MINUTES

MINUTES OF THE 5TH MEETING OF THE UNITED KINGDOM HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY. THE MEETING WAS HELD AT THE OXFORD HAEMOPHILIA CENTRE ON MONDAY AUGUST 20TH 1979.

Present

Dr J Craske (Chairman)
Dr H Davies
Miss R J D Spooner
Dr D Ellis
Dr J Trowell
Dr S Ghosh

1. Minutes of the previous meeting, held on January 29th 1979 were approved.

2. Matters arising from the minutes.

2.c. Study of chronic liver disease in patients at Oxford and elsewhere

Dr Ghosh presented the results of the studies on the Oxford Haemophiliacs. So far 179 patients with severe Haemophilia have been studied according to the agreed protocol. Patients were classified into four groups on the basis of their Aspartate Aminotransferase as follows:-

Aspartate Aminotransferase (Normal range up to 35 I.U./litre) Group	No. of Patients	Percent
1. Always normal	41	23.6
2. Occasionally abnormal	63	36.2
3. Persistently abnormal AsT (Between 35 and 70 I.U./Litre)	47	27.0
4. Persistently abnormal AsT > 70 I.U./litre	23	13.2

70 out of 174 patients for whom detailed records of liver function tests were available, had persistently abnormal liver function tests. 32 of these had been seen at the Liver Clinic, and 20 of these had significant chronic liver disease, as judged by their clinical features. There were no significant differences between the groups of patients, with respect of evidence of past infection with Hepatitis B virus. 88 out of the 107 patients studied, had evidence of past infection with Hepatitis B (82.2%). Prevalence of Anti HB_S increased from 75 per cent (8 out of 10 tested), in the 6 - 10 year age group, to 93.75 per cent in the 31 - 40 age group. Only three of these patients are known carriers of HB_SAg.

The lower prevalence of antibody over the age of 40 years (78.9%) may reflect

a) A decline of each level of Anti HB_S with age.
b) The longer survival of patients with mild Haemorrhagic disease.
c) A poor immune response with increasing age.

There was no difference between the proportion of patients in group three and four who were on regular treatment with National Health Service or Commercial factor VIII.

Ten patients were thought to be dependent on analgesics, some of which are known Hepatotoxic. None of these have been found to have abnormal Aspartate levels. These patients had some degree of dependence on alcohol, and two had Transaminitis. Dr Ghosh said that in his opinion the increased consumption of alcohol was associated with episodes of higher enzyme levels in these patients, but that two patients with elevated enzymes had background liver disease unrelated to alcohol.

It was agreed to continue this study and to obtain additional evidence of the relationship of 'Transaminitis' and overt chronic liver disease to the mortality in these patients and to other factors such as past treatment with different brands of factor VIII, the number of years since the first dose of concentrate and the age at first diagnosis. Dr Craske said he would arrange for blood samples from these patients to be tested for antibodies to Cytomegalovirus and Epstein-Barr virus.

The results of tests for Hepatitis A antibody (Anti-HA) by Radioimmunoassay (RIA) on fifty-four patients so far tested showed that 28.6 per cent were Anti-HA positive. The age prevalence of antibodies was 11 - 30 years, 15 per cent, 31 - 40 years, 37.5 per cent, 40 and over 83.3 per cent. There were problems in that some results could possibly be due to passively aquired Anti-HA present in transfusion concentrate. One patient, on re-testing three months later had reverted to Anti-HA negative. One half of the 6 - 10 age group were Anti-HA positive on first testing, but these results would be further investigated. It is likely that the results reflect the prevalence of Anti-HA in the normal population in the Oxford region and re-emphasise the fact that Hepatitis A is rarely related to treatment with factor VIII or IX concentrates. It was agreed to study a group of Oxford patients with mild Haemorrhagic Disease over the next year to obtain more evidence of the relationship of the various factors already studied to the incidence of Transaminitis. Dr Ghosh will visit the Edinburgh Haemophilia Centre to analyse the data accumulated on Dr Howard Davies' patients.

Chronic Hepatitis Form

Dr Craske circulated a revised draft of form H. After some discussion and modification, a final draft was agreed. Jean Spooner will circulate this for the final approval of the working party members.

Study of Transamanase levels for infusion of factor VIII

So far three patients had been studied. There was no obvious rise in enzyme levels within seven days of infusion of factor VIII in any of them.

Study of serum bile acid levels as an index of abnormal liver function

Sera from 20 patients had been accumulated at Oxford. Dr Davies said that results for some of the Edinburgh Haemophiliacs would be available shortly. This project will be reviewed when all the results from the Oxford patients are available.

2.f. Hepatitis Surveillance

Dr Craske said that the prevalence of Hepatitis appeared to be about the same over the past two years; compared with 1974, most of the overt Hepatitis occurred in mild Haemophiliacs many of whom had been transfused with concentrate for the first time, to cover an operation. Two thirds of the cases reported were Non-B Hepatitis. Over thirty of these had been confirmed as Non-A, Non-B Hepatitis. The earlier evidence in favour of two types of factor VIII related Non-A, Non-B Hepatitis had been confirmed by data collected during 1979. The incubation periods where this could be estimated, was between 8 - 60 days.

Priliminary evidence suggests that the non-B hepatitis associated with National Health Service factor VIII and IX had a mean incubation period which was longer than that of Kryobulin associated non-A, non-B hepatitis. Epidemiological evidence suggests that most of the non-B hepatitis associated with these products are of the same sera type. The difference in incubation periods observed between the two may be related to the higher dilution of each donation used to make National Health Service factor VIII and IX (3,000 donations of 200 millilitres) compared with Kryobulin (1,000 donations of 600 millilitres each).

Dr Craske said that there was evidence from a study of hepatitis in Manchester that non-A, non-B hepatitis unrelated to transfusion was endemic in North West England. So far this type of hepatitis has not been described after whole blood transfusions in the United Kingdom, b8t cases have been reported associated with transfusions of Cryoprecipitate.

Analysis of surveillance by computer

Jean Spooner presented the results of the contact rates of hepatitis in 1977 of jaundice in haemophiliacs related to the total number of patients reported as having received one or more bottles of each brand of factor VIII in that year. The evidence suggested that the incidence of hepatitis after transfusion with one of the cover products is higher than that associated with other brands. It was concluded that if confirmed, this would justify all the labour involved in compiling these reports. It was decided to include the data in the first Annual Research Report to the Department of Health and Social Security and in the 1979 report of the hepatitis working party.

First Annual Report to the Department of Health and Social Security Small Grants Committee; 1979 Hepatitis Working Party Report

Dr Craske said that the Department of Health and Social Security report had to be submitted within six weeks after September 1st. A meeting will be held in Oxford on 19th September to agree on the data to be included. This report will be the basis of the Annual Report of the hepatitis working party, which will be presented to the Reference Centre Directors' meetin in October and the United Kingdom Haemophilia Centre Directors' Annual Meeting in November.

Study of Hepatitis B in the relatives of Haemophiliacs

Dr Craske said that four cases of overt hepatitis B had been reported within the past two years in the relatives of haemophiliacs. Two of these had been in relatives who treated the index patient. A study had been started to determine the incidence of HB_sAg and antibody in the relatives of haemophiliacs treated at Oxford to asses the risk of transmission of this infection.

3. Proposed trial of Hepatitis B vaccine

Dr Craske said that field trials of the Merk, Sharpe, Doehme (M.S.D.) vaccine were at present being carried out in New York. The results of this trial would be available from May, 1980 onwards. There were problems in mounting the trial of the protective effect of this vaccine in haemophilia. Part of the protocol requires that a six month period elapses between the administration of the vaccine and the testing of its protective effect by exposure of the immunised subjects to transfusion of material possibly infected with hepatitis B virus. This is probably due to the slow immune response produced by humans to this vaccine.

Dr Reichle, the Medical Director of Europe for M.S.D. is due to visit the United Kingdom in December to hold further discussions on this topic.

Even if a trial of the protective effect of this vaccine in Haemophiliacs is not feasible, it will be necessary to carry out acceptance trials before general use of the vaccine can be recommended, particularly in view of the risk of haemorhage at the site of injection.

4. Recent Hepatitis Research

Dr Craske said that it was now established that intravenous infusion of factor VIII could induce Non-A, Non-B Hepatitis in chimpanzees. The evidence suggests that there were two types of Non-A, Non-B Hepatitis and implicated batches of factor VIII and IX are being collected with a view to further animal work in conjunction with Professor Zuckerman at the London School of Hygiene and also with the group of workers at the Bureau of Biologics in Washington, United States of America. Marmosets had not proved susceptible to this disease.

Two candidate viruses had been described but the association with Non-A, Non-B Hepatitis had not been confirmed. Dr Prince had recently described a Gel diffusion test, and similar results had been described at the Bureau of Biologics and in Japan. The Bureau of Biologics group had also devised an immunofluorescence test using chimpanzee liver. The Japanese work had not been confirmed because no further reagents were available.

The project at Oxford was proceding slowly. Small round viruses had been seen in the faeces collected from one patient three weeks after an intravenous infusion of factor VIII concentrate but this patient had not developed Hepatitis. Further cases would be studied in this way.

5. Future Projects

It was decided to collect more evidence concerning Chronic Hepatitis and the incidence of Hepatitis in family contacts of Haemophiliacs. The Canadian Red Cross was about to start a prospective study of factor VIII obtained from Canadian volunteer blood donors prepared by Hyland and Cutter Laboratories. The protocol had been prepared by Dr Craske at their request. It is hoped to develop the Radioimmunoassay test to see if the small round particles seen in the faeces of accute cases on Non-A, Non-B Hepatitis by Electronmicroscopy are associated with this disease.

6. Any other business

There was no further business.

7. Data of next meeting

This will be arranged in the new year and is dependent upon the decisions taken at the Reference Centre Directors' Meeting in October.

Yours sincerely

GRO-C

J Craske
Chairman