MULTIPLE MOLECULAR FORMS OF FACTOR VIII ANTIGEN IN NORMAL INDIVIDUALS AND VON WILLEBRAND'S DISEASE PATIENTS. T.S. Zimmerman, J.J. Klubert, T.S. Edington and C.F. Allamode. Scripps Clin. & Res. Inst., La Jolla, California and Univ. of Calif., Davis, California, U.S.A.

Factor VIII antigen is present in normal individuals in multiple molecular forms which can be separated according to size. The intermediate and larger forms preferentially bind to platelets in the presence of ristocetin. In order to evaluate the possibility that Factor VIII antigen forms of large size may be an artifact of in vitro aggregation, we have ultracentrifuged plasma on a 20% sucrose cushion at 37°C for 10 min at 350,000 xg (peak). The rate of clearing of Factor VIII antigen was compared to that of IgM, fibrogen, IgG, α1-antitrypsin and the S rate calculated to be between 15 and 18. These results indicate that Factor VIII-related antigen forms of high S exist even when plasma is maintained at physiological temperature and analyzed with minimal delay, suggesting that these large molecular forms also exist as such in vivo.

Two types of von Willebrand's disease (VWD) have been identified according to size of Factor VIII antigen forms present in plasma. In Type I all forms of Factor VIII antigen are present but are decreased in quantity. In Type II large forms are missing and smaller forms are present in normal or increased quantities. Factor VIII antigen was isolated from plasma of one patient with Type I and two patients with Type II VWD by counter immunoelectrophoresis. The Factor VIII antigen was then reduced and electrophoresed on SDS-containing polyacrylamide gels. The presence of carbohydrate was evaluated by staining with periodic acid-Schiff's reagent (PAS). The 210,000 MW Factor VIII antigen subunit from each patient was PAS-positive. Though subtle changes in carbohydrate content or composition could not be evaluated by this technique, a total defect of glycosylation is unlikely in this small sample of VWD patients.


The recent advent of techniques to purify the factor VIII/von Willebrand factor (F.VIII/VWF) protein from plasma to quantitate the F.VIII/VWF protein and to measure the VWF (plasma ristocetin cofactor) have greatly added to our understanding of von Willebrand's disease (VWD). The initial studies of antigen, procoagulant and VWF levels revealed a parallel reduction in all three activities in VWD suggesting a qualitative deficiency of the F.VIII/VWF protein and its bioologic activities.

Recent studies, however, have suggested three major forms of VWF. The first group of patients have a quantitative defect with a parallel reduction of the F.VIII/VWF protein and of the antigen, VWF and procoagulant activities. The second group of patients appear to have a qualitative defect of the F.VIII/VWF protein. These individuals have normal levels of the antigen and procoagulant activity; however, the VWF activity is reduced or absent. The third group of patients have a combination of a qualitative and quantitative deficiency. These variants resemble both previous groups in that there are reduced levels of the antigen, procoagulant and VWF activities, but usually greater reduction of the VWF activity.

Three major defects of the F.VIII/VWF protein have been recognized in VWD: 1) decreased plasma concentration of the F.VIII/VWF protein, 2) the apparent molecular weight of the protein is decreased and/or the largest molecular weight polymers are absent, and 3) there is a partial or total carbohydrate deficiency. For the F.VIII/VWF protein to express VWF activity, it must be of a minimal molecular size and have a specific carbohydrate content and/or sequence.