1. a) No organised clinical trials with Antihaemophilic Factor (Human) Method Four have been carried out in Great Britain. The product has, however, been administered to two patients in an emergency situation by Dr. G. I. C. Ingram, Department of Haematology, Louis Jenner Laboratories, St. Thomas' Hospital and Medical School, London S.E.1., and the results of these successful treatments are attached in Appendix 1.

The mean single dosage administered to the two patients was 4,424 AHF units and ranged from 2,300 to 5,750 units.

Both patients were successfully treated and eventually discharged from hospital. Some shivering and vomiting was observed in one patient after the initial doses of HEMOFIL but there were no subsequent reactions during treatment of from the second patient.

It was concluded that HEMOFIL allowed an adequate level of treatment in a situation where supplies of cryo-precipitate were limited.

1. The patient, an 80 Kg. male, received six infusions of antihaemophilic Factor (Human) totalling 18,500 AHF units. Each dose averaged 3097 AHF units and ranged from 2,300 to 4,480 units.

   Shivering and vomiting occured initially, but was relieved with chlorpheniramine maleate.

   The use of the AHF concentrate was most valuable

2. The patient, a 55 Kg. male, with an anti-Factor VIII antibody 240 Biggs-Bidwell units received two single doses of 6,900 AHF units and 4,600 units respectively (mean dosage 5,750 units)

   No reactions were reported, the large dose of HEMOFIL allowed neutralisation of the inhibitor and a reasonable response was obtained.

b) 1. 1. Since the product became available in the United States of America , a considerable amount of research in that country has been completed and published in the medical literature.

and 2. During a period of one year (1968 - 1969) a world-wide group of investigators treated a total of 54 patients with 127 infusions of the AHF concentrate. More than half of these patients received multiple infusions.

1. b)

One patient received 26 infusions totalling 29,718 units of AHF in a two week period.

4. The dosage employed in these trials ranged from 15 AHF units per kilogramme to 69 units per kilogramme with a mean of 40 units per kilogramme of body weight.

5. Results of the trials confirmed that after infusion of Factor VIII in concentrated form cessation of haemorrhage is prompt and post-transfusion levels of circulating Factor VIII approach normal values.

6. No allergic reactions were observed and fibrinogenaemia or hypervolaemia were not a problem.

7. It may be concluded that the advantages of haemophilia therapy using this new Antihaemophilic Factor (Human) Method Four concentrate are:

i) A higher potency of Factor VIII is contained in small volumes.

ii) Exact standardisation of AHF activity makes possible calculations of dosage necessary to produce the desired increase in circulating AHF levels.

iii) Sufficient amounts of the concentrate may be administered to patients with inhibitors to AHF, thus eliminating the need for bovine or porcine preparations.

iv) The AHF preparation can be given rapidly either by intravenous drip infusion or direct syringe injection thus reducing patient hospitalisation.

v) The concentrate may be used to prophylactically treat haemophilia A, thus preventing minor bleeding episodes by maintaining normal haemostasis.

2. Copies of five publications which report the results of a large proportion of these studies are included in Appendix 1

2. A. Shanbrom E., Fekete L. and Tse D: Modern treatment of Haemophilia with a potent, new AHF concentrate. Bibl. Haemat. 1971 38 854

1. Treatment of nineteen selected patients, with a history of allergic reactions to plasma products, who were actively bleeding at the time of AHF infusion.

2. All patients survived the treatment

3. The calculated dosage for these patients was 40 units of AHF per kilogramme of body weight.

4. Prompt cessation of haemorrhage was observed in all patients after infusion of the Factor VIII concentrate and the desired level of circulating Factor VIII was achieved.

5. No allergic reactions were observed in spite of previous histories of sensitisation. Neither Fibrinogenaemia nor hypervolaemia occured.

6. Ideally an AHF fraction should:

i) have high activity
ii) be inert antigenically
iii) have effective duration in vivo
iv) be stable for long periods
v) have no risk of hepatitis
vi) not induce anticoagulants or inhibitors
vii) be low in cost and readily available
viii) be effective intramuscularly

Antihaemophilic Factor (Human) Method Four fulfills most of these criteria. There remains a slight hepatitis risk with any such product from human plasma and at present the preparation must be administered intravenously.

B. Shanbrom E: Rapid correction of AHF deficiency by Antihaemophilic Factor (Human) Method Four, with special reference to inhibitors. Bibl. Haemat. 1970 34 52.

1. Clinical data is presented for three patients with circulating AHF inhibitors.

2. All patients completed the study

2. B. Continued

3. Total units of AHF infused ranged from 7,200 to 34,845 with a mean of 25,189.

4. Post-infusion levels of AHF and clotting times of patients were satisfactorily corrected.

5. No adverse reactions or contraindications were reported.

6. The predictable treatment of patients with AHF inhibitors is possible.

C. McMillan C.W., Webster W.P., Roberts H.R. and Blythe W.B.: Continuous intravenous infusion of Factor VIII in classic haemophilia. Brit. J. Haemat. 1970 18 659.

1. The effects of intravenous infusion of Factor VIII was studies in five children.

2. All patients completed the study

3. Three regimens of Factor VIII replacement therapy (steady infusion and two intermittent treatment) each totalling 50 - 51 AHF units per kilogramme per day were examined.

4. A steady level of circulating Factor VIII was maintained with continuous infusion. The level was approximately three times that attained from intermittant therapy.

5. Fibrile reactions which could not be related to sepsis were observed and controlled with oral diphenhydramine hydrochloride.

6. Continuous intravenous infusion of Factor VIII is a useful method for providing more precise replacement therapy in haemophilia.

D. Shanbrom E., and Thelin G.M.: Experimental prophylaxis of severe haemophilia with a Factor VIII concentrate. J.A.M.A. 1969 208 1853

1. A long term prophylactic study on one 39-year old sever haemophiliac.

2. D. Continued

2. Nineteen months after maintenance therapy with Antihaemophilic Factor (Human) the patient died.

3. Weekly prophylactic doses of approximately 2,300 units AHF were administered per infusion.

4. During the first 12 months of therapy no haemarthrosis or obvious bleeding tendencies were noted.

5. Hyperfibrinogenaemia or hypervolaemia were not observed furing therapy. Just before his death the patient exhibited a slight chilling reaction and fever from the last three or four infusions.

6. Observations in subsequent patients suggest that the widespread terminal haemorrhages exhibited by the patient under study could have been associated with active fibrinolysis. However, the patient's response to the new AHF concentrate was so predictable that a reliable formula for prophylactic dosage was developed. Routine prophylaxis of severe haemophilia may now be practical.

E. Honig, G.R., Forman E.N., Johnston C.A., Seeler R.A., Abildgaard C.F. and Schulman I: Administration of single doses of AHF (Factor VIII) concentrates in the treatment of haemophilic haemarthroses. Paediatrics 1969 43 26

1. Fourteen boys with severe or moderately severe AHF-deficient haemophilia were included in the studies.

2. All patients completed the course of treatment.

3. The mean dosage was 30 AHF units per kilogramme of body weight and ranged from 15 - 69 units per kilogramme

4. Immediate post-infusion levels of circulating AHF up to 142% of normal were achieved

5. No adverse reactions were recorded from single dose administrations of concentrate

2. E. Continued

6. Antihaemophilic Factor (Human) Method Four is comparable to other forms of AHF in its dose response relationship and its in vivo survival.

Other publications which describe the pharmacological action and therapeutical indications of Factor VIII are:

Robboy S.J., Lewis E.J., Schur P,H., Colman R.W.: Circulating anticoagulants to Factor VIII. Immunochemical studies and clinical response to Factor VIII concentrates. Amer. J. Med. 1970 49 742 - 752

Antihemophilic factor (human) (Hyland). Amer. J. Nursing 1968 68 131-133

Abildgaard C.F., Simone J.V., Corrigan J.J., Seeler R.A., Edelstein F, Vanderheiden J, Schulman I : Treatment of hemophilia with glycine-precipitated factor VIII. New Eng. J. Med. 1966 275 471 - 475

Brinkhous K.M., Shanbrom E, Robers H.R., Webster W.P., Fekete L, Wagner R.H.: A new high-potency glycine-precipitated antihemophilic factor (AHF) concentrate. J.A.M.A. 1968 205 613 - 617

Hirschman R.J., Itscoitz S.B., Shulman N.R.: Prophylactic treatment of factor VIII deficiency. Blood 1970 35 189-194

Dallman P.R., Pool J.G.: Treatment of hemophilia with factor VIII concentrates. New Eng J. Med. 1968 278 199-202