PTH 81/6

R. 4/9/81.

BLOOD TRANSFUSION RESEARCH COMMITTEE

Working Party on Post-Transfusion Hepatitis

Minutes of the second meeting held on Thursday June 25th 1981 at 10.30 am at 20 Park Crescent, London, W1N 4AL.

PRESENT: Dr H H Gunson (Chairman) (Director, Manchester RBTC)
Dr J Craske (Secretary) (PHLS Manchester)
Dr D B L McClelland (Director, Edinburgh and South East Scotland RBTC)
Dr Sheila Polakoff (PHLS, Colindale)
Dr H C Thomas (Royal Free Hospital, Medical School - representing Professor Dame Sheila Sherlock)

Dr Diana M Walford (DHSS)
Professor A J Zuckerman (London School of Hygiene and Tropical Medicine)

By Invitation: Dr R S Lane (Director, Blood Products Laboratory, The Lister Institute, Elstree, Herts)

In Attendance: Dr Helen Duke
Dr Barbara Rashbass

Dr Craske took the Chair initially owing to the delayed arrival of Dr Gunson.

1. Apologies

Apologies for absence were received from Dr J O'H Tobin and Professor Dame Sheila Sherlock who was represented by Dr H C Thomas. Dr W J Jenkins has tendered his resignation from the Working Party on his retirement from his post of Director, North East Thames RBTC.

2. Minutes

The Minutes of the first meeting held on 14 February, 1980 (PTH 80/5) were signed as a correct record.

3. Matters arising from the Minutes

3.1 Storage of HB Ag donations

This item was considered first at the request of Professor Zuckerman. He stated that there was still a problem with the supply of HB Ag positive plasma donations. It was important that a collection of plasma from HB Ag positive plasma donations of high titre, preferably HB Ag positive should be freed to provide the basis for the production of a British Hepatitis B vaccine, whatever the type that was finally produced in the UK. It was important to characterise each donation for HB markers. Dr Lane said that a panel of HB Ag positive donors had been collected by the Middlesex Hospital in collaboration with the North West London RBTC.

S104/18

Dr Walford said that the DHSS was actually considering what measures were needed to ensure an adequate supply of high titre HB Ag positive plasma, especially HB Ag positive plasma, which could form the storage of hepatitis B vaccine production. It was possible that plasma pheresis of selected donors might be performed for this purpose. It was agreed that this problem needed an urgent solution.

Dr Gunson, who had by now arrived and took the Chair, undertook to discuss the problem with the Chairmen of the Divisons of Blood Transfusion Centres to see what further measures might be needed to ensure a systematic identification and collection of HB Ag positive donors. It was pointed out that HB Ag positive carriers of hepatitis B virus might become very rare if current trials of treating these patients with DNA polymerase inhibitors proved successful.

3.2 Identification of agents carrying non-A, non-B hepatitis - verbal report by Professor Zuckerman.

Professor Zuckerman opened the discussion by giving a concise summary of the research work undertaken over the past 2 years to try and identify and characterise the viruses associated with non-A, non-B hepatitis in man.

Post Transfusion Hepatitis

There was evidence of 2 types of non-A, non-B hepatits associated with the transfusion of blood and blood products. This was based on reports of multiple attacks of hepatitis in humans, and cross challenge experiments in chimpanzees. One type, with a short incubation period (7-70 days) was usually associated with tranfusion of factor VIII manufactured in the USA. Small virus particles approx. 20-30 mm diameter have been described both in the USA and the UK associated with this type of hepatitis, and similar virus like particles have been described in acute phase sera from cases of hepatitis in Japan. However, confirmation of these observations was still awaited.

The second type associated with blood products especially factor IX had a longer incubation period. The two strains of virus "bred true" with respect to their incubation periods on serial passage in chimpanzees.

Epidemic non-A, non-B Hepatitis

Recently an epidemic form of non-A, non-B hepatitis has been described associated with large epidemics in India and Libya. The overall mortality was about 4% with a particularly high mortality in pregnancy. The evidence suggested that person to person spread was by the faecal-oral route and possible food and water. It was now evident that the large outbreaks such as the Dehli outbreak of 1953 were not due to hepatitis A, but were probably due to epidemic strains of non-A,non-B virus. This type of hepatitis was not associated with a high incidence of chronic sequelae as has been found with transfusion associated non-A, non-B hepatitis.

A fourth type of endemic non-A, non-B hepatitis had recently been found in Western Europe and the USA. It was probably spread by faecal-oral routes and was not associated with chronic sequelae. In a study of acute hepatitis in West London this type of hepatitis appeared to be common in women in the 20-29 year age group. In 210 patients there was evidence of hepatitis A (58%), in 98 (27%) there was evidence of hepatitis B out of a total of 368 patients found with acute hepatitis in a 3 year period. Five had both A & B

hepatitis. Two patients had EB virus infections, leaving 48 (13%) which were thought to be non-A, non-B hepatitis.

Attempts to devise a laboratory test by serological techniques had been unsuccessful. This had recently been shown in a collaborative survey involving 22 laboratories using precipitin tests. The reasons for the lack of success were not clear. Immune complexes may be involved. One observation by a group using a radioimmunoassay test appeared to identify coded specimens of serum known to contain non-A, non-B viruses in a second trial. Further work was needed to clarify the position.

Dr Howard Thomas said that efforts had been made at the Royal Free Hospital to develop a radioimmunoassay test for non-A, non-B hepatitis using radio labelled convalescent sera from haemophiliacs (PTH 81/5 tabled). Using a chequerboard system of testing, it had been found that only sera from 3 out of 100 patients tested had proved suitable for antibody labelling. This was possibly because of the high proportion of patients who became carriers after recovering from their acute hepatitis. Further work was needed with this test.

3.3 Identification of donors and units of blood associated with possible cases of non-A, non-B hepatitis

3.3.1 Screening of donors for transaminase levels

Dr McClelland tabled a protocol (PTH 81/2) for a prospective study of blood transfusion associated hepatitis in Edinburgh and Manchester. The protocol was based on a study recently completed in the USA. - 600 patients would be followed prospectively over the 2 year period. Apart from the desirability of obtaining accurated data concerning the incidence of non-A, non-B transfusion hepatitis in the UK, it was also important to obtain information as to whether the screening of blood donors by the alanine aminotransferase test (ALT) might be of value in the UK. It was also essential to obtain well documentated specimens of serum from known cases of non-A, non-B hepatitis for evaluation of any tests which might be of value for the diagnosis of this disease, and the screening of blood donors.

Professor Zuckerman pointed out that a study already had been undertaken in the early 1970's in 3 regions of the NBTS. 768 patients had been followed and 8 cases of overt post transfusion hepatitis were detected. In addition, 35 symptomless patients had been found to have elevated ALT levels. This had been before the realisation of the existence of non-A, non-B hepatitis but in retrospect the subclinical cases were likely to be non-A , non-B hepatitis. These sera were available for the evaluation of any candidate tests for non-A, non-B hepatitis. It is likely that a fresh project could cost from £50 - 100,000 to undertake. A careful evaluation of the need for such a project should be carried out before the Working Party could recommend to the MRC that a fresh study should be sponsored, as the administrative difficulties encountered in the last project had been very hard to solve.

An evaluation of the value of ALT screening of blood donors had been carried out at the RBTS at Edgware (North West Thames). Problems had been encountered as it had proved difficult to trace the fate of found donors to have raised ALT values. The value of this procedure in the UK at the present time was agreed by the Working Party to be of doubtful value.

Dr Lane said that the introduction of ALT screening might raise difficulties because if plasmapheresis were to be used as a source of plasma a large number of donors might be involved in any blood product so prepared.

Dr Polakoff pointed out that an effort should be made to follow up the patients involved in the original MRC study of post transfusion hepatitis, and enquires should be made to see if the original collection of sera from this project were still available, with adequate documentation to form the basis of material for further studies.

This was agreed to by the Working Party and the Chairman said that he would write to Professor Dame Sheila Sherlock and Professor Zuckerman (who had left the meeting) to see if the patient records and serum specimens were still available. Dr McClelland's project could then be reconsidered in the light of the specimens and clinical data available from the earlier study.

3.4 Hepatitis A Immune globulin

Proposals for donor selection production and evaluation of a trial batch of high titre IgG. (PTH 81/3)

Dr McClelland said that studies carried out by Dr Philip Mortimer at the Virus Reference Laboratory, Colindale, in collaboration with the Edinburgh RBTS had shown that the content of anti-HAV antibody from batches of human immunoglobulin prepared from English blood donations appeared to have decreased consistently between 1958 and 1981. Immunoglobulin prepared from Scottish plasma donations did not show this trend. Current information suggests that most batches of immunoglobulin still protect against hepatitis A when given as passive protection against hepatitis A. In the long term reconsideration should be given to the necessity for this preparation of anti HAV immunoglobulin from selected donors, eg those with a history of jaundice, or of increasing the dose given to passive prophylaxis. There was also a need for an International Standard for hepatitis A.

It was agreed by the Working Party that this matter might be referred to a special ad hoc group to consider with Dr Lane the question of the production of hepatitis A immunoglogulin of sufficient potency.

4. Transfusion of hepatitis by blood products

4.1 Report of the DHSS Advisory Group Testing for hepatitis B surface antigen

Dr Walford informed the Working Party that the report was finalised and endorsed, and would be ready for distribution shortly.

4.2 Hepatitis in Haemophilia - report by Dr Craske

Dr Craske summarised recent results (PTH 81/4 tabled) of the surveillance of reports of hepatitis made to the Oxford Haemophilia Centre by Haemophilia Centre Directors. The incidence and types of transfusion hepatitis remained unchanged. Non-A, non-B hepatitis and hepatitis B still occurred. Approximately 40-50 cases were reported per year out of a total of just over 2,000 patients who were treated with factor VIII, IX concentrate or cryoprecipitate.

Present data showed the following associations:

(1) Of 137 cases of overt non-A, non-B hepatitis reported to the Oxford Haemophilia Centre as being associated with transfusion of factor VIII or IX

concentrate, 70-80% depending on the brand implicated were associated with the first transfusion of concentrate that the patient had received, showing that this is the most common factor associated with this disease.

(2) Analysis of attack rates of hepatitis in patients receiving only one product in any year suggest that between 1977 and 1979 the ratio of the attack rates of non-A, non-B hepatitis for commercial brands of factor VIII vary between 4 and 20 compared with that of NHS factor VIII.

(3) Data base on the occurrence of multiple attacks of hepatitis and other observations provided further epidemiological evidence for the existence of more than one serotype of non-A, non-B hepatitis associated with transfusion hepatitis in haemophiliacs. One serotype occurred almost exclusively in cases associated with all the brands of Commercial Factor VIII manufactured in the USA. At least two serotypes were associated with transfusions of NHS factor VIII and Kryobulin, an intermediate type factor VIII similar to NHS material manufatured by Immuno Ltd. The hypothesis is that seemed to fit with the facts as known was that the PEG/glycine method for the preparation of factor VIII used in the USA inactivated one of the two serotypes and possibly concentrated the second. It was possible that the non-A, non-B hepatitis associated with US Commercial concentrate was a different type from the other two. However, this seemed unlikely. Both serotypes seemed to be associated with a equal incidence of chronic hepatitis.

Dr Craske concluded by saying that there was little information about the incidence of symptomless hepatitis and the relative risks of hepatitis due to different brands of factor VIII and IX. The DHSS were keen that a prospective study of patients undergoing elective treatment requiring concentrate should be undertaken to provide answers to these problems, and to provide a collection of well documented sera and other specimens for the use in development of serological tests for non-A, non-B hepatitis. The Working Party agreed to recommend to the MRC that such a study should be undertaken.

4.3 Removal of viruses from Blood Products

There was no fresh information available on this subject.

5. Any other business

There was none.

6. Date and time of next meeting

Early in 1982.

MRC

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Circulation
Members of the Working Party

2nd Meeting of the Working Party on Post-Transfusion Hepatitis

Enclosed is a copy of the minutes which have been approved by the Chairman.

GRO-C

Sandra Carpenter (Miss)