII Antibodies

Dr. Biggs presented a paper (Appendix A) which included statistics collected by the Directors from 1969 to 1974. She proposed that a six year study be published and asked Directors to contribute in the discussion to aspects of the report which they felt should be emphasised on publication. Dr. Biggs noted that the number of recorded haemophilic patients had now reached 2,450 and suggested that during the next year every effort should be made to identify all of the patients who are treated at hospitals which are not Haemophilia Centres.

There was a full discussion about the incidence of hepatitis and the problem of anicteric cases. Prof. Stewart thought that the cases of hepatitis should be more precisely defined according to the criteria on which the diagnosis was made. It was felt that future statistics should include LFT results (Dr. Craske, Dr. Kirk) though others felt that LFT results were often difficult to interpret (Dr. Maycock, Dr. Rainsford), and not all Centres carry out routine LFT's. It was pointed out that jaundice may occur from ABO incompatibility and from the absorption of blood products from large haematomata (Dr. Black, Dr. Stern). The influence on the pool size of material used for fractionation was discussed. Prof. Ingram said that NHS factor VIII was derived from pools of 500-750 donations whereas the commercial factor VIII was often derived from pools of 2,000 to 6,000 litres of plasma and that the probability of including an infected donation was greater

with commercial factor VIII. It was emphasised that material which was hepatitis B antigen positive was not issued for clinical use (Dr. Bidwell). Some early batches of commercial material had retrospectively been found to be suspect. These batches were passed for issue some time ago (Prof. Stewart) but all samples of commercial material are now supervised by the Standard's Institute and no known positives are issued (Dr. Barrowcliffe). Prof. Stewart pointed out that patients who were hepatitis B antibody positive were not at risk from this variety of hepatitis. Dr. Maycock said that although the screening of donors, as now carried out, would reduce the number of infected batches, all infected batches would not be excluded since the tests would not pick up all levels of hepatitis B virus and some hepatitis was caused by viruses not detected by the test e.g. Hepatitis A and long incubation time viruses other than those giving positive results for hepatitis B antigen or antibody.

Dr. Inglis said that mention should be made of home therapy on page 3 of the report and Dr. Biggs agreed with this suggestion.

Dr. Biggs said that the forms used for collecting data had become rather complicated and that these would for the future be divided into 3 sets:-

Set A: Annual Returns and Census data

- A(1): Annual returns of therapeutic materials used at Centres and notification of deaths during the year.
- A(2): List of haemophilic patients treated at the Centre during the year
- A(3): List of Christmas Disease patients treated at the Centre during the year

Set B: Additional Information for Census

B(1): Notification of new cases of haemophilia or Christmas disease

B(2): Notification of new cases of antibodies to Factor VIII or Factor IX.

Forms B(1) and B(2) should be returned to Oxford throughout the year as the new cases arise.

Set C: Hepatitis Survey

C(1): Entry form from Dr. Kirk's survey (to be completed by Centres wishing to take part in this survey for each patient entered).

C(2): Form for notification of materials used during the 6 months prior to the development of jaundice and the results of LFT's if available

C(3): Form notifying each case of jaundice (hepatitis) and detailing the symptoms and history of illness.

C(4): Hemofil Return. This form should be completed for all Centres using Hemofil and will be forwarded to Dr. Craske so that he can complete his study.

Forms C(1), (2) and (3) are to be used for Dr. Kirk's survey. C(4) is for Dr. Craske's survey. Those Directors who are not contributing to Dr. Kirk's or to Dr. Craske's survey should complete forms C(2) and C(3) and return these to Oxford as soon as a case of hepatitis has been identified. No special forms are required for the antibodies survey as the information for this survey is obtained from Forms B(2), A(1), A(2) and A(3).

ACTIONS It was agreed that a report of the 6 year survey should be written by Dr. Biggs and the draft circulated to Directors for amendment. It was also agreed that the reference

centre Directors should co-operate to identify patients who were treated at hospitals other than Haemophilia Centres. It was agreed that the collection of basic data on hepatitic and factor VIII and IX antibodies should continue.

(b) Social Surveys

(i) Dr. Biggs said that during the year she had received information about the Haemophilia Society Survey and about Dr. Jones survey in Newcastle and about Dr. Prentice's work in Glasgow and felt that there was no useful place for a comprehensive national survey to be undertaken on behalf of all Directors. For this reason she felt that the National effort should be concentrated on the simple identification of patients who received treatment at hospitals other than Haemophilia Centres.

(ii) Mr. Tanner, on behalf of the Haemophilia Society, said that they had sent out 17,000 Questionnaires and that he hoped that they would have a full report by the end of the year.

Dr. Jones said that information about patients could be obtained from the Hospital Activity Analysis Departments of the Regional Authorities. Dr. Swinburne said that Transfusion Service Directors often had lists of haemophilic patients.

(c) The Incidence of Hepatitis in Home Contacts of Haemophiliacs

Prof. Ingram said that his survey had shown that HbAb positive patients were no risk to their relatives or house contacts and that there had been too few HbAg positive patients for any valid conclusions to be drawn about their possible infectivity.

(d) The British Standard for Factor VIII

Dr. Bidwell said that she had started to make a factor VIII standard in her Laboratory and then heard that the

Standard's Institute would make the standard as of old. She had encountered one difficulty which was that, as assayed in Oxford, average normal plasma assayed at 0.8 International Units per ml. She was now obliged to label bottles of therapeutic material in terms of International Units. Thus, the apparent amount of therapeutic activity per bottle seemed to have decreased. In fact no actual decrease had occurred.

Dr. Barrowcliffe for the Standard's Institute said that the 4th British Standard Plasma was still available but its activity could have deteriorated. A new standard would be ready by the end of 1975. Dr. Barrowcliffe said that he was studying the possibility of calibrating the new standard for other activities including factor VIII-related antigen. He thought that it might be necessary to have a new standard plasma every year.

Dr. Cash and Dr. Boulton noted that the price of commercial factor VIII depended on the units of activity per ampoule and thus depended on the value assigned to the British Standard. Dr. Barrowcliffe said that all batches of commercial factor VIII were tested and it would be helpful if Directors would send him their assay results for commercial preparations.

(e) The Trial of Prophylactic Treatment of Haemophilic Patients at Alton

Dr. Aronstam gave a report on the trial of prophylaxis at the Lord Mayor Treloar College at Alton. He presented the data which was being prepared for publication. He said that there was evidence that the boys in the treatment group were protected for 48 hours following a dose of factor VIII. Dr. Aronstam said that he had encountered difficulty in organising

the trial and felt that an extension of the trial should not include a placebo dose. Dr. Cash said that prophylaxis at the rate of 14u/kg. twice weekly would result in an annual dosage of more than 70,000 units of factor VIII per patient per year for a patient weighing 50 kg. It was pointed out that quite small doses were often effective for "on demand" therapy and that even less might be required for prophylaxis. Dr. Stewart proposed that the trial be continued on a regime of two doses a week at 2 dose levels e.g. 7u/kg. and 14u/kg. for each dose.

ACTION It was agreed to recommend that the trial be continued at 2 dose levels.

THE PROPOSED PILOT STUDY OF HEPATITIS IN HAEMOPHILIC PATIENTS

Dr. Craske said that he hoped to continue his study of hepatitis in patients who had received hemofil.

Dr. Kirk introduced a paper, circulated at the meeting, on a proposal to study the incidence of hepatitis in haemophilia patients who received material of known types. He was proposing, as a pilot study, to keep detailed records on the following patients:-

- A) At Treloar College, 20 patients receiving cryoprecipitate, 10 patients receiving Kryobulin and 5 patients receiving Elstree Factor VIII
- B) At Newcastle, 40 patients receiving Hemofil
- C) At Oxford, 15 patients receiving Oxford factor VIII and 10 patients receiving Hemofil.

Any Director who would like to contribute to the Study should contact Dr. Kirk at Lord Mayor Treloar College, Froyle, Nr. Alton, Hants. A requirement for participation in this trial is that a patient should receive only one type of material

for treatment and that samples for virology testing be collected and sent to Dr. Cossart at the Virus Reference Laboratory.

There was some discussion about the collection of samples for LFT and virus testing and it was felt that it was important to arrange for as many tests as possible but it was also felt that frequent testing of patients, particularly those on home therapy, could be difficult. Therapeutic material should be saved for virus testing in case new types of test were developed.

VON WILLEBRAND'S DISEASE WORKING PARTY

Dr. Bloom introduced his paper (Appendix B) about von Willebrand's disease. Dr. Bloom said that the purpose of the survey was to find out how many cases of von Willebrand's disease there were in the country, to determine the test systems used for diagnosis and to study any molecular variants of the disease that might be discovered. Directors wishing to take part in this study should contact Dr. Bloom at the University Hospital of Wales, Cardiff.

IMMUNOLOGICAL STUDY OF SYNOVIAL MEMBRANES

Dr. Rainsford introduced Appendix C. Dr. Rainsford said that antibodies to fibrinogen were now recognised as a factor in rheumatoid arthritis and that, in co-operation with the MRC Rheumatoid Research Unit at Taplow, he wished to study the synovial membrane in patients having operations on joints. It seemed possible that an antigen-antibody response might be a factor in the pathology of the joint disease in Haemophilia. Dr. Rainsford asked Directors to inform him at the Lord Mayor Treloar College, Froyle, Nr. Alton, Hants should a joint operation be proposed. Dr. Rainsford said that he would personally arrange for the collection of specimens and that the

Directors would receive reports on his findings.

A STUDY OF HOME THERAPY

Prof. Ingram said that a study of home therapy in haemophilic patients was being organised at the St. Thomas' Hospital and the Oxford Haemophilia Centres. The project was in receipt of a DHSS grant and proposed to study the Social background of home therapy.

Dr. Jones asked the meeting some questions which were answered by show of hands:- 25 Centres were now using home therapy, at 20 Centres commercial concentrate was used for somepart of the home therapy programme, at 2 Centres British NHS concentrate was used and at 12 Centres some cryoprecipitate was used for home therapy. At 26 Centres commercial concentrate was used for some hospital treatment. Dr. Chalmers said that he had been refused permission to replace cryoprecipitate with commercial concentrate.

THE ORGANISATION OF HAEMOPHILIA CENTRES

Dr. Waiter said that the draft document from the DHSS on the organisation of Haemophilia Centres was not quite ready but that it would be circulated as soon as possible. The document had been approved by the Regional medical officers, by the Regional Transfusion Directors, by the Colleges and by the Joint Consultants Committee. Dr. Waiter said that the treatment of Haemophilia was progressing towards treatment in the home. For this reason the^{Royal}/College of General Practitioners had emphasised that it was very necessary that General Practitioners be kept informed of the treatment of particular patients at the Centres.

Drs. Stuart and Scott said that the staff provided for treating haemophilic patients were grossly inadequate, could

the Directors make some suggestions about minimum staff needed at the various Centres. After some discussion it was concluded that the needs of the Centres would be too diverse for any general recommendation to be made. Mr. Tanner said that the opinion of the Haemophilia Society and of patients in the various localities should be taken into account. The Society had ideas about what patients expected from a Haemophilia Centre.

It was suggested that a system of visiting the Centres could be set up to determine the needs of the Centres and to see the extent to which the Centres conformed to the DHSS recommendations. The reports of such visitors could help the Directors to present a case to Regional Administrations for the staff and facilities that they needed.

ACTION It was decided to ask Professor Blackburn to organise a working party on the staffing of the Haemophilia Centres and to examine the possibility of organised and official visiting to the Centres. The purpose of the visiting would be to help Directors to deal with local difficulties.

THE SUPPLY OF FACTORS VIII AND IX

Dr. Maycock said that an Expert Group had met at the DHSS on the 20th March, 1973. This group had suggested that a target be set for the production of freeze dried factor VIII concentrate from 275,000 blood donations annually by 1975. It was, at that time (1973), planned that cryoprecipitate from 100,000 donations annually should also be made. Thus by 1975 it had been planned that material from 375,000 donations would be available.

In 1974 some financial provision was made and the planned increase in the production of plasma was now nearly complete.

It could be estimated that 90 per cent of the target increase in plasma would be met by 1977. The increase involved a 3x increase in production at Elstree. Dr. Maycock said that the objective was the supply of 55,000 doses each containing 250 units of factor VIII at Elstree and Oxford.

Dr. Wallace said that 40% of all whole blood was separated into plasma and red cells in the West of Scotland. They planned to make plasma from 20,000 donations into cryoprecipitate and a further 20,000 was to be sent for fractionation to Edinburgh. In fact, they had demand for 25,000 cryoprecipitates and thus the plasma for fractionation had been eroded. Dr. Wallace said that cryoprecipitate had some advantages in comparison with freeze-dried concentrate. Dr. Wallace said that he hoped that transfusion Centres would retain their skill in making cryoprecipitate even when freeze-dried concentrate were more freely available.

Dr. McDonald said that they planned to fractionate plasma from 62% of all blood collected in Edinburgh. Dr. Maycock said that he was planning to use 25 - 30% of all plasma in England.

Dr. Jeffreys said that the Fractionation Centre at Liberton was nearly commissioned and was at present fractionating 300 litres of plasma a week. They planned to fractionate 1,000 litres a week and to provide 14,000 to 15,000 doses of 250 units of factor VIII by mid 1977.

Dr. Chalmers asked how the NHS concentrate was to be distributed when it became available. He said that it would be most important to be assured of a regular supply.

Dr. Cash said that the target of 375,000 donations was quite inadequate. The MRC Working Party estimate of 500,000

donations was a minimum estimate and the need was likely to exceed this amount. Dr. Cash said that there was a difficult lag phase between the collection of plasma and its issue as concentrate.

Dr. Waiter said that she hoped that the haemophilic patients would realise that the supply of factor VIII was not inexhaustible and that they should not undertake activities of excessive physical danger. Mr. Prothero said that it was difficult to define excessive physical danger.

Mr. Tanner asked what the Haemophilia Society could do to help. Prof. Stewart asked if plasmaphoresis might not need to be used to collect plasma. Dr. Stuart asked if the Directors should for the time being be asked to buy more commercial concentrate so that plasma could be sent for fractionation.

ANY OTHER BUSINESS

Prof. Ingram reported on a correspondence that he had had with the DHSS on prescription charges for haemophilic patients. He said that he had received a letter from the DHSS on the subject and that copies were available for the Directors to read.