

0003

HEPATITIS IN HAEMOPHILIA ASSOCIATED WITH THE USE OF  
FACTOR VIII CONCENTRATES

A PROSPECTIVE STUDY

P R O T O C O L

INTRODUCTION

The transfusion of blood or its derivatives has been linked with the transmission of viral hepatitis for many years. The discovery that the HBsAg was associated with hepatitis 'B' infection (1) led to methods of screening blood and donors for this antigen. At present the third generation tests, e.g. Ausria II are used, which are 1,000 fold more sensitive than the original methods of agar gel diffusion. Despite this increased sensitivity the results of preventing hepatitis 'B', by excluding HBsAg positive donors, have been disappointing. Various authors have estimated the efficiency of solid phase radio-immunoassay in preventing post transfusion hepatitis as between 11% (2) and 59% (3). This failure to prevent post transfusion hepatitis may be explained by the following hypotheses:-

- (a) That current methods of detecting HBsAg are still not sensitive enough.
- (b) That other known viral agents are responsible, e.g., hepatitis 'A', EB virus cytomegalo virus.
- (c) That other, as yet unknown viruses, cause a significant amount of post transfusion hepatitis which is supported by the recent work of Feinstone et al (4).

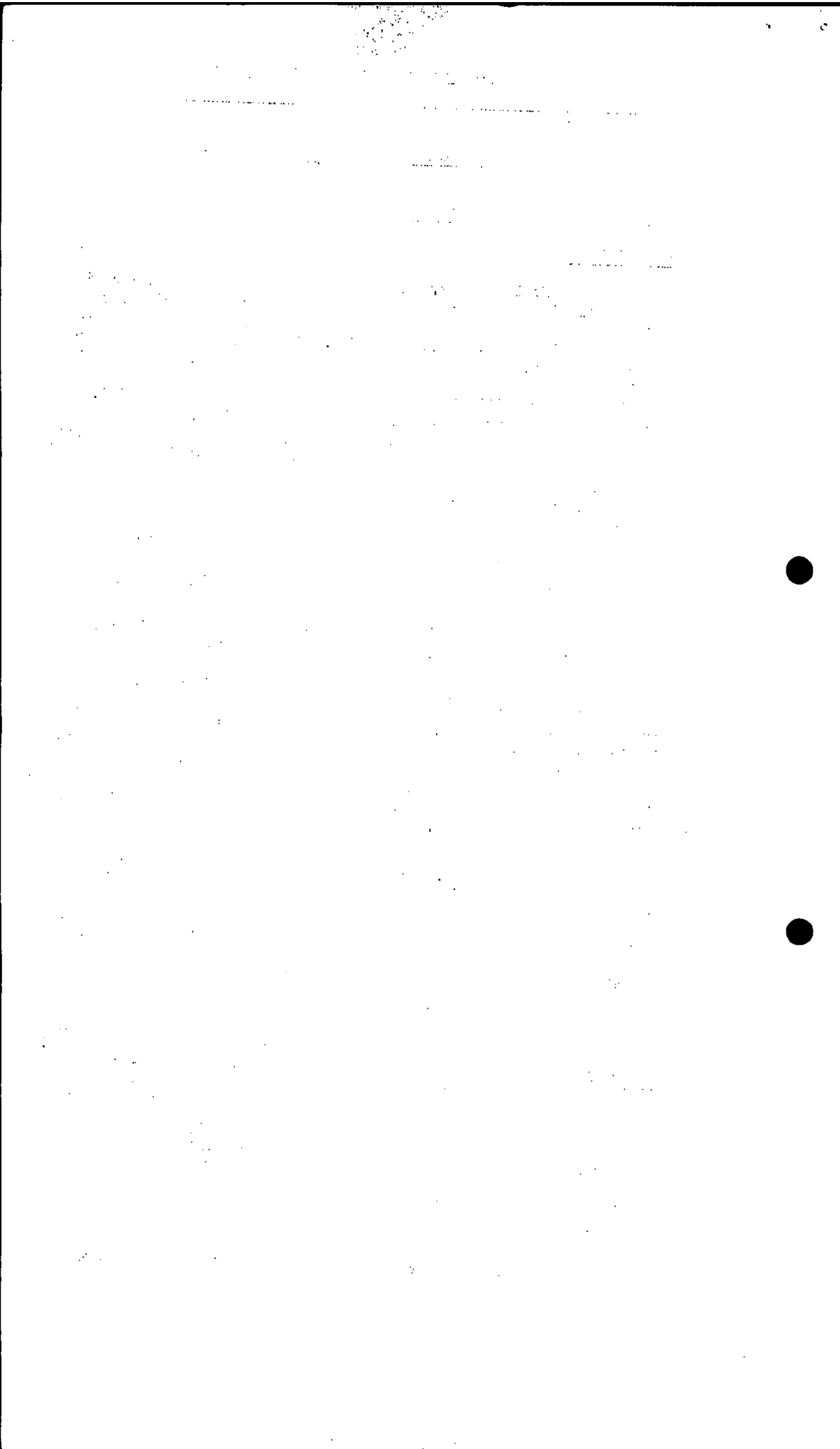
The introduction of large pool factor VIII concentrates into the routine management of haemophiliacs has revolutionized their treatment. Surgical procedures can now be safely performed since the therapeutic level of factor VIII necessary can be accurately predicted. Furthermore, the treatment of bleeding episodes in patients with inhibitors to factor VIII has been made possible since high concentrations can be given in a relatively small volume. Home therapy programmes have been possible because of the stability of these products, which do not require low temperature refrigeration. However, treatment with factor VIII concentrates does expose the patient to a much larger risk of contracting transfusion hepatitis since the fractionated product is processed from donor pools. Furthermore, commercial factor VIII concentrates are made from very large pools of some 2,000 - 6,000 litres of plasma from paid donors. An outbreak of both non-'B' hepatitis and 'B' hepatitis associated with concentrates of this type has recently been reported by Craske et al (5).

It has been suggested by Prince (6) that recipients of all commercial blood have a ten-fold higher risk of developing non-'B' post transfusion hepatitis than recipients of all volunteer donor blood. For these reasons it is proposed to conduct a prospective study of hepatitis in order that the following question will be answered :

"Does the administration of factor VIII concentrates to haemophiliacs on regular replacement therapy, significantly increase the incidence of transfusion hepatitis?"

It is hoped that the following additional points will emerge from this study :

- (a) Any difference in the attack rates between commercial factor VIII concentrates and home-produced concentrates, viz., Oxford and Elstree.



- (b) The assessment of the value of a positive HBsAb test in the protection of the patient from the development of hepatitis.
- (c) Further information on hepatitis due to unknown viruses or agents other than hepatitis 'A', 'B', EB or cytomegalo virus.
- (d) The role of R.I.A. testing for HBsAg of factor VIII concentrates in the prevention of post transfusion hepatitis 'B'.

#### METHOD

At present, the Treloar, Newcastle and Oxford Haemophilia Centres have agreed to co-operate in this study and Directors, or others deputising for them, will select patients for each of the following treatment groups :

<u>CENTRE</u>	<u>Cryopre- cipitate</u>	<u>CONCENTRATES</u>			
		<u>Kryobulin</u>	<u>Hemofil</u>	<u>Elstree</u>	<u>Oxford</u>
Alton	20	10	-	5	-
Newcastle	-	-	40	-	-
Oxford	-	-	10	-	15

Patients will be categorized as mild or severe in relation to their bleeding frequency and will, as far as possible, be allocated evenly over the various treatment groups. In practice this will not be feasible since there will be a tendency to use concentrates for patients having HBsAb or HBsAg and cryoprecipitate for those who are antibody negative. Each patient will be treated with the same type of material throughout the study and where possible, batches should be arranged sequentially in order that the patient may receive the same batch of his particular brand over a period of three months. This will be difficult to achieve and the co-operation of the manufacturers has been sought in making large batches available.

#### Eligibility Criteria :

- (a) All patients with classical haemophilia on regular replacement therapy are eligible for inclusion. Patients with factor VIII antibodies, or mild haemophiliacs not on regular replacement therapy, will be excluded.
- (b) Patients for whom major surgical procedures are planned will be excluded.
- (c) In the case of the Alton group, Lord Mayor Treloar College boys must be able to complete three academic terms or otherwise be excluded.
- (d) It is preferable that on entry the patient has normal liver function as measured by Serum Bilirubin, S.G.O.T./P.T. and Alkaline Phosphatase. However, abnormal results by these parameters will not exclude a patient from admission.
- (e) Each patient admitted must remain on the allotted therapeutic material for a minimum time of eighteen months. In the case of the College boys, arrangements will be made with their home centres that the allotted material is available for treatment during the vacations.

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- (f) All patients or their parents/guardians must give their informed consent. The following points will be made clear :
- (i) By limiting the transfused material to one type, the degree of donor exposure should be decreased
  - (ii) That it will be necessary for blood samples to be taken at fortnightly intervals. In the Oxford and Newcastle groups local arrangements must be made to obtain the requisite samples, since these patients are all on home therapy.

#### PROCEDURE

Entry - After the eligibility criteria have been satisfied, the study will commence for an individual patient on the day he attends either for routine replacement transfusion or to collect home treatment supplies. Prior allocation to a therapeutic material will have been made by the appropriate Director. Baseline clinical and laboratory information will be recorded on Form C.1, which on completion should be returned to Dr. Peter Kirk.

Blood samples will be collected and separated into two aliquots of 10mls. One will be assayed locally for bilirubin, S.G.O.T. and alkaline phosphatase; the other 10mls. will be allowed to clot and the serum separated and stored frozen - the date of the sample being recorded.

Data Recording - When blood has been obtained from all members of that particular treatment group Form C.5 should be completed and forwarded, with the samples, to Dr. Y. Cossart at Colindale. HBsAg and HBsAb tests will be performed and the results recorded on Form C.5; one copy being sent to the home centre and the other to Dr. Peter Kirk. The results of the baseline L.F.T.'s will be recorded on Form C.2. This form should be used to record all the routine transfusions received by an individual patient, either at his Centre or by home treatment. In the latter case it is suggested that the patient is given this form and records the date, time of transfusion, site of bleed, dose and batch number administered.

Illness - In the event of a patient developing symptoms suggestive of hepatitis, particularly non specific ones such as dyspepsia or a 'flu-like illness, Form C.3 should be completed. Serum and faecal samples should be collected and forwarded to the Virus Reference Laboratory. This procedure should be followed if the liver function tests suggest hepatitis.

In the outbreak of non-'B' hepatitis, which occurred last year at Lord Mayor Treloar College, it was found that the period of illness and abnormal liver function tests was relatively short. In one case, signs, symptoms and laboratory tests reverted to normal in ten days. Hence, should a patient become ill it will be necessary for serial blood samples to be taken for L.F.T.'s - perhaps twice weekly, depending on the clinical state of the patient.

The Sickness Record Form (C.3) incorporates all the information which has hitherto been completed on Form 3 of the M.R.C. Cryoprecipitate Working Party. For the patients involved in this study it will only be necessary to complete the Sickness Record Form. However, should hepatitis occur during the first six months after entry, it will be necessary to record the transfusion history on M.R.C. Form 1 for the relevant period.

Treatment - Lord Mayor Treloar College boys require special arrangements for their treatment during the Christmas, Easter and Summer vacations to ensure continuity of therapy. College boys on concentrates have been selected from the following Centres only - Oxford, The Royal Free

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1. The first part of the document discusses the importance of maintaining accurate records of all transactions.

2. It is essential to ensure that all data is entered correctly and consistently.

3. The following table provides a summary of the key findings from the analysis.

4. The results indicate a significant increase in efficiency over the period.

5. The data shows a clear trend towards improved performance.

and Newcastle. Arrangements are being made with these Centres that the boys receive only the therapeutic material to which they have been allotted. Those boys on cryoprecipitate have been selected from treatment centres where only this material is available.

In the event of treatment being required at centres other than the above mentioned, e.g., annual holidays, it will be necessary for the patient to carry with him an adequate supply of his allotted concentrate. Additionally, he will have a supply of printed postcards which will be completed and posted at the time of transfusion by the Centre staff. Any deviation from the prescribed material should, therefore, be apparent. Should a patient be transfused with material other than his allotted type, data will only be assessed up to this point. He will continue in the study until six months have elapsed after the date of this transfusion.

Commercial manufacturers, viz., Travenol Laboratories and Serological Products have agreed to reserve large batches of concentrates for this study. The Directors, or their deputies, will be responsible for ensuring that a patient receives only his allotted material for a period of eighteen months after entry. Batches should be arranged so that an individual receives preferably only one batch over a three month period.

HBsAg Testing of Concentrates - A sample of each batch of every type of concentrate used should be forwarded to Dr. D. McGrath at the National Institute for Biological Standards, Holly Hill, Hampstead, London, NW3, where they will be tested by a radio-immunoassay technique.

Analysis and End of Study - The records will be analysed at regular intervals and the study will be completed if a statistically significant difference (at the 5% level) is found between the attack rates of hepatitis among patients who have been treated with the different preparations of factor VIII concentrate.

Possible Future Extension of Study - It is proposed to acquaint all the United Kingdom Haemophilia Directors with this pilot study on the 18th September, 1975, in Glasgow, and invite their participation. Should they agree, the Protocol will be adhered to, apart from the differences stated below :

- (a) Fortnightly samples will be collected but not sent to the Virus Reference Laboratory. Samples will be stored frozen, at the home centre.
- (b) In the event of illness, the Sickness Record Form will be completed and arrangements will be made to retrospectively test the stored serum samples at the Virus Reference Laboratory.

#### SUMMARY

Although this is, in principle, a simple study the operation and organization of batches of material will present some problems. However, the actual units of factor VIII used will be no greater than in the normal day to day treatment and the study may indeed be viewed as a rationalization of replacement therapy, since the probable donor exposure to each participant should be less than that experienced prior to his entry to this study.

RJK/RCS  
September 1975

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REFERENCES

1. Prince, A.M.: An antigen detected in the blood during the incubation period of serum hepatitis. Proc. Nat. Acad. Sci., Wash 60: 814-821 (1968).
2. Goldfield, M.; Bill, J.; Elack, H.; Pizzute, W. and Srihongse, S.: Hepatitis associated with the transfusion of HB Ag negative blood. In: Hepatitis and blood transfusion, p. 353-361. Ed. G.N. Vyas, H.A. Perkins and R. Schmid (Grune and Stratton, New York, 1972).
3. Helske, T.: Carriers of hepatitis 'B' antigen and transfusion hepatitis in Finland. Scand. J. Haematol., Suppl. 22 (1974).
4. Feinstone, S.M.; Kapikian, A.Z.; Prucell, R.H. et al.: Transfusion associated hepatitis not due to viral hepatitis type 'A' or 'B'. New Engl. J. Med. 292: 767-770 (1975).
5. Craske, J.; Dilling, Nancy; Stern, D.: An outbreak of hepatitis associated with intravenous injection of factor VIII concentrate. Lancet ii 221-222 (1975).
6. Prince, A.M.: Post transfusion hepatitis: Etiology and prevention. In: Transfusion and Immunology, 1975, p.88.

