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0673 REDUCED POLYMERIZATION OF FACTOR VIII/VON WILLEBRAND FACTOR IN VARIANTS OF VON WILLEBRAND'S DISEASE.

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F.VIII/vWF was isolated from plasma (1-3 ml) by preparative counter immunoelectrophoresis using rabbit anti-human F.VIII/vWF IgG. F.VIII/vWF was separated from IgG in the immunoprecipitants, without reduction, by SDS-1% agarose electrophoresis and analyzed by scanning at 540 nm. Multiple forms of F.VIII/vWF were observed in a series of increasing M.W. ($1\text{-}10.10^6$) when testing normal (n = 5) and hemophilia A (n = 2) plasmas, cryoprecipitate (n = 3), or purified F.VIII/vWF (n = 3). Glutaraldehyde cross-linked IgM was used as marker. In classical vWD (n = 3), all molecular forms of F.VIII/vWF were present but in reduced quantities. In such cases, VIII:C, VIIIR:Ag (Laurell and I.R.M.A.) and VIIIR:RCo were reduced to the same extent (30-40%) and there was no qualitative abnormality of F.VIII/vWF. In variants of vWD (n = 4, unrelated cases), only the 5 bands of lower M.W. ($1\text{-}5.10^6$) were present and in greater amounts than normal. These patients also lacked VIIIR:RCo and showed an abnormal 125-I-radio-crossed immunoelectrophoretic pattern (lack of the large, slow-moving, forms of VIIIR:Ag) and an abnormal dose response curve by I.R.M.A.. Similarities of the results by SDS-agarose electrophoresis in cryo-supernatant (n = 4), prepared from normal plasma, and in variants of vWD suggest that F.VIII/vWF demonstrates a reduced polymerization of the apparently normal lower M.W. multimers. This study provides a molecular basis for the different types of vWD.

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0674 APPARENT 'DOMINANT' AND 'RECESSIVE' INHERITANCE OF VON WILLEBRAND'S DISEASE (VWD) WITHIN THE SAME KINDREDS. POSSIBLE BIOCHEMICAL MECHANISMS

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In each of two vWd kindreds the inheritance pattern exhibited both 'recessive' and 'dominant' features. In one family a severely affected patient had factor VIII clotting activity (VIIIC) 0-1u/dl, factor VIII related antigen (VIIIRAg) <0.01u/dl, ristocetin co-factor (VIIIRiCoF) <3u/dl, and bleeding time (BT) >15 min. He developed an inhibitor to VIIIRiCoF during cryoprecipitate (cryo) treatment. His VIIIC response to cryo (? large aggregate VIIIRAg) was much less than to Hemofil (? smaller aggregate VIIIRAg) and the antibody inhibited cryo-VIIIRiCoF more than Hemofil-VIIIRiCoF. He had symptomless related parents both of whom had slightly reduced levels of VIIIRAg and he apparently had homozygous recessive disease. However another affected family member had apparently typical heterozygous vWd (VIIIC 9u/dl, VIIIRAg 3u/dl, VIIIRiCoF <3u/dl, BT >15 min). Similarly in the second kindred both a severe(VIIIRAg <0.01u/dl) and also moderately affected patients with classical intermediate vWd were present (eg VIIIRAg 20u/dl). Consanguinity was not demonstrable in the extren patient's symptomless parents but their levels of VIIIRAg were slightly reduced. It is suggested that this mixed inheritance may be associated with the fact that VIIIRAg/RiCoF exists as a series of homologous oligomers of which the largest exhibit greatest platelet-related activities. The variable inheritance pattern may be due to interaction between maternally and paternally derived protomers or related biosynthetic pathways so that various series of oligomers are produced in the offspring.

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0675 ABNORMAL FACTOR VIII MOLECULE IN MILD VON WILLEBRAND'S DISEASE.

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In 22 cases with normal levels of the three entities of factor VIII (VIII:C, VIIIR:AG and VIIIR:WF), FVIIIR:AG showed a faster anodal mobility and a lower concentration measured by immunoradiometric assay than that found with Laurell's immunoelectrophoresis. Moreover, the factor VIII protein elution by agarose gel filtration of plasma and cryoprecipitate was delayed. Seven of those cases belong to a family in whom one of the member showed frequent bleeding episodes. In these individuals the FVIIIR:AG precipitation with Concanavalin A was determined and appeared decreased.

On the other hand in 19 out of 20 subjects with classic moderate von Willebrand's disease (in whom the three entities of factor VIII were occasionally reduced in parallele), FVIIIR:AG also showed a faster anodal mobility and the factor VIII protein elution by agarose gel filtration was delayed.

All these results suggest that patients with moderate von Willebrand's disease show a qualitatively deficient factor VIII molecule synthesis, while the mildest cases may have normal levels of the three entities of the factor VIII .