11 MAR 1977

PUBLIC HEALTH LABORATORY SERVICE

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9th March, 1977.

Dr. W.d'A. Maycock,
Blood Products Laboratory,
Lister Institute of Preventive Medicine,
Elstree,
Herts WD6 3AX

Dear Dr. d'A. Mayoock,

Thank you for your letter of the 22nd February, and for your suggestions regarding the modifications of the protocol. I agree with nearly all the points which you raise and I have revised the protocol in the light of your suggestions, and I enclose a copy of this.

Can I suggest a provisional date for a meeting when Dr. Kirk and I can come and see you at Elstree. I am coming down to a meeting in London on Thursday 31st April, and therefore, can arrange to come to Elstree at 2p.m. on the 30th April. Dr. Kirk is also free on this date. Perhaps you will let me know whether this will be convenient to you.

With regard to the report about Hemofil hepatitis, I take your comment about a definition of hepatitis; this was only prepared as a preliminary report to the Haemophilia Directors meeting, and I shall shortly revise it in a form suitable for publication.

Taking the point in your letter about selection of batches of Factor VIII for study, I have no strong views as to how this should be done, except that it would seem to me that it would be better to use a random method, which closely resembles your normal method of distribution. I think Dr. Ellis's suggestions are excellent and we should devise a system which would enable us to incorporate his proposals, even though this means that some selection of batches will have to be made in advance.

With regard to your comments about the definition of hepatitis in the Hemofil survey, I made the point of only including cases which can be diagnosed clinically as hepatitis. The object of this was to avoid the problems of assigning undue significance of a single abnormal transaminase test, and I would suggest that we follow a similar rule in this survey. This will make the two sets of data comparable and also save us having to ask for additional liver function tests on these patients. Haemophiliacs as you know, tend to be investigated as little as possible as the physicians like to do as few venepunctures as possible, I have therefore re-phrased the definition of hepatitis under 'Method' to emphasise the clinical criteria rather than placing undue reliance on the results of transaminase tests.

With regard to Form C3, I enclose an upto date version of this and you will see that Yvonne Cossart's name has been removed from it.

Kindest regards,

Yours sincerely,

GRO-C

J. Craske.
Consultant Virologist

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PROTOCOL

Surveillance 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 ~~brands~~ of Factor VIII in an effort to find out if the incidence and type of hepatitis produced in recipients compared with that after treatment with Edinburgh and ~~Elstree~~ Factor VIII (NHS "Intermediate" concentrate)

This protocol is concerned with the surveillance of selected batches of Elstree Factor VIII. ~~There are~~ 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 Elstree ~~Plasma Fractionation Unit~~ by Dr. d'A. Maycock by the normal method of distribution. 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. A serum aspartic or alanine aminotransferase level of more than twice the normal value of the local hospital biochemitry laboratory will be considered as evidence of abnormal liver function. Cases will be only considered as hepatitis which are reported as having had two or more criteria positive other than abnormal LFT's as shown on the medical sickness Form C3. Details of the blood products received for six months prior to the onset of hepatitis will be recorded on Form C (revised). If necessary doubtful cases will be clarified by correspondence with the Director of the Haemophilia Centre or reference to the patients notes if available. An attempt will be made to collect acute and convalescent specimens for 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 will be recorded on Form 4C 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 in the cases of hepatitis.

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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.

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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PROTOCOL

Surveillance 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. Details of the blood products received for six months prior to the onset of hepatitis will be recorded on Form C (revised). If necessary, instances in which the diagnosis is uncertain will be clarified by correspondence with the Director of the Haemophilia Centre or reference to the patient's notes if available. ~~An attempt will be made~~ to collect acute and convalescent specimens ~~for~~ 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 will be recorded on Form 4C 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 the cases of hepatitis.

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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 attach 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.

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 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: 9/365