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REPORT ON 13TH MEETING OF THE UK HAEMOPHILIA CENTRE DIRECTORS, MANCHESTER, 13 SEPTEMBER 1982

The meeting was chaired by Professor A L Bloom who, at the end of the meeting was unanimously re-elected for a further term of 3 years. No representatives of the DHSS (or SHHD) were present.

1. Minutes of last meeting were approved.

2. Reports of meetings of Haemophilia Reference Centre Directors during the year:

(a) In March, at Royal Free Hospital:

(i) It was agreed to recommend to the DHSS that the Edinburgh and Glasgow Centres be "recognised" as Reference Centres by the SHHD.

(ii) Dr P Jones was asked to prepare a document re-defining the roles of Reference Centres and of Ordinary Centres (see later).

(b) In September at St Thomas' Hospital.

At this meeting, Dr F E Preston had suggested that the haemophilia centres keep a register of patients with inherited platelet disorders.

3. Annual Returns for 1981 (see separate enclosure), presented by Dr C Rizza.

(a) Table 1:

It was noted that the average usage of FVIII per haemophiliac treated in the UK in 1981 was 28,584 u. 2217 patients were treated (2107 in 1980) and 63,371,000 units were given - 10% as cryoprecipitate, 35% as NHS AHF and 55% as commercial AHF. (The cryoprecipitate figure is "derived" from local estimates of cryoprecipitate potency).

Gm figures - $1.1 \times 10^6/10^6$

Dr P Kernoff suggested that a more realistic indication of patients requirements might be given if the average amount used per severe haemophiliac was to be ascertained, but the meeting felt that it would not be realistic to arrange the collection of the necessary data from the already complicated annual return forms.

The total amount of FVIII used in the UK for haemophiliacs, carriers and vW syndrome patients was 65,701,000 units.

The contribution of NHS concentrate was 34.2% (22,472,000 u) (14,505,000 in 1980, being 25.16% of total). Dr C Prentice asked how much in 1981 came from PFC; the answer given was approximately 3.5 m u.

(b) Table 6 (Home Therapy Usage):

It was noted that there has been a slight increase in patients on HT - 938 in 1980; 1021 in 1981. The amount used per patient on HT was 31,240. A question was asked concerning the average total consumption by HT patients of AHF, but (like last year) no answer is possible without much more detailed information.

(c) Haemophilia A with FVIII Antibodies (Tables 1, 3 and 5):

131 patients (121 in 1980) were treated. Average consumption of FVIII per patient was c 50,000 u in the 114 patients receiving this, but most patients also received other materials (porcine FVIII nonactivated human FIX (all NHS), FEIBA or Autoplex) - See Tables and below.

Total Usage	1980	1981
NHS FIX	314,000	377,000
Porcine FVIII	378,000	924,000
FEIBA	647,000	1,119,000
Autoplex	81,000	336,000

Number of patients known to have FVIII. Abs is 265 - 5.96 of all known haemophilia A, and 11.27% of all patients treated in 1981 (2,217 + 265 ÷ 114).

(d) Christmas Disease (Tables 2, 4, 5 & 7)

Total 368 patients (355 in 1980), using 9.851 mu. (26,769 each - 23,301 in 1980).

HT 157; using 5.214 mu (33,210 each at home).

Including carriers, and Haemophilia A with FVIII Ab, total FIX usage was 10.276 mu of which only 0.023 mu was commercial (ie 10.253 mu was NHS). This is well within production capacity - R Lane).

5 patients with FIX Ab were treated out of 6 known patients. One had 1,100u FEIBA only; the others had 12,5000 U NHS FIX. (31,250 each).

(e) Treatment according to age and severity (all registered patients) - Tables10 & 11

(i) (a) Haemophilia A - 44.5% of all cases are "severe" (0.06 u/ml).

(b) Haemophilia B - 35.6% of all cases.

(ii) 8% of all haemophilia A and 9% of all haemophilia B have not had their clotting factor activities registered. Four HA patients in this category are on home therapy, as are 2 with HB.

(iii) Of severe patients, 24% of HA and 26% of HB were not treated.

(iv) In both HA and HB, the maximum age incidence of known cases is in the 2nd decade of life (21.5% in both cases).

(v) Assuming incidence in first decade is at least as much as in later life, the true number of people with HA is at least 4,888 (currently 4,443 are on register - 4,356 in 1980), and total no of severe HA is 2,135 (1918 on register)

For people with HB, the true number will be about 860 (currently 798 on the register - 781 in 1980), and about 305 will be severe (284 on register).

(f) Causes of Death (Table 9)

(i) The teenager who died of cerebral haemorrhage had Christmas Disease with a FIX Ab.

(ii) Both men age 30-39 had haemophilia A with FVIII Ab.

(iii) The two men who died of "haemorrhage (misc)" age 40-49 had psoas bleeds and had haemophilia A with FVIII Ab.

4. Supplies of Factor VIII - Dr Lane

(a) From now on, the managerial, manufacturing, the QA structure for the Oxford PFL and Elstree BPL are shared. All routine manufacture will go to Elstree.

(b) The latest refurbishment programme is now complete, and from August 1982, Elstree BPL will be in full productivity with a nominal capacity of about 30 mu FVIII pa but an actual capacity of more like 45 mu FVIII pa. Delays in the programme have resulted in "some hold-up" of the plasma throughput.

Note 30 mu = approximately 150,000 Kg plasma from NBTS (ie 200u/Kg - FEB). This is about 40% of blood from NBTS (150,000 Kg at 200 mls/donation = 750,000 donations = 37.5% of 2 million).

However, current industrial dispute is causing NBTS to reduce collections as the red cell demand is lower than usual and this is expected to reduce supplies of plasma to BPL ("low output equilibrium").

(c) If up to 45 mu pa is to be prepared, more plasma from NBTS is required - ie more money from Regional Authorities, who, however may be influenced by the unrealistically cheap prices of commercially available AHF.

Efficient utilisation of the NBTS's 2m donations could increase plasma to PFC to 200,000 Kg, ie 50% of donations giving 200 mls of FFP, from which 45 mu FVIII could be expected.

More FVIII could be prepared cost effectively by certain strategies which included plasmaphereses, optimal additives and improvements in yield. Dr C R M Prentice opined that in order to reach the 100 mu target (which Dr Lane agreed as desirable) a plasmapheresis programme was strongly implied. Dr Lane agreed that a limited pp programme could indeed ease the burden on the NBTS to produce multiple components from single donations. He also suggested that small pool cryoprecipitate from regional BTS's could be freeze-dried at Elstree. An "optimal additive" policy, by increasing to 250 mls the volume of plasma sent from each freshly separated donation could also contribute, as could better fractionation yields.

(d) In order to accommodate such an anticipated increased input, plans for an entirely new laboratory on the Elstree site are getting advanced. Approval is expected soon and a commissioning date for 1985/86 is hoped for. With enough plasma etc, this could provide self-sufficiency in FVIII etc for England and Wales.

(e) Packaging:

Dr Lane had received letters from the Chairman (Dr Bloom) and Dr K Shinton requesting an improvement in BPL FVIII packaging. Dr Lane accepted these requests in principle and hopes to be supplying water with each freeze-dried vial. He commented that the water should not be separated from the vials; and that although storage should ideally be at 4°C, storage at ambient temperatures for up to 2 months would not result in destabilisation.

(f) Factor IX:

In the near future the vial contents should become uniform at about 600 u/vial.

Questions:

Dr Ludlam - Will there be spare fractionation capacity at Elstree? Answer - Yes.

Dr Edgecombe - What about the problems of safety of yield? Dr Lane - Good point; he has apparently been notified of a process about to be patented whereby FVIII can be made hepatitis-free with little loss of yield. Although he did not disclose the manufacturer, he stated that if this process became verified, it may be necessary for BPL to pay for the use of the patent. (This was re-iterated the following day).

5. Criteria for Re-definition of Roles of Reference Centres and Ordinary Centres.

Dr P Jones had been asked by the Reference Centre Committee to make proposals for an update on HC(76)4. (This is enclosed).

It was felt that disturbing features in the annual reports (an unacceptable number of patients with no recorded factor levels, also a high number of untreated severe cases) which had not improved over the last 2 or 3 years implied that tighter uniformity of practice was necessary throughout the UK.

There was strong support from the Chair regarding the genetic counselling facilities which, it was felt, could only be given at a reference-centre level as these are the only places where a sufficient number of abligate carriers could be used to provide data which could be validly assessed statistically for control purposes. (Note - FEB agrees).

There was considerable discussion re the responsibility for issue of "green cards". Dr Jones expressed views were less forcible than his written ones. There seems little doubt that this will be re-drafted.

NB - Edinburgh's "Reference" Region is to include all of East of Scotland.

6. Reports of Working Parties:

(a) Nurses - Sister Fearns reported on the last years' activities. A symposium is to take place on 17-18 September 1982 at Newcastle which had attracted 58 registrants. Under consideration by the Committee was the legal consideration of nurses duties, and teaching and training schemes for patients starting home therapy.

Professor Bloom asked if the committee could give consideration to the drawing up of a Job Description for Haemophilia Centre Nurses.

(b) Social Workers - Mrs Lovey:

BASW/UKHS special interest group. Open to all professionals interested in social aspects.

Two meetings to be held each year; September 1981 at Royal Free Hospital, May 1982 at the London Hospital. Next planned for November 1982 to discuss unemployment among haemophiliacs. Are discussing with DHSS the allowances.

Noted also:

(1) Now sickness benefits are more than unemployment benefits;

(2) Group will consider means of how best to use social workers in haemophilia centres in view of declining resources from local authority social work resources.

(c) Factor VIII Quality Control Study (Dr G Savidge)

Briefly reported disturbing performances of FVIII assays (VIIIC and VIIIRAg) in routine haematology laboratories throughout UK.

Normal plasma - VIIIC less than 10% to more than 190%

VIIIRAg 30% to 150%.

25% FVIII plasma - slightly better.

NB - These included many laboratories which were not haemophilia centres.

(d) Hepatitis (Dr J Craske)

A detailed case review of hepatitis in haemophiliacs will be ready in about 6 months.

Interim report of a clinical study of mild haemophiliacs to assess risk of symptomless hepatitis in non users versus occasional users.

	Patients with Previous Exposure	Patients with No Previous Exposure	Total
NANB	6	9	15
No hepatitis	11	0	11
	17	9	26

∴ 9/9 unexposed got NANB; 7 had received Oxford PFL FVIII; 1 had US commercial VIII; 1 had NHS FIX. Three of these 9 were symptomless.

Doses used ranged from 400 u to 17,000 u. The 7 receiving Oxford FVIII had been exposed to 1100 to 1400 donors each.

∴ 1st exposure to VIII or IX will cause NANB hepatitis.

(Note, in discussion, it seems as if not all Christmas Disease patients exposed to NHS FIX concentrates for first time get NANB stigmata, but all haemophiliacs do with NHS FVIII).

Assessment of "hepatitis reduced" or "free" materials would have to be by similar studies as primates are in short supply, eg chimps. ? o

Note: diagnosis after excluding hep A, B, CMV and EBV is by prior enzumes being normal, and subsequent enzymes being "significantly" raised. Full protocols available from Dr Craske.

Hepatitis B Vaccine

Licensed by DHSS from May 1982.

To be marked from September 20 1982 (MSO) but at first, only enough to immunize 15,000 people in the UK. Each distinct health authority has opportunity to reserve.

Note only licensed for im use, and in patients older than 6 months. Oxford are trying sc immunising regimes.

Persons eligible - get advice from local health authority, but - for staff is mostly staff in mental handicap hospitals; excludes renal unit staff.

Regime: 3 doses, one month and six months apart.

Response: satisfactory in majority only after 3rd dose.

Acquire Immunodeficiency Syndrome

This is a wasting disease with deficient cell-mediated immunity, possibly associated with an infectious element.

Patients are likely to acquire disorders such as pneumocystis, kaposi sarcoma, fulminating herpes simplex etc.

Mortality 40-50%

Three cases have occurred in haemophiliacs in the USA, possibly associated with parenteral drug abuse.

There is a remote possibility of transmission via commercial FVIII.

(e) Home Therapy Working Party (Dr P Jones)

84% of patients predicted as requiring home therapy in UK are now on such therapy. Dr Jones asked permission for this to be wound up. Meeting agreed.

(f) Treatment of Patients Who Have FVIII Antibodies (Dr C Prentice)

A trial of Autoplex vs factor VIII is in progress at 9 participating centres in UK.

Aim is to get 3 or 4 patients in trial from each centre (c 30 total), and to record the response to treatment in 5 paired episodes.

Doses 50u/Kg each (even though "units" are not biologically equivalent): Up to 2 times in 24 hours (1st dose assessed @ 8L).

Age: 2 years and upwards

Antibody Levels greater than 5 Bethesda units and a history of previous increasing antibody levels.

Bleeding Episodes Haemarthrosis only, bleeding must be current ("active"), no therapy with antifibrinolytic agents.

Assessment 8h, 5 days, 3 weeks. Top level monitored, but no other coagulation parameter.

Ethical Approval. Each centre to have approval of local ethical committee. Each patient (or guardian) to give written informed consent.

Progress So far 6 patients and 9 bleeding episodes. Anticipate completion of trial in 15 to 18 months.

(g) Factor VIII and FVIII Ab assay WP. (Dr C Rizza, Dr I Peake and Dr T Barrowcliffe).

(a) FVIII Ab Assays

Dr Peake presented same data as at Bergamo. In summary, 9 UK centres worked on 9 samples. 1 sample was normal plasma; one was a commercial ("Immuno") standard and 7 were ABO from haemophiliacs. The 9 centres were asked to perform a Bethesda assay.

Results

All centres marked the NP as lowest.

All centres marked sample 5 as either the highest or second highest.

In general, the centres ranked the samples in similar order, but 2 were much more inconsistent. When these 2 were excluded the between lab variation was still high and using any one of the samples as a "standard" did not help. Statistical analysis indicated that the problem lies in the performance of the assay, and that perhaps the introduction of a 2nd (± 3rd) standard within the run might help, but this would increase the cumbersomeness of the assay.

(b) Calibration of 10th British Standard for FVIII (Dr Barrowcliffe).

Dr Barrowcliffe presented the case for setting up a freeze-dried plasma standard calibrated for all FVIII activities (and also for other factors). If all HC labs were to use plasma standards there would be more agreement about the results and there would be no difference whether the assay technique were 1 stage or 2 stage. However, as a result of careful comparison of 10th British stand against the 2nd International standard (which is a concentrate preparation of 1.1 u per ampoule) versus another plasma standard, the apparent assigned potency of FVIIIC to the 10th BS would increase from 0.65 u to 0.69 u/vial. The other characteristics of the 10th BS (plasma) are: VIIIRAg 0.75 u/vial; FIX 0.66 u/vial ATIII 0.93 u/vial.

Standards for concentrate assays and plasma samples.

At present, concentrates should be assayed against a concentrate standard; patients samples should be assayed against a plasma standard. There is some doubt as to what standard should be used for patients plasma after treatment with concentrate, but the suggestion is to use the plasma standard. (Cryoprecipitate has usually been assayed versus plasma standards - FEB). The main cause for discrepancies has been the 2-stage assay on concentrates. It should not be too difficult to get reasonable correlation between concentrate standards and plasma standards by 1-stage assays.

(c) Potency of concentrates; Is the label correct? (Dr Rizza)
9 centres in USA and 6 in Europe were asked to send to Oxford their own determination of the potency of their own purchased FVIII concentrates to be compared with the manufacturers' stated potency. All centres except 3 used one stage assays and in all cases, the local standards used were prepared from pools of 20-40 normal plasmas frozen at -40°C. 5 centres also had freeze dried plasma standards.

The results were:

61% of batches were within 20% of labelled potency.

33% were more than 20% BELOW labelled potency.

5% were more than 20% ABOVE labelled potency.

The mean was 15% below labelled potency. 2 of the 7 companies were generally satisfactory, but the other 5 were consistently low.

Since January 1982, Oxford has assayed all concentrates (by 2-stage method against concentrate standards). None are more than 14% different from labelled potency. NB since August 1981 (Toronto) manufacturers have been calibrating their house standards directly against the WHO standard rather than the secondary BOB standard.

Dr Rizza concluded by stating that future work of the working party would include work on the cause for the different values for FVIII obtained by 1 stage or 2 stage assays, and the effects of Ae(OH)3 adsorption versus Barium Citrate.

(h) von Willebrand's Disease Working Party (Dr Tuddenham)

557 patients have been notified to the WP (1074 on an Oxford register).

Complete data (VIIIC, RAg, RiCof and BTs) are given for 356:

7. Date, Time and Place of Next Meeting

Oxford, October 1983.

4/10/82