# HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY

## STUDY OF THE INCIDENCE OF CHRONIC SEQUELAE OF FACTOR VIII ASSOCIATED B AND NON-B HEPATITIS

### PILOT PROJECT

Study of the patients at the Oxford Haemophilia Centre who were transfused with six infected batches of Hemofil in 1974-5.

### INTRODUCTION

The introduction of commercial Factor VIII in 1974 for the treatment of British haemophiliacs was associated with an overall incidence of transfusion hepatitis of 17.7%[1]. Two types of hepatitis were observed; hepatitis B, and Non-B hepatitis with an incubation period of between 8 and 67 days. Subsequent work[2] has shown that up to 20% of patients on long term treatment with freeze dried Factor VIII have abnormal liver function tests for periods of at least six months.

The question arises as to whether these changes are indicative of early chronic liver disease, which in a proportion of patients may be the forerunner of chronic active hepatitis or cirrhosis. A recent report[3] shows that "Non-A, Non-B" hepatitis can be the forerunner of chronic sequelae in patients who contract both overt and symptomless infections. It is intended to follow up all patients treated with these infected batches in 1974-5.

### METHODS

All patients treated at the Oxford Haemophilia Centre with these infected batches of Hemofil (see Table 1) will be contacted. Patients who have received other batches of Hemofil will be included and an attempt will be made to match these with control patients. The patient's general practitioner will be invited to co-operate by furnishing details of the patient's general health. The clinical treatment records at the Oxford Haemophilia Centre will be consulted.

A clinical Research Fellow of Registrar grade will be appointed for this work.

### STUDY PATIENTS

Patients will be visited in their own homes or seen when they attend the

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Haemophilia Centre at the Churchill Hospital. A medical history will be taken of their general health since the time they received Hemofil in 1974. Special attention will be given to symptoms associated with liver disease. Patients will also be given a general physical examination. Blood will be taken in 1cc aliquots for liver function tests and for tests for hepatitis B antigen and antibody. At least two serum specimens will be stored. Liver function tests will include serum bilirubin, alkaline phosphatase, alanine and aspartic aminotransferase, serum albumin and globulin and examination of electrophoretic strip.

CONTROLS

A second series of patients will be chosen who are matched for age, severity of coagulation defect and transfusion history, with that of the study patients. These will be chosen from patients treated at the Oxford Haemophilia Centre. If possible, these will be divided into two categories:-

1) Patients on treatment with freeze dried Factor VIII concentrate who had not received transfusions of the designated batches of Hemofil (see Table 1), and Hemofil other than the designated batches.

2) Patients mainly treated with Cryoprecipitate. It is possible that some patients in this group will have to be selected from patients treated at other Haemophilia Centres at a later stage in the project.

HOUSEHOLD CONTACTS

It is also hoped to obtain evidence of any secondary spread of hepatitis in close household contacts of the study patients. The closest adult contact to each index patient will be asked to co-operate in the study, e.g., mother, spouse or father, and an enquiry will be made of any illness suggestive of hepatitis in the six months following the first attack of hepatitis associated with Hemofil in the index patient or, in the absence of hepatitis, six months from the date of first transfusion of one of the batches of Hemofil shown in

Table 1.

Blood for $HB_sAg$ and antibody and liver function tests will be requested from adult contacts. Children who are in contact with study patients will be excluded from these investigations unless they also attend the Oxford Haemophilia Centre for treatment of a coagulation defect, when blood will be taken as above when the patient next attends for treatment, subject to parental consent. Investigations of children in household contacts will be limited to a general enquiry as to any episode of jaundice which might be related to a transfusion of Hemofil in the index patient.

SELECTION OF PATIENTS FOR FURTHER INVESTIGATION

The results of the medical history, physical examination and liver function tests will be analysed, and patients will be assigned to one of the following categories:-

1) Asymptomatic (i.e. no symptoms or signs suggestive of chronic liver disease) with normal liver function tests - NO FURTHER FOLLOW UP INDICATED.

2) Asymptomatic with abnormal liver function tests (i.e. serum enzyme levels at least twice the upper limit of normal ) - POSSIBLE ASYMPTOMATIC CHRONIC LIVER DISEASE, FURTHER FOLLOW UP REQUIRED.

3) Symptoms and signs suggestive of chronic liver disease and abnormal liver function tests - PRESUMPTIVE CHRONIC LIVER DISEASE, FURTHER INVESTIGATION REQUIRED.

4) Patients with symptoms suggestive of liver disease with normal liver function tests. These will be re-evaluated when they next attend for treatment, or 4-6 weeks later, to exclude the possibility that they were in the prodromal phase of an acute attack of hepatitis when first seen. Blood will be taken on that occasion for further liver function tests and $HB_sAg$ examination.

FURTHER INVESTIGATION

The results of the preliminary investigations of each patient will be reviewed in consultation with Dr. Joan Trowell, Nuffield Department of Clinical Medicine, at the Radcliffe Infirmary, Oxford and further investigations carried out as thought appropriate. All of the tests will be included on as many patients as possible, as shown in Table 2. Liver biopsy will not be performed unless the opinion is formed after review that this is essential for the clinical management of that individual patient.

FURTHER LIVER FUNCTION TESTS

Irrespective of any further tests indicated above, patients in categories 2 and 3 (see page 3) will be bled when they next attend for treatment after six months from their first investigation, before treatment, and blood sent for $HB_sAg$ tests and liver function tests. Patients who, in the absence of any other changes suggestive of liver disease, have abnormal liver function tests on both occasions will be considered to have "chronic abnormal serum enzyme levels". All patients in categories 2 and 3 on page 3 will be subject to this rule. Patients where liver function tests have returned to normal levels within six months will be excluded from this analysis.

RESULTS

The results of the above investigation will be analysed in relation to obtaining the following information:-

a) The association of chronic liver disease with a Hemofil associated non-B hepatitis, hepatitis B or both.

b) Length of time that a patient has been treated with freeze dried commercial or NHS Factor VIII, or both.

c) Age of the patient and severity of coagulation defect.

d) History of hepatitis not associated with Hemofil.

e) Evidence that liver function was normal before treatment with the designated batches of Hemofil.

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f) The duration of elevated serum transaminases, or the time at which they were first shown to be abnormal.

g) If two attacks of hepatitis occurred after treatment with Hemofil, whether there is any evidence of a return to normal liver function between the two episodes of acute hepatitis and its relation to any chronic sequelae observed.

Patients will be finally classified according to the following criteria:

1) Asymptomatic patients - no evidence of chronic liver disease.

2) Asymptomatic patients with consistently elevated serum enzyme levels - probable early chronic liver disease.

3) Patients with clinical symptoms or signs suggestive of active chronic liver disease.

REVIEW OF PROJECT

After one year the project will be reviewed and further investigation of other categories of patients, e.g., those contracting Kryobulin associated hepatitis will be considered for investigation.

J. Craske.
8.2.78.

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REFERENCES


1) Commercial Factor VIII associated hepatitis in the U.K. 1974-5 - A retrospective survey. J. Craske, et al (1978) J. of Hyg. (Camb.) In press.

2) Prospective study of Factor VIII associated hepatitis - Haemophilia Centre Directors' Hepatitis Working Party. Unpublished observations. 1977.

3) Development of chronic liver disease after acute Non-A, Non-B post transfusion hepatitis. R.G. Knodell, et al (1977) Gastroenterology, 72, 902-909.

TABLE 1

PATIENTS TREATED AT THE OXFORD HAEMOPHILIA CENTRE

IN 1974-5 WHO RECEIVED HEMOFIL

| BATCH | RIA TEST FOR $HB_sAg$ | HEPATITIS NON-B | (OVERT) B | TOTAL TRANSFUSED |
|---|---|---|---|---|
| 0591V053A1 | NT | | | |
| 0591V046A1 | NT | | | |
| 0591V065A2 | POS | 12(10.3%) | 3(2.5%) | 116 |
| J591X013A1 | POS | | +2 | |
| 0591V081A1 | POS | | | |
| 0591X023A1 | POS | | | |

2 others had Hepatitis B not due to Hemofil

and a third hepatitis of unknown type.

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TABLE 2

FOLLOW UP OF FACTOR VIII ASSOCIATED HEPATITIS - Information required.

1) History general health.

?previous attacks of hepatitis.

Contact with other cases.

Previous Factor VIII therapy.

2) History of acute attack of hepatitis causing patient to be included in survey.

Relation to Factor VIII therapy, e.g., new product.

Other factors possibly relevant, e.g. presence of Factor VIII inhibitors.

3) Clinical findings in acute attack.

$HB_sAg$/Antibody status before and during attacks (if known)

LFT's before attack (if known)

4) Secondary cases. Family history.

5) Clinical assessment and examination.

Clinical Investigations X-rays, Ultrasound, liver biopsy?? (see page 4)

Laboratory tests

Initial screen $HB_sAg$ and antibody.

LFT's including alamine and aspartic aminotransferases.

Full blood count.

After review Some of following - LE cells, plasma protein BSP's and anti-nuclear antibodies.

Mitochondrial, smooth muscle, where appropriate.

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## SURVEILLANCE OF N.H.S. FACTOR VIII

## PROTOCOL A

## TRANSFUSION ASSOCIATED JAUNDICE IN HAEMOPHILIACS

Study of incidence of jaundice after transfusion with Elstree Factor VIII.

OBJECT

Following the study of the incidence of hepatitis after transfusions of Hemofil[1,2], it has been decided to undertake a study of different preparations of Factor VIII in an effort to find out how the incidence and type of hepatitis observed in recipients compares with that observed after "NHS intermediate concentrate" i.e. prepared either at Protein Fractionation Centre, Edinburgh ("Edinburgh Concentrate"), Blood Products Laboratory, Elstree ("Elstree Concentrate"), or Plasma Fractionation Laboratory, Oxford ("Oxford Concentrate").

This protocol is concerned with the surveillance of batches of Elstree Factor VIII. So many batches of this concentrate are now issued that it was decided to study a number of specified batches in designated centres rather than try to study a large number on a nationwide basis. In addition it is hoped to include batches possibly associated with cases of hepatitis reported to the Oxford Haemophilia Centre.

METHOD

1) Directors of Haemophilia Centres who agree to take part in the study will be supplied with batches from the Blood Products Laboratory, Lister Institute, Elstree (Director, Dr. W.d'A. Maycock) via the appropriate RTC or direct. Cases of hepatitis possibly associated with the use of these products will be reported to the Oxford Haemophilia Centre using Form C3, the medical sickness form. Cases will be only considered as hepatitis which are reported as having had three or more symptoms or signs positive other than abnormal LFT's as shown on the medical sickness Form C3. A serum aspartic or alanine aminotransferase level of more than twice the normal value of the local hospital biochemistry laboratory will be considered as evidence of abnormal liver function.

Cases of hepatitis will be classified as "B" or "Non-B". A patient will be considered as suffering from hepatitis B when a serum specimen is positive for Hepatitis B surface antigen byreverse passive haemagglutination (RPHA) or radioimmunoassay within one month of the onset of acute hepatitis. Serum specimens taken before this should be negative by one of these tests.

Alternatively seroconversion to a positive serum antibody test for Hepatitis B surface antibody (Anti $HB_s$) or Hepatitis B core antibody (Anti $HB_c$) or both will indicate recent Hepatitis B. Non-B hepatitis will be defined as cases of acute hepatitis where tests for recent Hepatitis B infection as defined above are negative.

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Asymptomatic cases of Hepatitis B will be defined as patients who become positive for $HB_sAg$ or seroconvert by both of the antibody tests, without overt symptoms or signs of acute hepatitis.

Patients who are known carriers of $HB_sAg$ will be excluded from assessment. Details of the blood products received for six months prior to the onset of hepatitis will be recorded on Form C (revised). If a diagnosis of hepatitis is suspected, it is requested that Dr. Craske at the Manchester Public Health Laboratory should be consulted concerning the range of laboratory tests to be carried out and the number of blood samples to be taken. Forms, containers and packaging can be obtained on request. If necessary, instances in which the diagnosis is uncertain will be clarified by correspondence between Dr. Craske and the Director of the Haemophilia Centre or reference to the patient's notes if available. The Haemophilia Centre Director should attempt to collect acute and convalescent specimens from as many cases as possible.

2) At the end of each year each Haemophilia Centre will be asked to complete a record of transfusions giving the numbers of batches transfused to each patient and the dates administered for each designated batch of Factor VIII. These transfusions will be recorded on Form C, one or more forms being used for each batch, and returned to the Oxford Haemophilia Centre. Transfusion records for batches of Elstree Factor VIII other than those designated will be included if they are associated with cases of hepatitis.

3) At the end of a two year period the results will be analysed to obtain the following data:

1) The number of B and Non-B hepatitis cases related to each batch.

2) The attack rates for each type of hepatitis related to age, batch, severity of Factor VIII deficiency. They will be initially classified as B or Non-B hepatitis.

3) The mortality and incidence of chronic sequelae related to the above factors.

4) The incidence of Hepatitis B associated with the results of tests for $HB_sAg$ on each batch of concentrate.

5) Whether any of the above factors are related to the incidence of hepatitis observed in the haemophiliacs.

6) Whether the age of first transfusion with Elstree Factor VIII affects the incidence of hepatitis.

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References

1) Craske J., et al (1975) ii 221.

2) Hemofil associated hepatitis in the U.K. 1974/75. A retrospective survey. J. Craske and P. Kirk.
Report to Haemophilia Centre Directors, 1977.

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FORM C (4c)

# HEPATITIS SURVEY

(To be completed only by Centres willing to asssit with Dr. J. Craske's Survey)

Centre:

Virus Testing Laboratory**:

ELSTREE FACTOR VIII CONCENTRATE Batch No.:

| Patient's Name | Number of bottles used or issued for home use | Dates* | Samples taken for HBAg./HBAb. testing*** | Comment |
|---|---|---|---|---|
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* The total number of bottles given during periods of approximately 1 month can be shown against inclusive dates.

** Please enter the name and address of laboratory which normally undertakes HBAg./HBAb. tests for your Centre.

*** Please enter "Yes" where appropriate. It is not necessary to give test results.

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FORM C (Revised)

## HEPATITIS SURVEY

To be completed by all Haemophilia Centres for Haemophilia and Christmas Disease patients who develop jaundice (hepatitis) and to be returned to Oxford Haemophilia Centre with Form C3, unless Form C3 has already been sent to Oxford or Alton.

Centre:
Full name of patient: d.o.b.:

Coagulation defect: Factor VIII/IX level:

Date of onset of hepatitis:

Date(s) of previous attacks of hepatitis:

Material(s) received during the 6 months prior to the onset of the present attack:-

| Type | Date(s) | Batch Nos.* | Total number of factor VIII or factor IX units |
|---|---|---|---|
| Plasma | | — | |
| Cryoprecipitate | | — | |
| Oxford Factor VIII Concentrate | | | |
| Elstree Factor VIII Concentrate | | | |
| Edinburgh Factor VIII Concentrate | | | |
| Abbott Factor VIII (Profilate) | | | |
| Armour Factor VIII (Factorate) | | | |
| Cutters Factor VIII (Koate) | | | |
| Hyland Factor VIII (Hemofil) | | | |
| Immuno Factor VIII (Kryobulin) | | | |
| Other Human Factor VIII** | | | |
| Porcine/Bovine Factor VIII | | | |
| Oxford Factor IX | | | |
| Edinburgh Factor IX | | | |
| Commercial Factor IX** | | | |

Other Material(s) possibly implicated in this attack of hepatitis (please give details):-

General Clinical Comments (if any):

* Not applicable to plasma or cryoprecipitate
** please give the name of the manufacturer and/or trade name of product

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Form C3 (Revised)

# HEPATITIS SURVEY

## Sickness Record Form

This form should be completed if the patient is suspected, on clinical or laboratory grounds, of having contracted hepatitis. If the patient is included in Dr. Kirk's Survey please send with this form a specimen of serum (2mls. glass screw capped container) and wherever possible, a sample of faeces (universal container) to Virus Reference Laboratory, Public Health Laboratory Service, Colindale Avenue, London, NW9. If the patient is not included in Dr. Kirk's Survey, please return this form to Oxford Haemophilia Centre.

Name of Patient: d.o.b.: Male/Female

Case No.: Coagulation Defect:

Type(s) of therapeutic material received during the 6 months prior to development of hepatitis:

Has the patient previously received treatment with large pool freeze-dried factor VIII or factor IX concentrate? Yes/No

Approximate date of onset of hepatitis:
Estimated incubation period:
Any other details:

G.P's Name and address:

Symptoms and Signs (delete as applicable)

| | |
|---|---|
| Asymptomatic | Yes/No |
| Jaundice | Yes/No |
| Anorexia | Yes/No |
| Arthralgia | Yes/No |
| Rash | Yes/No |
| Nausea | Yes/No |
| Vomiting | Yes/No |
| Tobacco aversion | Yes/No |
| Abdominal pain | Yes/No |
| Urine discoloured | Yes/No |
| Pale stools | Yes/No |
| Raised L.F.T.'s | Yes/No |

Contact with Hepatitis- within previous six months (tick or delete where applicable)

| | |
|---|---|
| No information | ( ) |
| No contact | ( ) |
| Contact with ABAg-Case | Yes/No |
| Carrier | Yes/No |
| Contact with hepatitis (unspecified) | Yes/No |

Type of Contact:

| | |
|---|---|
| No information | ( ) |
| Household not spouse | ( ) |
| Spouse | ( ) |
| Boy/girl friend | ( ) |
| Other than above (specify): | |

Present Condition of Patient: Well/Ill/Deceased

Laboratory Results:-

| $HB_sAG$ | | $HB_sAB$ | | Type of Test |
|---|---|---|---|---|
| Date | +/- | Date | +/- | |
| | | | | |
| | | | | |
| | | | | |

Other Sources of Infection - within previous six months (tick where applicable)

| | |
|---|---|
| Drug abuse (Parenteral) | ( ) |
| Tattooing | ( ) |
| Renal Unit | ( ) |
| Travel Abroad | ( ) |

Transfusion abroad:-

(i) Where _____

(ii) When _____

Haemophilia Centre:

Signed:
Date: 9/284