Introduction

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When Eric von Willebrand, almost 80 years ago, first described a family with a new hemorrhagic disease, he could hardly imagine that his seminal discover was opening new frontiers of research in a fascinating area of investigation, still very active and fruitful at the beginning of the third millennium. Moving from the recognition, in early '70, that the intriguing bleeding disorder called after his name (von Willebrand disease, VWD) is caused by quantitative or qualitative defects of the plasma protein von Willebrand factor (VWF), we are now understanding more and more its molecular structure, functional domains, multimeric assembly and pleiotropic functions. VWF is produced by megakaryocytes for storage in platelet α-granules and by endothelial cells in Weibel-Palade bodies, as a fully processed and multimerized molecule. From the sites of storage VWF is secreted in a highly regulated manner into plasma or abluminally to form a component of the subendothelial matrix. VWF has a double action. The first is initiation of hemostasis at the site of vascular injury, by promoting platelet adhesion to the subendothelium and platelet aggregation. The second is to act as carrier of factor VIII (FVIII), thus protecting this factor from proteolytic inactivation and increasing its concentration within the forming hemostatic plug. These properties explain why hemorrhage or thrombosis may be favoured by reduced or enhanced activity of VWF. More recently, the critical role of the molecular size of VWF has become clear by the demonstration that ultralarge, highly thrombogenic multimers secreted by endothelial cells need to be reduced in size by a specific plasma metalloprotease called ADAMTS-13. Congenital or acquired defects of this enzyme are associated with the occurrence of intravascular platelet-rich thrombi in patients with thrombotic thrombocytopenic purpura. The crucial role of VWF and the delicate balance that should be maintained between its diverse functions require highly regulated processes to control its synthesis, post-translational modifications, cellular processing, secretion and interactions with other hemostatic proteins.

In this regard, the topics of this symposium are good examples of exciting new findings in basic and clinical research.

As shown by Lillicrap the genetics of VWD remains a fascinating field of investigation and an instructive example of the structure/function relationship occurring in a complex multidomain oligomeric protein. The genetic background of the partial quantitative deficiency of VWF (VWD type 1), continues to be intriguing and baffling, in spite of the fact that a European and a Canadian study (the latter led by the author) have completed an initial evaluation of enrolled families and underlying genetic defects. However, it seems already clear that in a large proportion of affected families no linkage to VWF gene locus can be found, calling for other genetic or epigenetic causative factors. Furthermore, in those with identified mutations very few recurring mutations are detected, thus making of little use a diagnostic approach to VWD based upon genotyping. Clinical skilfulness in selecting cases that deserve detailed laboratory investigation to make a definite diagnosis, remains fundamental.

Haberichter and Montgomery introduce us into the intimacy of the mechanisms that regulate storage and the coordinated secretion of VWF and FVIII in plasma. They move from the clinical observation that desmopressin causes an immediate parallel increase of both substances in plasma when administered to normal subjects as well to patients with mild deficiencies of VWF or FVIII. In severe VWD, no VWF or FVIII are released by desmopressin whereas, in severe hemophilia A VWF but not FVIII is released. On the basis of these observations and the lack of exchange between infused FVIII/VWF and storage compartments, as shown by transfusion experiments in severe VWD and hemophilia A patients, they come to the concept of a single releasable pool of both

FVIII and VWF that implicates the endogenous synthesis of both factors. With sophisticated experiments implying co-culture of human cells engineered with genetic constructs encoding for FVIII or for the propeptide and/or mature subunit of VWF followed by confocal microscopy analysis, they demonstrate that the propeptide is essential for VWF storage and that co-storage of FVIII in endothelial cells does occur only if it is synthesized in presence of VWF. Furthermore, although the liver appears to be the organ responsible for constitutive factor VIII production, it is not responsible for its releasable pool, as shown by the failure of desmopressin to release FVIII in severe hemophilia A patients after liver transplantation. Co-synthesis and co-storage of both FVIII and VWF in the same cell would reconcile all the experimental evidences but such a cell remains elusive at the moment.

Federici *et al.* discuss the efficacy and safety of secondary long-term prophylaxis in VWD on the basis of their experience in a small cohort of patients treated in Milan. They place this new approach in the right perspective by showing that among 452 patients in their database, 20% of cases needed at least one treatment with FVIII/VWF concentrates during the last 2 years, but only 12% of them (2.4% of the initial cohort, mainly type 3 cases because of hemarthrosis or type 2 cases because of gastrointestinal bleeding caused by angiodisplasia refractory to on demand treatment) met the criteria for inclusion in the prophylaxis program. Thus clinicians should be aware of this possibility, which remains experimental until the results of ongoing prospective international studies are available.