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REPORT ON ATTENDANCE AT THE HAEMOPHILIA DIRECTORS' MEETING - FRIDAY 9 OCTOBER 1981

Haemophilia Reference Centres

I attended this meeting on behalf of Dr Cash and the Scottish Blood Transfusion Service Directors. The meeting was under the Chairmanship of Professor A Bloom of Cardiff with Dr C Rizza as meeting secretary and Miss R Spooner as notes secretary.

Many items were discussed and the following are the highlights. Some, such as the Annual Report and hepatitis incidents, accompanied pre-circulated reports, copies of which are included with this summary.

The first item of interest was the report from Professor Bloom of the two meetings of the Haemophilia Reference Centres Directors, one in February 1981 and one in September 1981. At these meetings it was reported that Belfast Haemophilia Centre has been recognised by the Northern Ireland Health Authority as a registered Haemophilia Centre under the Directorship of Dr E Mayne.

There had apparently been considerable discussion at the meetings concerning the request by DHSS to devise a scheme whereby the purchase of commercial clotting factors could be returned to DHSS rapidly. A proposed scheme was to distribute the commercial products to the various haemophilia centres from their Regional Blood Transfusion Centres. It was concluded that for the foreseeable future this proposal could not be proceeded with. However, the Health Department's desire to have accurate data on the use of commercial concentrate was noted. For example, the entry in MIMS for commercial factor VIII, thus in theory enabling general practitioners to prescribe without an easy return to SHHD figures. It was also noted that even hospital pharmacy returns are very slow and there is apparently a desire by SHHD to collate regular figures frequently, ie monthly or quarterly, so as to enable plans for the development of Elstree to proceed smoothly. The meeting then discussed this and basically it was agreed that different areas could develop their own solutions to this problem, for example in certain regions it may not even be necessary to take the haemophilia reference centre contracts at all, and the contracts could be devised on a local basis. The problem is complicated because in England the reorganisation schemes for the new district health authorities is being proceeded with. This does not affect the Scottish situation.

Professor Bloom reported that Dr I Chanarin had written to him stating, in summary, that "the DHSS be advised that plasma fractionation facilities be handed over to private enterprise". The Chairman recalled that at the last meeting of the Haemophilia Directors this proposition had been discussed and the meeting agreed that such a development would be of great detriment to the

NBTS.

At the meeting of the Haemophilia Reference Centre Directors in September, there had apparently been some discussion about the publication of data which had been discussed at the Haemophilia Centre Directors' Meetings. The Chairman then proposed that such data could be published so long as (a) the author had obtained prior approval from Professor Bloom, in his capacity as Chairman, beforehand; and (b) so long as such obligation did not preempt any future publications because of copyright problems.

Figures for Annual Return for 1980

The figures for the annual return for 1980 were then discussed. These are appended and are largely self-explanatory. The main points are that throughout the United Kingdom, in 1980, apparently 56,000,000 units of factor VIII have been used and the average usage per patient was 26,600. Of this, the rise was almost entirely accomplished by increased use of commercial factor VIII concentrates, 27,000,000 units in 1979 and 35,000,000 units in 1980. The use of NHS products remain static at about 14,000,000 units in each year. There has also been a decline in the use of cryoprecipitate.

It should be realised that the figures for home therapy that are included in the table and which appear to indicate that each home therapy patient consumed an average of about 26,000 units of factor VIII in the year, refer only to the therapy given to them at home. Many such patients have also received treatment in hospital and therefore the average total factor VIII given to home therapy patients may well be considerably higher than 26,000 units.

For Christmas Disease, it should be noted that there is a slight increase in relative patients, 355 as opposed to 344 in 1979. The minute amount of commercial factor IX which was used was commented on and no explanation was given. However, it was also commented that there are one or two occasions when patients from abroad or the Republic of Ireland may not have access to NHS products, and therefore commercial factor IX has to be used.

In Table 3, which summarises the treatment of haemophiliacs with antibodies, there has been an increase in the use of porcine factor VIII, as only 279,000 were used in 1979. It is of interest that the percentage of haemophiliacs with antibodies has not shifted since the mid 1960s, ie 5.9 - 6% (Table 5).

Home treatment of von Willebrand's Disease patients (Table 8) indicates some usage of commercial factor VIII. There were some comments about the lesser degree of effectiveness of commercial concentrates in this disease. However,

Professor Bloom replied that there are some von Willebrands with antibodies who therefore do not respond to cryoprecipitate. In such cases, the coagulant activity of factor VIII can only be increased by large doses of commercial materials. There is no data on the number of patients with von Willebrand's disease and inhibitors.

There followed some discussion. It was recalled that at the Glasgow meeting it was prognosticated that by the mid-1980s, approximately 80,000,000 units of factor VIII would be required each year. This figure has been revised upwards to 100,000,000 units per year at the Haemophilia Reference Centre Directors' Meetings. Dr Lane then was asked to speak on various aspects of English factor VIII production from the NBTS. He said that the first phase of restructuring of BPL should be complete by January 1982. This should enable BPL to procure 30,000,000 units of factor VIII as intermediate product. For this it would be necessary to get 150,000 litres of plasma from the NBTS region. At present, the amount of plasma sent to BPL from the NBTS region is only 20% of the total blood procurement.

He also commented that work on the fractionation process could result in an increase of yield.

He also commented that during 1981, it is hoped that BPL will be able to produce 20,000,000 units, an increase on the 14,000,000 units (total UK) used in 1980.

In the long term, ministerial approval to redevelop the BPL capacity should enable 100,000,000 units of intermediate product to be made. He commented that this depends upon the capacity of the laboratory to deal with the volume of plasma which he gave a figure of 430,000 Kg.

He mentioned that support would be required from all parties. Firstly for collaboration and money to improve the yield and secondly for all parties (NBTS Directors and Haemophilia Directors) to persuade each Regional Health Authority that national autonomy is a good thing. He reminded the meeting that other products are produced by the BPL and that the commercial companies charge on these other products in Britain so as to reduce the price of factor VIII. Furthermore, if the German factor VIII and albumin market shrink (a distinct prospect in view of der Spiegl) this could produce upward pressure on UK prices.

Dr Lane was then asked several questions:

Dr Chalmers asked what the prospects were for producing factor VIII by genetic engineering. Dr Lane replied that in his view it could not possibly be until

toward the end of the 1980s. He commented that it would be necessary to produce both albumin and factor VIII in step as these are the two main bulk products from plasma fractionation. Because of the relative simplicity of the albumin molecule, he suggested that the production of albumin by genetic engineering was probably closer than that of factor VIII. He therefore cast some doubt on the value of investigating in a programme of this nature at this stage.

Dr Harrison then asked what the prospects were of producing sterile IX, along the lines of the Bayer product from Germany. Dr Lane commented that the description that this product is "essentially free of hepatitis", is a classic of obfuscation. There is no absolute scientific basis for establishing the freedom of hepatitis. BPL is actively reviewing sterilising procedures and is also reviewing the possibility of producing plasma from accredited donors by plasmapheresis, thereby giving a smaller donor pool. (This topic is referred to later when referring to Dr Craske's talk).

Dr Prentice then asked if the figure of 100,000,000 units of factor VIII was a UK figure or just from BPL. Dr Lane replied that the actual aim would probably have to be more in the nature of 130,000,000 units nationally.

An unidentified physician asked on the role of plasmapheresis of normal donors and Dr Lane said that this was being looked at, but reminded the meeting that the US programme of accreditive plasmapheresis donor stations would not be permitted in the United Kingdom (ie the conditions are not good enough). FEB then mentioned the production of "Supernine" by the SNBTS fractionation plant and also commented that there are alternative ways of increasing the plasma yield from blood transfusion services apart from plasmapheresis systems.

Dr Shinton - Role of Haemophilia Reference Centres and Haemophilia Centres

Dr Shinton presented his view that the role of the haemophilia reference centres and of the haemophilia centres should be reviewed. In particular, he indicated the increasing experience of new Consultant Haematologists with haemophilia, and also that the reorganisation of the health services in England was going to lead to a new distribution of financial control. Professor Bloom commented that there is also pressure from patients to get therapy available more locally, but there is a danger of taking this too far as there is a need for a certain optimum number of patients to be treated in one Centre to obtain expertise. He then informed the meeting that Dr Peter Jones has been asked to redraft a document on the function of haemophilia centres to replace the present health circular in operation.

Dr Preston then commented that home therapy expansion had reduced some trainees' experiences of the treatment of haemophilia and this was confirmed by Mr Prothero of the Haemophilia Society, especially out-of-hours. Professor Bloom then commented that this could lead to therapy by inexperienced persons being more expensive.

Haemophilia Nurses Association

Sister Fearns from Newcastle reported on the establishment of a new Society of Haemophilia Nurses. Some drug company support has been obtained for the organisation of symposia etc. Professor Bloom then proposed that a representative of the Haemophilia Nurses Association be present at future meetings of the Haemophilia Directors. This was approved.

Special Interest Group of Social Workers

The establishment of this group, partly funded by the British Association of Social Workers and by the Haemophilia Society, was presented by Mrs Miller of the Royal Free Hospital. The aims are similar to those of the Nurses Association, but taking in the activities of other professions related to medicine and especially the social workers. Professor Bloom proposed that a representative of this group be present at future meetings of the Haemophilia Directors and this was accepted.

Any Other Business

A letter from the Haemophilia Society notified the meeting that a Mr D Watters has been appointed as Co-ordinator of the Haemophilia Society. Also, a second appointment, a Sister Turk, as "Assistant Co-ordinator/- Services".

AFTERNOON SESSION

Report of Chairman of Working Parties

1. Dr Craske reported on the Hepatitis Working Party. He presented the tables (copies enclosed). He made the following recommendations:

   (a) There should be continued surveillance offered by the Working Party; and

   (b) The Working Party should expand to enable investigation of the incidence of sub-clinical hepatitis. Initial investigations have revealed that of four patients who have received their first dose of large pool material, all four developed hepatitis in two cases of which this is overt. Hepatitis B was not involved in any of these.

He commented that the high contamination rate of NHS products in his opinion, should encourage development of an accredited small pool of donors. 1177

He reported that work is continuing on the incidence of chronic hepatitis which involves the transfusion histories of patients with or without liver histology.

He reported the development by NS&D of the hepatitis B vaccine and they have requested a trial in haemophiliacs.

Sterile Factor IX

He commented that the Bayer process may work but that the innoculation of chimpanzees was virtually unobtainable for regular use. He therefore warned the meeting to be careful of claims based on just a few reports and there is no way of really testing the product apart from patient trials. Furthermore, each batch must be tested separately and there must be a heavy reliance placed on production methods quality control. There is no test of such quality control. In the discussion that followed several points were made. Dr Kernoff indicated that the figures submitted indicate that the US commercial products are equally good, if not better, than NHS products. Dr Craske said that they were in fact equally bad. He admitted that the inference that the US concentrates have a higher rate is not necessarily true as studies in Oxford on the NHS concentrate indicate a comparable contamination and attack rate to commercial concentrates. Dr Kernoff argued that there were compelling clinical reasons that if a product gives only a ten per cent attack rate first time, this should be used. Dr Craske replied that, however, a ten per cent attack rate will accumulate to effectively 100 per cent if multiple transfusions are given.

Dr Barrowcliffe indicated that the US commercial products are fractionated by a wide variety of methods and this could affect the degree of contamination of each of the brands.

P Jones commented that the medicines licenses record the source of plasma in all commercial products. Dr Wolford commented that this information is indeed taken but is absolutely confidential and not obtainable to the Haemophilia Directors.

Home Therapy Working Party

1. Prophylaxis

A trial at Lord Mayor Tralerle Hospital had been carried out to investigate claims that the in vivo survival of one brand (Armour HP Factorate) was considerably longer than other brands. It was compared with intermediate product haemophil in severe patients without antibodies and not bleeding at the time. Twelve patients were examined using a randomised cross-over technique and each patient was given a dose calculated to produce a 50 per cent rise of

factor VIII. Specimens were taken at 0, 15 minutes, 3 hours, 6 hours, 12 hours, 24, 36 and 48 hours and each sample assayed twice by one and two stage methods. Assays of CAg were also carried out. The result was that there was no difference between either product on both one stage and two stage assays. (FEB noted that the graphs presented were linear/linear!) In each case the half-life was about 7 - 10 hours.

2. Prophylactic Trials at Other Centres

These are continuing at 23 centres, although ten centres are providing the bulk of patients. In all, there are 178 patients with haemophilia A, 13 patients with haemophilia B and 2 with VWD.

Home Therapy

Dr Jones commented that there are a significant number of patients on home therapy who have more than 10 per cent basal level of factor VIII. He queried the reason for this. Secondly, he is still asking the question on whether every patient for home therapy is actually getting it. There is a large range of home therapy rate from the different Centres.

As far as the level of therapy per patient per year is concerned, he said that his own Centre's figures indicated that the annual consumption of each patient had now reached a plateau, ie was about 25,500 units. This is in spite of a steady orthopaedic programme.

Factor VIII Standards Working Party

Dr Rizza and Dr Barrowcliffe reported. Dr Rizza outlined that there has been considerable work on the standardization of Factor VIII assays - of all types (CAG, RAG and RICOF).

The ninth and tenth British Standards are being calibrated.

Investigations have continued into the discrepancy between one and two stage procedures. The partial role of aluminium hydroxide adsorption was discussed and the tentative proposal of barium chloride may be a better substitute. This is not ready for routine use yet.

There have also been investigations into the apparent discrepancy between the labelled value and actual contents in commercial concentrates. The factor VIII sub-committee of the ISHT (Chaired by A Bloom) is investigating this problem. At least part of the answer may well be due to the use of different standards. Dr Barrowcliffe then reported in detail on various aspects.

He pointed out that the international reference standard is of concentrate, whereas the British Standard is plasma and he outlined plans to get a plasma

to calibrate and use as an international standard. Specifically, a CPD plasma (80/511) has been investigated and compared with an ACD plasma (79/504). This latter is the current British Standard. These have been compared against fresh normal plasma, collected according to a specification (minimum of 15 donors; 0.109M citrate). Results have indicated that the CPD and ACD standards are no different from each other on either one or two stage procedures. However, there is quite a spread when the CPD standard is compared against a concentrate and there is a roughly 20-fold difference between one stage and two stage methods.

The specific values of 80/511 are: C:74 (0.69-0.79) RAG.89 (0.84 - 0.95) and RICOF .79 (0.72 - 0.84). The temperature stability of this product indicates that at -20 there is only 0.05% loss of C activity in a year and 0.72% loss of CAG activity. At 4°C the losses are 1.2 and 6.4 respectively, at 20°C, 7.5 and 21.8 and at 37°C, 43.1 and 66.9%.

It is therefore proposed that this be the standard used against fresh normal plasma for all four parameters. Inter-laboratory agreement on this is good. If this is accepted, it should then be used as the international standard for assays on concentrates used for treatment.

Von Willebrand Working Party - Chaired by Dr Tuddenham

The main findings are enclosed as a separate report. Comments from the floor were made regarding the Rokitanski - Duguid scheme, which is designed to document those people with severe von Willebrand's Disease (IRMA RAG less than 10%) so that when non-invasive tests for atherosclerosis become available, these patients could be assessed. The two Centres for these records are at Harvey Weiss in New York and Dr P Mannucci at Milan. Therefore, Milan has the names of the patients from Europe. Scandanavia apparently has the highest incidence and the UK data is the least complete.

Ruben Mibashen -- Ante Natal Diagnosis of Haemophilia and Christmas Disease

Dr Mibashen reported his experience up to date. He now has 99 cases from the UK, of which 47 are from the London area, plus 69 from Europe, 4 from the USA and 4 from South Africa. He made several interesting points about patient management and diagnosis. For example, on the genetic data, he commented that it was necessary to carry out the heterozygote status investigations, even if the patient is pregnant. This includes checking relatives for CRM positivity. (eg by IRMA). He also commented that for managing the patient it is best to see them before they have had the amniocentisis for fetal sexing.

The outcome so far is that in 80 pregnancies and 81 foetuses, he has obtained

pure blood from 80 foetuses and 29 have been terminated for haemophilia A, haemophilia B or VWD and two for other reasons. Forty-nine pregnancies have continued, resulting in 34 normal deliveries, five pre-term deliveries and ten so far undelivered. There has been no maternal complications, fetal death or incorrect diagnosis.

He went on to report on the incidences of repeated fetoscopies in successive pregnancies; for example one patient has had three fetoscopies, all resulting in the diagnosis of a haemophilic foetus which has been aborted. She is currently awaiting the diagnosis of a fourth pregnancy. Another case has had two successive haemophilic pregnancies diagnosed and two have had one haemophilic pregnancy followed by a normal pregnancy diagnosed.