circulation, it binds to vWF, which is produced by endothelial cells and, to a lesser degree, by megakaryocytes, which are the source of the vWF that is found in platelet α-granules. vWF stabilizes factor VIII, which has a half-life of about 2.4 hours when free and 12 hours when bound to vWF in the circulation.

Circulating vWF exists as multimers containing as many as 100 subunits that can exceed 20×10^6 daltons in molecular mass. In addition to factor VIII, these multimers interact with several other proteins involved in hemostasis, including collagen, heparin, and possibly platelet membrane glycoproteins. The most important function of vWF is to promote the adhesion of platelets to the subendothelial matrix. This occurs through bridging interactions between platelet glycoprotein Ib-IX, vWF, and matrix components such as collagen. Some vWF is secreted from endothelial cells directly into the subendothelial matrix, where it lies ready to promote platelet adhesion if the endothelial lining is disrupted (Fig. 14-26). Endothelial cells and platelets also release vWF into the circulation. Upon vascular injury, this second pool of vWF binds collagen in the subendothelial matrix to further augment platelet adhesion. vWF multimers may also promote platelet aggregation by binding to activated GpIIb/IIIa integrins; this activity may be of particular importance under conditions of high shear stress (such as occurs in small vessels).

Factor VIII and vWF protein levels are measured by immunological techniques. Factor VIII function is measured specifically by performing coagulation assays with mixtures of patient plasma and factor VIII-deficient plasma. vWF function is assessed using the ristocetin agglutination test. This assay is performed by mixing the patient's plasma with formalin-fixed platelets and ristocetin, a small molecule that binds and "activates" vWF. Ristocetin induces multivalent vWF multimers to bind platelet glycoprotein Ib-IX and form interplatelet "bridges." The resulting clumping (agglutination) of platelets is measured in a device called an aggregometer. Thus, the degree to which patient plasma promotes ristocetin-dependent platelet agglutination reflects the vWF activity of the sample.

Von Willebrand Disease

Von Willebrand disease is the most common inherited bleeding disorder of humans, affecting about 1% of adults in the United States. The bleeding tendency is usually mild and often goes unnoticed until some hemostatic stress, such as surgery or a dental procedure, reveals its presence. The most common presenting symptoms are spontaneous bleeding from mucous membranes (e.g., epistaxis), excessive bleeding from wounds, or menorrhagia. It is usually transmitted as an autosomal dominant disorder, but rare autosomal recessive variants also exist.

Von Willebrand disease is clinically and molecularly heterogeneous; several hundred vWF variants have been described, few of which have been formally proven to be disease-causing. Three broad categories of von Willebrand disease are recognized, each with a range of phenotypes:

- **Type 1 and type 3 von Willebrand disease are associated with *quantitative defects* in vWF. Type 1, an autosomal dominant disorder characterized by a mild to moderate vWF deficiency**, accounts for about 70% of all cases. Incomplete penetrance and variable expressivity are commonly observed, but it generally is associated with mild disease. **Type 3 (an autosomal recessive disorder) is associated with very low levels of vWF and correspondingly severe clinical manifestations.** Because a severe deficiency of vWF has a marked effect on the stability of factor VIII, some of the bleeding characteristics resemble those seen in hemophilia. Type 1 disease is associated with a spectrum of mutations, including point substitutions that interfere with maturation of the vWF protein or that result in rapid clearance from the plasma. Type 3 disease is usually caused by deletions or frameshift mutations involving both alleles.
- **Type 2 von Willebrand disease is characterized by qualitative defects in vWF**; there are several subtypes, of which type 2A is the most common. It is inherited as an autosomal dominant disorder. vWF is expressed in normal amounts, but missense mutations are present that lead to defective multimer assembly. Large and intermediate multimers, representing the most active forms of vWF, are missing from plasma. Type 2 von Willebrand disease accounts for 25% of all cases and is associated with mild to moderate bleeding.

Patients with von Willebrand disease have defects in platelet function despite a normal platelet count. The plasma level of active vWF, measured as the ristocetin cofactor activity, is reduced. Because vWF stabilizes factor VIII, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the PTT in von Willebrand disease types 1 and 3. However, except in rare type 3 patients, adverse complications typical of severe factor VIII deficiency, such as bleeding into the joints, are not seen.

Even within families in which a single defective vWF allele is segregating, wide variability in clinical expression is common. This is due in part to modifying genes that influence circulating levels of vWF, which show a wide range in normal populations. Persons with von Willebrand disease facing hemostatic challenges (dental work, surgery) can be treated with desmopressin, which stimulates vWF release, or with infusions of plasma concentrates containing factor VIII and vWF.

Hemophilia A (Factor VIII Deficiency)

Hemophilia A, the most common hereditary disease associated with life-threatening bleeding, is caused by mutations in factor VIII, an essential cofactor for factor IX in the coagulation cascade. Hemophilia A is inherited as an X-linked recessive trait and thus affects mainly males and homozygous females. Rarely, excessive bleeding occurs in heterozygous females, presumably as a result of inactivation of the X chromosome bearing the normal factor VIII allele by chance in most cells (unfavorable lyonization). About 30% of patients have no family history; their disease is caused by new mutations.

Hemophilia A exhibits a wide range of clinical severity that correlates well with the level of factor VIII activity. Those with less than 1% of normal levels have severe disease; those with 2% to 5% of normal levels have moderately severe disease; and those with 6% to 50% of normal levels have mild disease. The varying degrees of factor VIII deficiency are largely explained by heterogeneity in the causative mutations. As with β-thalassemia, the genetic lesions include deletions, nonsense mutations that create stop codons, and mutations that cause errors in mRNA