

VIII:C AND VIII:CAg RESPONSE IN HAEMOPHILIA A AFTER INFUSION OF F VIII CONCENTRATES, FRESH CITRATED PLASMA OR HEPARIN PLASMA. I.M. Nilsson, L. Holmberg, L. Borge and A.C. Kristoffersson. Department for Coagulation Disorders, Allmänna Sjukhuset, Malmö, Sweden

VIII:C (one-stage) and VIII:CAg (solid phase IRMA using both two homologous nonhaemophilic antibodies and a haemophilic antibody against VIII:C, Holmberg et al 1979, Scand. J. Haemat. 23, 17) were studied in 8 patients with severe, and 2 with mild, haemophilia A after administration of 3 different f VIII concentrates (AHF-Kabi, Hemofil, high purity Factorate) or fresh citrated plasma or heparin plasma. The recovery of VIII:C was about the same for all the preparations (70-100 %), but that of VIII:CAg considerably less (30-50 %). When the concentrates were added in vitro to the haemophilia plasma (the patients all multitransfused) the recovery of VIII:C was about 100 % but that of VIII:CAg only 30-50 %. In normal plasma the recovery of VIII:CAg was 100 %. When the concentrates were added to haemophilia plasma depleted from IgG (protein A Sepharose) the recovery of VIII:CAg was about 100 %. This indicates that most haemophiliacs have antibodies reacting with the f VIII coagulant protein with little or no interference with the coagulant activity. The half-life of VIII:C was about 12 h, but that of VIII:CAg only 3 h or less. We also infused fresh citrated plasma into 2 haemophiliacs, but the results were the same. The response to transfusion observed in haemophilia indicates a change in the native properties of f VIII already on collection of blood. This might be due to the decalcification with citrate. Thus, in preliminary experiments using fresh heparin plasma the curves for the disappearance rate of VIII:C and VIII:CAg were parallel.

## 0589

10:30 h

POLYELECTROLYTE FRACTIONATED PORCINE FACTOR VIII CONCENTRATE IN THE TREATMENT OF HAEMOPHILIACS WITH ANTIBODIES TO FACTOR VIII:C. P.B.A. Kernoff, N.D. Thomas, P.A. Lilley and E.G.D. Tuddenham. Haemophilia Centre & Haemostasis Unit, Royal Free Hospital, London, England.

Antibodies to procoagulant factor VIII (anti-VIII:C) occurring in patients with haemophilia neutralise porcine factor VIII:C less readily than human factor VIII:C in vitro. Porcine factor VIII concentrate (porcine VIII) therefore has potential advantages in the treatment of such patients. Polyelectrolyte-fractionated porcine VIII (PE porcine VIII) lacks a major drawback of earlier preparations of porcine VIII in that it contains negligible quantities of platelet aggregating factor (PAF). The purpose of this study was to make a preliminary clinical assessment of the therapeutic value of PE porcine VIII. Over 6 months, 12 courses of treatment were given to four patients with circulating anti-VIII:C. Bleeding episodes treated ranged from the potentially lethal to moderately severe joint and muscle haemorrhages. Duration of courses was from 24 hrs. to more than 3 weeks. Clinical responses were strikingly good and no patient developed thrombocytopenia. Occasional mild pyrogenic-type transfusion reactions were encountered, but these were easily controlled. Dose-response relationships were most favourable in patients with low pre-infusion levels of anti-VIII:C activity against PE porcine VIII but excellent clinical responses could be obtained without achieving high plasma VIII:C levels. Multiple courses of therapy (up to 6) were given to individual patients without evidence of loss of clinical or laboratory efficacy, or an increased tendency to adverse reactions. There was no evidence of resistance in the patient who was treated daily for more than 3 weeks. Only 1 course of therapy was followed by a classical anamnestic rise in anti-VIII:C, and this course had included human factor VIII. PE porcine VIII appears to have a low immunogenic potential, and is a rational and effective therapeutic alternative for patients with anti-VIII:C.

## 0588

10:15 h

FACTOR VIII COMPLEX IN NON-HEMOPHILIC PATIENTS WITH ANTIBODY TO FACTOR VIII:C. M.P. Croissant and J.P. Allain. C.N.T.S., Paris, France.

An antibody to Factor VIII in non-hemophiliacs is a rare occurrence. The presence of low but detectable Factor VIII:C (VIII:C) and high Factor VIII antigen (VIII:Ag), together with high antibody levels, suggests a complex influence of anti-VIII:C on Factor VIII metabolism.

We have studied Factor VIII complex in 16 non-hemophilic patients with anti-VIII:C. VIII:C, VIII:Ag and VIII:Roof were measured by standard techniques and VIII:C antigen (VIII:CAg) by a liquid phase immunoradiometric assay using radio labelled anti-VIII:C Fab' fragments purified from a hemophiliac.

The plasma from all patients had low VIII:C (0.01 - 0.24 u/ml) and high VIII:Ag (1.4 - 8.8 u/ml) content. VIII:Roof was approximately 50% of the VIII:Ag level. An increase in electrophoretically fast-moving VIII:Ag was observed in some cases.

VIII:CAg was tested in 13 patients. Two patterns of the dose response were observed. In most samples obtained from patients with low affinity anti-VIII:C whose VIII:CAg ranged from 0.19 - 2.45 u/ml, the dose response paralleled that of the control. In patients with high affinity antibodies the dose response curve was less steep than control, suggesting a competition between the patient's antibody and the hemophilic anti-VIII:C Fab' fragments for the VIII:C antigenic sites.

The Factor VIII complex was studied sequentially in 3 patients during immunosuppression. The results showed that: 1) when VIII:C normalizes, VIII:Ag levels and electrophoretic mobility progressively return to normal; 2) levels of VIII:Ag are inversely correlated to the VIII:C irrespective of VIII:CAg levels; 3) high VIII:CAg levels correspond to VIII:C-anti-VIII:C circulating immune complexes.

In non-hemophilic patients low VIII:C, high VIII:CAg and high VIII:Ag indicate the presence of an anti-VIII:C inhibitor. Measurements of various components of Factor VIII in these patients are not only a means for monitoring the effect of therapy but also provide a rare opportunity to study the metabolism of Factor VIII in man.

## 0590

10:45 h

INCREASED CIRCULATING IMMUNE COMPLEX LEVELS IN HEMOPHILIA PATIENTS POST-INFUSION. M.W. Hilgartner, R.D. Inman, and C.H. Miller. Department of Pediatrics, New York Hospital-Cornell University Medical Center and Division of Rheumatology, Hospital for Special Surgery, New York, N.Y. U.S.A.

Elevated levels of circulating immune complexes (CIC) have been reported in a significant proportion of hemophilia patients tested by Raji cell, Clq binding, and staphylococcal binding (SBA) methods. The clinical significance of these complexes is unclear, as is their relationship to transfused material. By SBA, we found elevated CIC levels ( $>10$  ug/ml) in 90% of severe hemophiliacs and 75% of multiply-transfused controls, all more than 72 hours post-transfusion. This was in contrast to our previous finding elevated CIC in 50% of hemophiliacs and 29% of controls by Raji cell assay.

Using the SBA, seven patients were tested at intervals after Factor VIII concentrate infusion. Five showed increased CIC levels. The peak level occurred after the Factor VIII clotting activity had peaked and was declining. Two subjects showed rapid clearance of the complexes, while the others remained elevated at 24 hours. Factor VIII-related antigen was detected in isolated complexes from 2 patients. Our previous finding of HB<sub>2</sub>Ag in such complexes suggests heterogeneity and perhaps different clearance patterns.