HLA-based antibodies. HLA-matched platelets are collected from compatible donors using apheresis at frequent intervals until the patient's platelet count recovers, and they are no longer transfusion dependent. Many blood banks and transfusion services have attempted to address the problem of platelet HLA alloimmunization through prevention They provide blood products that have undergone filtration to reduce their white blood cell content, a process called *leukoreduction*. Because contaminating leukocytes are the primary sources of exposure to HLAs, their removal can be quite effective in preventing subsequent alloimmunization, even in chronically transfused patients.

BLEEDING CAUSED BY VON WILLEBRAND DISEASE

Disorders of the functional ligands for platelet adhesion to the vasculature cause bleeding that clinically resembles the bleeding associated with platelet or vascular disorders (e.g., epistaxis, GI bleeding). vWF is synthesized in endothelial cells and megakaryocytes and functions in plasma to mediate platelet adhesion to the damaged site (see Fig. 51-1). vWF is a large, multimeric protein; the largest multimers contain the greatest number of adhesive sites and confer greater hemostatic ability than smaller vWF molecules. In patients with low vWF levels, platelet adhesion to damaged vessels is delayed and results in mucosal bleeding and a prolonged bleeding time. vWF is also the carrier protein for factor VIII, and deficiency of vWF or abnormal vWF-VIII binding leads to rapid clearance of factor VIII, decreased factor VIII levels, and a prolonged aPTT.

vWD can manifest clinically with bleeding that resembles a platelet defect and a coagulation factor defect. The many mutations in the *VWF* gene have been phenotypically grouped into three major subtypes of vWD (E-Table 51-1).

Type 1 von Willebrand Disease

Most patients have type 1 vWD, a mild to moderate quantitative decrease in all vWF multimers. This condition is commonly caused by a heterozygous mutation and has a dominant pattern of inheritance. Type 1 vWD is characterized by equivalent decreases in factor VIII, vWF antigen, and Rcof activity. Rcof measures the ability of the patient's plasma (which contains vWF) to agglutinate normal platelets in the presence of ristocetin. Patients with type 1 vWD usually have mild to moderate bleeding, often only in relation to surgery or dental procedures.

Patients with type 1 vWD are treated with DDAVP, which stimulates endothelial cells to release stored vWF and leads to an increase in plasma vWF antigen, Rcof, and factor VIII levels. DDAVP, given subcutaneously at a dose of 0.3 μg/kg, usually yields excellent results. However, tachyphylaxis to DDAVP occurs because endothelial cells require time to synthesize new vWF after repeated DDAVP administration.

vWF concentrates must sometimes be used in patients with more severe type 1 vWD or in those who are undergoing a more prolonged hemostatic challenge. Bleeding in type 1 vWD during pregnancy is rare. Because the vWF level rises significantly in pregnancy, vWF antigen and Rcof levels usually normalize during the second or third trimester and eliminate the bleeding risk at that time. Most pregnant women with type 1 vWD have no bleeding complications with delivery and do not require therapy during pregnancy or in the early postpartum period.

Type 2 von Willebrand Disease

Type 2 vWD is characterized by heterozygous mutations of variable penetrance that produce a qualitative defect in the vWF molecule. The most common type 2 disorders have a relative lack of the larger vWF multimers (see E-Table 51-1). High-molecular-weight vWF multimers are absent in type 2A disease, and these patients show disproportionately low Rcof activity compared with the vWF antigen level.

The molecular defect is related to mutations in the A2 domain of vWF that render the molecule more susceptible to the vWF-cleaving protease (i.e., ADAMTS13). Patients with type 2A vWD respond to vWF concentrate and less commonly to DDAVP.

The abnormal vWF molecule in type 2B vWD has an increased affinity for platelets, which causes the loss of high-molecular-weight multimers from the circulation and often produces thrombocytopenia. Platelet aggregometry in type 2B vWD (see E-Table 51-1) shows an abnormal increase in low-dose ristocetin-induced platelet agglutination; in the laboratory, the addition of the patient's vWF to normal platelets similarly increases ristocetin-induced platelet agglutination and confirms the abnormal vWF. DDAVP induces release of the abnormal vWF in patients with type 2B vWD, causing thrombocytopenia and is therefore contraindicated. vWF concentrate should be used instead.

Type 2M vWD has laboratory findings similar to those in type 2A, but it has high-molecular-weight multimers. The defect in this rare type of vWF is most often a mutation in the vWF that reduces binding to its platelet ligand GPIbα. Some patients with type 2M vWD respond to DDAVP, but most require vWF concentrate.

In type 2N vWD, the abnormal vWF molecule has decreased binding affinity for factor VIII, which decreases factor VIII survival and produces a bleeding phenotype similar to hemophilia A. The low factor VIII levels do not respond to high-purity factor VIII infusions, unlike true hemophilia A, but they improve with vWF concentrate. Rcof and vWF antigen levels are normal in type 2N vWD because the mutation in the factor VIII binding site does not affect vWF function or survival. The diagnosis of type 2N vWD should be considered in females who have hemophilia A. Tests for vWF binding to factor VIII are available in reference laboratories.

Type 3 von Willebrand Disease

The rare patient with type 3 vWD has a complete deficiency of vWF, often as a result of the inheritance of two abnormal vWF alleles (i.e., compound heterozygote). Patients with type 3 vWD have no or extremely low levels of Rcof and vWF antigen and factor VIII levels of 3% to 10% of normal, and they usually have severe bleeding that may mimic hemophilia. Type 3 vWD does not respond to DDAVP and requires vWF concentrates to treat bleeding.

Acquired von Willebrand Disease

The acquired form of vWD usually appears as a severe, type 2A–like defect without larger vWF multimers in a patient with no history of bleeding. Acquired vWD is caused by abnormal clearance of the larger vWF multimers and is associated with monoclonal gammopathies, lymphoproliferative disorders, myeloma,