IN CONFIDENCE

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CENTRAL BLOOD LABORATORIES AUTHORITY
CENTRAL COMMITTEE FOR RESEARCH AND DEVELOPMENT
IN BLOOD TRANSFUSION

Minutes of the sixth meeting of the Central Committee for Research and Development in Blood Transfusion, held on 9 July 1985 in the Board Room The Crest.

PRESENT: - (Chairman)

IN ATTENDANCE: (Secretary CBLA)
(DHSS)

7/85 Apologies for Absence

Apologies for absence were received from who had replaced as representative of the Scottish Home and Health Department, and

8/85 Minutes

The minutes of the meeting held on 2 April 1985 were approved as correct record subject to the following amendment:

Item 4/85 4.1 (d) Final paragraph, penultimate line, after Hospital add in 'on patients from the Hammersmith Hospital'.

9/85 Matters Arising from the Minutes

9.1 Genetic Engineering and Blood Products

A paper prepared by the Secretary confirming recent discussions that had been held with in regard to genetic engineering and blood products was noted.

In addition, a paper prepared by Professor Brownlee outlining a proposal for a tripartite scientific collaboration between Oxford University, Celltech and CBLA was discussed.

The Secretary said that the proposed collaboration, in the CBLA Chairman's view, was suitable for the Authority and the Chairman had consequently written to BTG who held the patents for work. A favourable response to the Chairman's letter had been received from BTG. The Chairman would be meeting the Chairman of Celltech on 23 July 1985.

It was noted that proposed collaborations would extend initially over one year. said that considerable achievement could be made during this time but this would depend on the collaboration. He referred to previous problems encountered by BPL when dealing with Celltech and emphasised the necessity for a solid tripartite arrangement. echoed concern stating that past experience of dealing with Celltech in the BTS was less

than satisfactory. shared concern over Celltech but said that the Authority had no alternative in this case as BTG held the patent and wished to work through Celltech. In answer to a question raised by it was noted that BTG would be required to use another group if Celltech were not interested in the collaboration.

stressed that Celltech would have to commit itself financially towards fermentation costs before any money was committed by the Authority to downstream processing.

After further discussion it was agreed to put the following views to the CBLA:

(i) The project was still considered important to follow through.

(ii) An answer was required urgently from Celltech on whether or not it wished to proceed with the collaboration. It was agreed that the meeting to be held on 23 July between the Chairman of the CBLA and the Chairman of Celltech was an appropriate time for a decision to be made.

(iii) Whilst a one year collaboration agreement was satisfactory in the short term, there needed to be a clause in the agreement which allowed an extension of investigative time.

(iv) Consideration would need to be given to the question of allocation of resources for the project.

Dr. Lane stressed that the production of Factor IX from a genetically engineered source was a major project in its own right, constituting an expansion of Research and Development and needed to be funded appropriately.

The collaboration would be further discussed at the meeting of the CBLA on 24 July.

Consideration was given to the idea of setting up a small sub-committee of the Central Committee to maintain the momentum on this collaboration. It was noted in addition that , had requested the setting up also of a sub-committee within the BTS to discuss the implications of genetic engineering and recombinant DNA technology. suggested that one sub-committee could be set up and deal firstly with the production of Factor IX and then, if necessary, have its membership adjusted to deal with issue. This was agreed.

It was agreed that should be invited to act as Chairman of the newly formed sub-committee. would discuss the remaining membership with in the near future.

9.2 Clinical Trials of Alpha-1-Anti Trypsin

reported that no further information had been received from Consultants at Papworth or Addenbrookes Hospital regarding production of Alpha-1-Antitrypsin in connection with heart and lung transplants.

A new "virus-safer" factor VIII concentrate of high specific activity

The major contaminants in "intermediate purity" factor VIII concentrates are fibrinogen and fibronectin which limit solubility and potency and complicate further processing to inactivate viruses. Measures used to remove them from factor VIII (cold precipitation, PEG, etc.) have usually resulted in unacceptable losses of factor VIII. We have found that by adding high concentrations of sodium heparin to cryoprecipitate extract, more complete precipitation of fibrinogen and fibronectin can be obtained with very little co-precipitation of factor VIII. Factor VIII can then be recovered from the heparin supernatant by precipitation with high concentrations of glycine and sodium chloride. At this stage, heparin is removed in the supernatant, 2-4 fold purification is achieved and the factor VIII is concentrated to high potency. The heparin precipitation method is the subject of UK Patent Application 850882.

Unheated concentrates made from the plasma of unremunerated donors in England and Wales have so far caused a very much lower incidence of HTLV III infection than have US concentrates, but the incidence of NANBH transmission is almost as high. Factor VIII concentrates of "intermediate purity" tend to lose more than 10% of their VIIIC activity on dry heating e.g. at 60-70° for 24-72h and become less easily soluble. pH and prekallikrein activator levels are also affected. However, the new "high purity" concentrate, depleted of fibrinogen and fibronectin, is a much better subject for dry heating and other virus inactivation methods. The new concentrate (8Y) now being introduced in England and Wales has been dry- heated in the final vial at 80° for 72h. The only significant change in the concentrate on heating has been a mean loss of 6% in F.VIIIC activity.

The concentrate is now in full scale (1200 kg plasma) production at BPL and the F.VIIIC yield is beginning to overtake that obtained for the less severely heated intermediate purity concentrate (HLH) pressed into service early in 1985 in response to concerns about HTLV III transmission. Current limitations on centrifugation capacity preclude further scale-up for the moment but a very active programme of process development is intended to remove such obstacles as well as improving efficiencies.

The immediate safety and efficacy of the 8Y concentrate have been demonstrated by clinical trial. Eight patients at three Haemophilia Centres receiving 14 infusions of three batches of concentrate have shown dose responses in the range 1.1-2.9, and a mean half-disappearance time of 10h, entirely consistent with recent experience of unheated concentrates.

Evidence for reduction or elimination of viral transmission is being sought after infusions in haemophiliacs who have been treated with concentrate either for the first time or after a long interval, and who are thought to be susceptible to infection with hepatitis B, NANBH and HTLV III. This trial is at a critical stage, but several patients have already safely passed the point at which the first evidence of NANBH transmission would have been expected.

An application is being prepared for a product licence for 8Y, with only provisional evidence of reduced infectivity; this may be granted in November.

9.3 Bridge Anticoagulant Neutralising Reagent (BANA)

Consideration was given to a copy of a letter dated 19 April 1985. DHSS had written to advising him of the correct way to proceed in pursuing his work on the isolation of BANA. A copy of a recent publication in the USA press outlining aspects of work was also noted.

In the following discussion, confirmed his willingness to test material within his Oxford laboratory. It was subsequently agreed that would write to confirming offer and asking him to contact I accordingly. It would be stressed to that he would not be personally allowed to test the material at Oxford and that several batches of his material would need to be delivered to Oxford for testing.

10/85 AIDS

10.1 Anti-HTLV III Testing in the NBTS

The Chairman confirmed that there were five company tests now available for anti-HTLV screening. It was his view, however, that until a proper evaluation of the tests had been carried out within PHLS and the BTS the introduction of the tests should not be used for routine screening of blood donations. By not knowing the prevalence of antibodies in the donor population, the BTS was yet unaware of the most effective test especially as far as false positive results were concerned. It was noted that 6,000 donor samples were due to be tested at Edgware and Manchester and results would be analysed as the studies continued. Six PHLS laboratories in addition to PHLS Colindale were being set up as reference laboratories.

referred to his capacity of Chairman of Haemophilia Centre Directors and said that, whilst he appreciated the need for a proper evaluation of the tests, as a representative of 'users' his immediate priority was the protection of recipients of Factor VIII. He therefore considered that any undue delay in introduction of the tests would be unreasonable.

informed the committee that excess plasma products released onto the market from BPL were likely to require licencing by FDA and, in addition, any intermediates shipped to other manufacturers could also precipitate inspection of BPL's facilities and the plasma collection centres by FDA in due course. He said that part of the FDA requirement would be routine screening of donations by an FDA approved test for HTLV-III antibody. The Chairman said that it was possible that an FDA approved test was not necessarily the most appropriate for the BTS.

It was agreed that DHSS should be made aware of comments via the CBLA.

Factor IX concentrate heat-treated to inactivate viruses

Factor IX concentrate 9D (also containing factors II and X) is licensed for treatment and prophylaxis of congenital deficiencies. Potential applications in acquired deficiencies are currently deterred by the danger of virus transmission. When "susceptible" patients, not previously treated with large-pool concentrates, are assiduously followed after their first infusion of factor IX concentrate, almost all show evidence of infection with NANBH, although there may be no clinical symptoms. Factor IX concentrates used in the US and Europe have been shown to transmit HTLV III and there is no reason to believe that UK concentrates made from infective pools would not do so.

Factor IX concentrate 9D withstands dry heating in the final vial almost as well as factor VIII concentrate 8Y, showing 10-15% loss of factor IX coagulant activity after 72h at 80°. Laboratory tests show that, although activated factor IX and factor X are diminished by heating, a small amount of the clotting enzyme thrombin is released from factor II. The concentration of thrombin produced is not thought to be physiologically significant, but we have taken the precaution of adding a very small amount of our antithrombin III concentrate before freeze-drying and heating. This effectively neutralises thrombin as it is formed. No other property of the concentrate is significantly affected by heat treatment.

All factor IX concentrates also carry the risk of inducing thromboembolism in a few categories of high risk patients, e.g. those with liver damage or undergoing extensive surgery. Laboratory tests have been developed to measure the content of "activated" factors in concentrates, but these tests do not confidently predict untoward clinical side-effects. Any new concentrate, or new processing stages added e.g. to inactivate viruses in the concentrate, should therefore be tested in animals before clinical trial; the preferred animal model in the UK is post-infusion detection of minimal DIC in dogs.

The new concentrate 9A, dry-heated after addition of AT III, has now been shown to be even less reactive than the parent 9D in the dog DIC model. Clinical trial of immediate safety and efficacy has been planned in five Haemophilia Centres, to start on 12th July. Preliminary arrangements have been made, subject to satisfactory safety trials, to proceed to treatment of patients susceptible to NANBH and HTLV III transmission, starting in August. Current production of factor IX concentrate in PFL and BPL has been easily adapted to incorporate the addition of AT III and heating in the ovens developed for heating factor VIII. It may be possible to replace the unheated product completely with 9A by October, but stock levels will be low and may be affected by increasing demand for acquired deficiencies should 9A and the similarly heat-treated 8Y concentrate prove not to transmit viruses.

Application for a new product licence will be made in the autumn when all data on immediate safety and efficacy are to hand.

Factor VII concentrate will also be dry-heated and its progress to clinical trial is expected to follow the same path as 9A.

Heat-treated factor IX (II and X) concentrate is already providing a safer source of thrombin for clinical and laboratory use.

10.2 Use of Heat Treated Factor VIII and Factor IX Preparations

Two progress reports prepared by one relating to a new "virus-safer" factor VIII concentrate of high specific activity, the other relating to Factor IX concentrate heat treated to inactivate virus, were discussed.

It was noted that an application was being prepared for a product licence for Factor VIII Y, with only provisional evidence of reduced infectivity.

referred to clinical trials, of Factor VIII Y that had taken place involving 21 patients and said that the product had proved to be clinically effective during the initial crucial period of 9-16 weeks.

With regard to Factor IX it was noted that clinical trials of immediate safety and efficacy had been planned in five Haemophilia Centres, to commence on 12 July 1985.

11/85 Date and Time of Next Meeting

The next meeting would be held at Elstree on Tuesday 12 November 1985 at 11.00 am.

16.7.85