MINUTES OF THE 11TH MEETING OF THE U.K. HAEMOPHILIA CENTRE DIRECTORS HEPATITIS WORKING PARTY HELD AT THE OXFORD HAEMOPHILIA CENTRE AT 11A.M. ON THE 19TH JANUARY, 1983.

PRESENT:	Dr. J. Craske (Chairman)	-	Manchester
	Dr. C. Rizza	-	Oxford
	Dr. J. Trowell	-	Oxford
	Dr. E. Preston	-	Sheffield
	Dr. P. Kernoff	-	Royal Free Hosp., London
	Dr. H. Thomas	-	Royal Free Hosp., London
	Mrs. M. Fletcher	-	Oxford Haemophilia Centre
	Dr. R. Lane	-	Blood Products Laboratory, Elstree, Herts.
	Miss R. Spooner	-	Oxford Haemophilia Centre
	Dr. C. Ludlam	-	Edinburgh
	Professor A. Bloom	-	Cardiff (by invitation)

APOLOGIES FOR ABSENCE: None

Dr. Craske welcomed Professor Bloom to the meeting.

1) The Minutes of the previous meeting held in Manchester on September 13th, 1982 were tabled by Dr. Craske. He apologised for not being able to circulate these before the meeting. This was due to shortage of secretarial help at Manchester. It was agreed that members of the Working Party would let Dr. Craske have any comments on the Minutes at a later date.

2) MATTERS ARISING FROM THE MINUTES

a) Prospective study of factor VIII and IX associated hepatitis: implications of trials to evaluate the hepatitis risk of 'hepatitis reduced' factor VIII and IX.

Dr. Lane said that following the last meeting of the Working Party a meeting had been called at the Blood Products Laboratory, Elstree, to discuss the strategy for the evaluation of 'hepatitis reduced' concentrate. The problem was that there was a loop hole in the licensing regulations which allowed any Director of a Haemophilia Centre to evaluate a product simply by notifying the Licensing Authority of any patient treated under the scheme. However, there was no limit on the time during which this could be done. Therefore there was a danger that a series of separate observations would be made without any requirement of the manufacturer to present to the Licensing Authority the necessary information to ensure the potency, reliability and freedom from side effects of the product. Any product could come into general use without ever undergoing consideration for a product licence. This removed all guarantees of quality assurance which the Medicines Act was designed to ensure. The physician prescribing the preparation was also personally liable for any harm or side effects which might subsequently come to light. The only way by which a company could be called to account would be by a civil action against the company instituted by the Haemophilia Centre Director involved. There was an urgent need to formulate the criteria whereby 'hepatitis reduced' concentrate could be properly evaluated for the risk with regard to the transmission of non-A, non-B hepatitis. It was also necessary to investigate any other side effects which might be a hazard associated with the use of the product, as proteins might have been partially denaturated by the pasteurisation process used to inactivate hepatitis viruses. It was possible that side effects

could be caused by the formation of immune complexes and fibrinogen degradation products such as fibrinectin.

Professor Bloom said that as a result of the meeting he and Dr. Rizza had attended they had written to each Haemophilia Centre Director requesting them not to take part in trials of 'hepatitis reduced' products on a named patient basis without taking advantage of an evaluation where the powers of the Medicines Commission, under the Medicines Act, could be exercised in the interests of the patient. Feiba had been used widely in the U.K., but had never been granted a product licence as it had been used on the named patient basis. It had only lately been compared with Autoplex in a clinical trial, and the results had been inconclusive.

Dr. Lane said that it was unlikely that chimpanzee safety tests would be possible after the first batch of 'hepatitis reduced' concentrate was produced and that the results of clinical trials in susceptible patients must be available to evaluate these products. It was also likely that factor VIII activity would be reduced by about 50% as a result of the pasteurisation process.

In discussion it was suggested that trials on a named patient basis often provided the best means of obtaining preliminary information about a new product. It was pointed out however, that this method did not provide a guarantee of the product under the Medicines Act, and that there was still a danger that a drug firm might use the information obtained to create a climate where it appeared unethical to withhold the product for general clinical use.

There were three possible procedures:-

1) evaluation on a named patient basis

2) the granting of exemption from a clinical trial certificate by the Licensing Authority, In the U.K. this was the National Institute of Biological Standards. The clinician organised trials prior to the granting of a new product licence. This procedure was not so costly or lengthy as that of obtaining a clinical trial certificate.

3) Clinical Trial Certificate. This involved a full application for a new product licence with all the trials organised by the manufacturer. The procedure was lengthy and costly.

Dr. Lane said that if all Haemophilia Centre Directors collaborated the manufacturers would be obliged to follow whatever procedure was adopted.

It was agreed that the Working Party would attempt to obtain the collaboration of all Haemophilia Centre Directors in the organisation of trials under alternative 2.

Questions which should be asked were:

i) the risk of non-A, non-B hepatitis when given to susceptible patients. In view of the results of the Oxford prospective study, these should be patients with no prior exposure to factor VIII or IX concentrate. It was probable that there would not be enough susceptible patients for the inclusion of control groups in the study of each product. Ideally, five batches should be studied, each batch being given to two patients. This would detect any variation between batches. A follow-up for one year was essential.

ii) In view of the reduced factor VIII yield in these products in-vivo survival studies of the coagulation factors would be essential. These could be conducted in patients with severe coagulation defects on regular factor VIII treatment. Patients would also be observed for toxic and allergic side effects.

Dr. Craske agreed to modify the prospective study protocol to include these points and to circulate it to members of the Working Party and the U.K. Reference Centre Directors. It would then be circulated to all Haemophilia Centre Directors who would be asked to notify Dr. Craske of the brand of product, number of patients under trial and batches included in the trial. Information would be returned to Dr. Craske on a suitable proforma so that all the information about the products could be pooled and a final report made available to the U.K. Haemophilia Centre Directors.

Dr. Rizza said that Dr. Savage had replied to the circular letter that he was contemplating taking part in a European trial of the Travenol 'hepatitis reduced' factor VIII. This was presumably on a named patient basis. It was hoped to induce a change to option 2.

It was also agreed that patients included in clinical trials should be followed up later to look for evidence of immune complex formation and other complications. This could be done with infrequently treated patients. Most patients in the Oxford study did not require fresh treatments for 12 to 18 months after the episode at entry to the study.

b) Acquired Immune Deficiency Syndrome (AIDS)

Dr. Craske reviewed the developments in the field since the last meeting of the Working Party. At Dr. Kernoff's suggestion, he had written to Dr. Dale Lawrence at the Communicable Disease Centre (CDC), Atlanta, Georgia, U.S.A., who was the co-ordinator of the surveillance of AIDS cases in haemophilia A patients in the U.S.A.

So far 10 cases of AIDS had occurred in haemophilia A patients. They had none of the predisposing causes such as heroin addiction, promiscuous homosexuality, or treatment with immunosuppressive drugs, and had occurred in areas of the U.S.A. where cases had not been found before. All except one patient were patients with severe coagulation defects on regular factor VIII therapy. The youngest was aged 7 years, both Pneumocystis carinii and Kaposi's sarcoma had been found in this group of whom 5 had since died. It seemed possible that factor VIII or other blood products administered to these patients might be implicated.

The CDC AIDS Task Force were working on the hypothesis that an infective agent was involved, possibly a virus specific for human T-cells in the same way that E.B. virus was specific for human B-lymphocytes. Further support for this hypothesis had come from the report of three cases associated with whole blood or platelet transfusions. Two were in adults who had developed AIDS, 14 and 18 months respectively, after transfusion to cover operations. In one case, one of the two donors implicated was known to be a young man in his twenties from New York. However, further investigations of these donors was not at present possible owing to medico-legal problems. The third case was that of a twenty month old boy from California who had been transfused with blood platelets at birth for Rh haemolytic disease of the newborn. Fourteen months later he developed an AIDS-like syndrome with an auto-immune type thrombocytopenia One of the donors of a unit of platelets was a young homosexual who subsequently developed classical AIDS and died in August 1982. Incubation periods of the

cases was between 6 months and 2 years.

The main defect in these cases was a disorder of cell medicated immunity (CMI). This consisted of a lymphopenia with a count of less than 1,000 cells per cubic millimetre, failure to react to skin test antigens used for detection of CMI, failure of lymphocytes to transform after stimulation of mitogens such as phytohaemagglutinin in vitro, and the reduced ratio of T-helper to T-suppressor lymphocytes of less than 1.0. The latter marker was a phenotypic marker for lymphocytes so that many other factors were associated with altered ratios such as virus infections, pregnancy, treatment with steroids and certain drugs. Two recent papers in the New England Journal of Medicine suggested that transfusions of freeze dried factor VIII concentrate may be a factor.

The Americans were keen for the U.K. Haemophilia Centre Directors to collaborate in the reporting of cases of AIDS possibly associated with transfusions of U.S. commercial factor VIII. No cases have so far been found in the haemophilia B patients. Dr. Craske said that he had been sent the detailed protocols of the National Haemophilia Foundation Survey by the Americans. The Working Party should consider the kind of survey which should be undertaken in the U.K. He suggested that a retrospective survey might be conducted where Haemophilia Centre Directors were asked to report patients suspected to have the clinical features of AIDS-like disease. The American forms were very comprehensive and could be used for this. In discussion, it was pointed out that the two recent papers in the New England Journal of Medicine described studies of T-helper/suppressor ratios in haemophilia A patients. The main finding was that patients treated with freeze dried concentrate had lower ratios than those patients on Cryoprecipitate and normal controls. The degree of depression of ratios were not as profound as in the classical AIDS syndrome. Dr. Craske said that one study which might be contemplated was a prospective study of the effects of various factors of cell mediated immunity in haemophilia A patients, especially the comparison of the effect of NHS factor VIII treatment compared with that of U.S. commercial factor VIII. He agreed to draw up a form for the reporting of AIDS cases and to consider what further information would be needed in a retrospective study.

Prospective studies. It was essential to standardise tests if different laboratories were performing tests for CMI in the same project.

It was also reported that there had been an outbreak of Mycobacterium tuberculosis infection in young severely effected haemophiliacs at the Birmingham Children's Hospital. Skin lesions appeared to be the main lesion involved. In view of the altered response to tests of CMI reported in haemophiliacs, it was important to determine whether haemophilia A patients on freeze dried concentrates were more susceptible to tuberculosis than healthy children not treated regularly with blood products.

c) Hepatitis B Vaccine: Immunisation of staff and patient groups

In response to questions from other members of the Working Party, Dr. Craske said that preliminary results of trials of the Merck, Sharp and Dohme (MSD) hepatitis B vaccine showed that intramuscular or subcutaneous routes of injection were equally immunogenic. The vaccine was not yet licenced for use in the U.K. by the subcutaneous route. Results of other trials

suggested that the immune response in children less than 1 year old was very vigorous and that the dose of MSD vaccine for this group could be reduced to 5 micrograms per dose of vaccine. The immune response was best in patients below the age of 30 years.

The main groups of patients suitable for immunisation would be:-

1) severe haemophiliacs at first diagnosis as young children

2) patients with mild coagulation defects who are about to undergo a procedure requiring treatment with factor VIII or IX concentrate.

There was some discussion as to whether passive immunisation with hepatitis B immunoglobulin (HBIG) would be required. Dr. Lane said that it would be possible to prepare special batches of HBIG for intravenous use. A new type of immunoglobulin prepared by Cohn fractionation for use intravenously was shortly to be launched by the Blood Products Laboratory. It was agreed that combined active/passive immunisation using intravenous HBIG should be studied in a few patients before it was recommended for general use. It was cost effective to screen patients for anti-HB_s and anti-HB_c antibody prior to immunisation if the expected antibody rate was at least 20%.

The staff at Haemophilia Centres did not seem to run a high risk of contracting hepatitis B. Dr. Craske said that sera from 30 staff had been tested for anti-HB_c at Manchester and only 2 had been found to be positive. Both these individuals had probably acquired their hepatitis B in situations not related to working in Haemophilia Centres. Unfortunately, the question of immunisation of staff in individual Haemophilia Centres would depend upon the availability of the vaccine locally, and would have to compete with other demands for this vaccine from other categories of staff in local Health Authorities.

3) ANY OTHER BUSINESS

There was none.

4) DATE OF NEXT MEETING

To be arranged.

J. Craske
6.4.83.