

HETEROZYGOSITY AND HOMOZYGOSITY IN VON WILLEBRAND'S DISEASE : A STUDY OF 108 CASES. I. Shoa'i, J.-M. Lavergne, N. Ardailou, F. Ala and D. Meyer. Institut de Pathologie Cellulaire, Hôpital de Bicêtre, Paris, France and Iranian National Blood Transfusion Service, Tehran, Iran.

Factor VIII/Willebrand Factor (F.VIII/WF) resides on a multimeric glycoprotein under autosomal control. Von Willebrand's disease (vWd) may be related to a quantitative (inability to produce F.VIII/WF) or to a qualitative defect (production of an abnormal F.VIII/WF). The study of 108 cases illustrates the various genetic defects. In 33 cases from 21 families, the severity of the disease was consistent with a homozygous state. All showed a total lack of Factor VIII related antigen (VIII:AG) by immunoradiometry, contrasting with low (1-5%) but detectable Factor VIII procoagulant activity (VIII:C). 4 of these patients developed antibodies which precipitated VIII:AG and neutralized Willebrand Factor activity (VIII:WF). In 16 of these 21 families, the parents were first cousins and 84% of the 48 relatives studied showed an abnormally high ratio of VIII:C to VIII:WF -together with a qualitatively normal protein- consistent with a heterozygous state. A further 8 unrelated patients showed a less severe defect (5-20% of VIII:C, VIII:AG and VIII:WF) with a qualitatively normal protein. The remaining 19 patients had higher levels of VIII:AG than of VIII:WF and a qualitatively abnormal protein as demonstrated by electrophoretic mobility, agarose elution pattern, precipitation by concanavalin A and dose-response curve by immunoradiometry.

Thus we document homozygotes and three types of heterozygotes : a) parents of homozygotes, with reduced amounts of a normal protein; b) heterozygotes with 5-20% of a normal F.VIII/WF; c) heterozygotes with a "variant" of vWd, i.e. a qualitatively abnormal protein.

ELECTRON MICROSCOPIC STUDIES OF THE FACTOR VIII-VON WILLEBRAND FACTOR PROTEIN. V.J. Marder, L. Tranqui-Pouit, G. Hudry-Clergeon, V. Atichartakarn and M. Sussillon, Dept. of Medicine and the Specialized Center of Research in Thrombosis, Temple University, Philadelphia, Pa. and the Laboratoire d'Hématologie, Centre d'Etudes Nucleaires, Grenoble, France.

Preparations of human Factor VIII which were homogeneous by SDS-polyacrylamide gel electrophoresis were examined by electron microscopy after negative staining with phosphotungstic acid. Most striking were large oval and circular forms, usually present in loose groupings of four or more molecules. Approximately 80% were oval-shaped and the mean axial dimensions of 167 such molecules, considered to be prolate ellipsoids, were  $725 \text{ \AA}$  and  $346 \text{ \AA}$  (axial ratio about 2:1). The 34 circular forms had a mean diameter of  $545 \text{ \AA}$  and were considered to represent a separate though related molecular entity, either of spherical or oblate ellipsoidal shape. A variety of smaller forms was also present in these preparations including round molecules of 110-330  $\text{ \AA}$  in diameter, irregular ovoid shapes with filamentous transformation and filaments of variable length and thickness. Based on calculations of volume relative to that of fibrinogen, the molecular weight of the predominant prolate ellipsoid form is about 3 million daltons, a value which is consistent with reported estimates of molecular size obtained by ultracentrifuge or gel filtration studies.