- *Disorders of platelet secretion* are characterized by the defective release of certain mediators of platelet activation, such as thromboxanes and granule-bound ADP. The biochemical defects underlying these so-called *storage pool disorders* are varied, complex, and beyond the scope of our discussion.

Among the *acquired defects* of platelet function, two are clinically significant. The first is caused by ingestion of *aspirin and other nonsteroidal anti-inflammatory drugs*. Aspirin is a potent, irreversible inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A_2 and prostaglandins (Chapter 3). These mediators play important roles in platelet aggregation and subsequent release reactions (Chapter 4). The antiplatelet effects of aspirin form the basis for its use in the prophylaxis of coronary thrombosis (Chapter 12). *Uremia* (Chapter 20) is the second condition exemplifying an acquired defect in platelet function. The pathogenesis of platelet dysfunction in uremia is complex and involves defects in adhesion, granule secretion, and aggregation.

Hemorrhagic Diatheses Related to Abnormalities in Clotting Factors

Inherited or acquired deficiencies of virtually every coagulation factor have been reported as causes of bleeding diatheses. Bleeding due to isolated coagulation factor deficiencies most commonly manifests as *large posttraumatic ecchymoses or hematomas*, or *prolonged bleeding* after a laceration or any form of surgical procedure. Unlike bleeding seen with thrombocytopenia, bleeding due to coagulation factor deficiencies often occurs into the gastrointestinal and urinary tracts and into weight-bearing joints (hemarthrosis). Typical stories include the patient who oozes blood for days after a tooth extraction or who develops a hemarthrosis after minor stress on a knee joint.

Hereditary deficiencies typically affect a single clotting factor. The most common and important inherited deficiencies of coagulation factors affect factor VIII (hemophilia A), and factor IX (hemophilia B). Deficiencies of vWF (von Willebrand disease) are also discussed here, as this factor influences both coagulation and platelet function. Rare inherited deficiencies of each of the other coagulation factors have also been described.

Acquired deficiencies usually involve multiple coagulation factors and can be based on decreased protein synthesis or a shortened half-life. Vitamin K deficiency (Chapter 9) results in the impaired synthesis of factors II, VII, IX, X and protein C. Many of these factors are made in the liver and are therefore deficient in severe parenchymal liver disease. Alternatively, in disseminated intravascular coagulation, multiple coagulation factors are consumed and are therefore deficient. Acquired deficiencies of single factors occur, but they are rare. These are usually caused by inhibitory autoantibodies.

The Factor VIII-vWF Complex

The two most common inherited disorders of bleeding, hemophilia A and von Willebrand disease, are caused by qualitative or quantitative defects involving factor VIII and vWF, respectively. Before we discuss these disorders it will be helpful to review the structure and function of these two proteins, which exist together in the plasma as part of a single large complex.

Factor VIII and vWF are encoded by separate genes and are synthesized in different cells. Factor VIII is an essential cofactor of factor IX, which converts factor X to factor Xa (Fig. 14-26; Chapter 4). It is made in several tissues; sinusoidal endothelial cells and Kupffer cells in the liver seem to be major sources. Once factor VIII reaches the

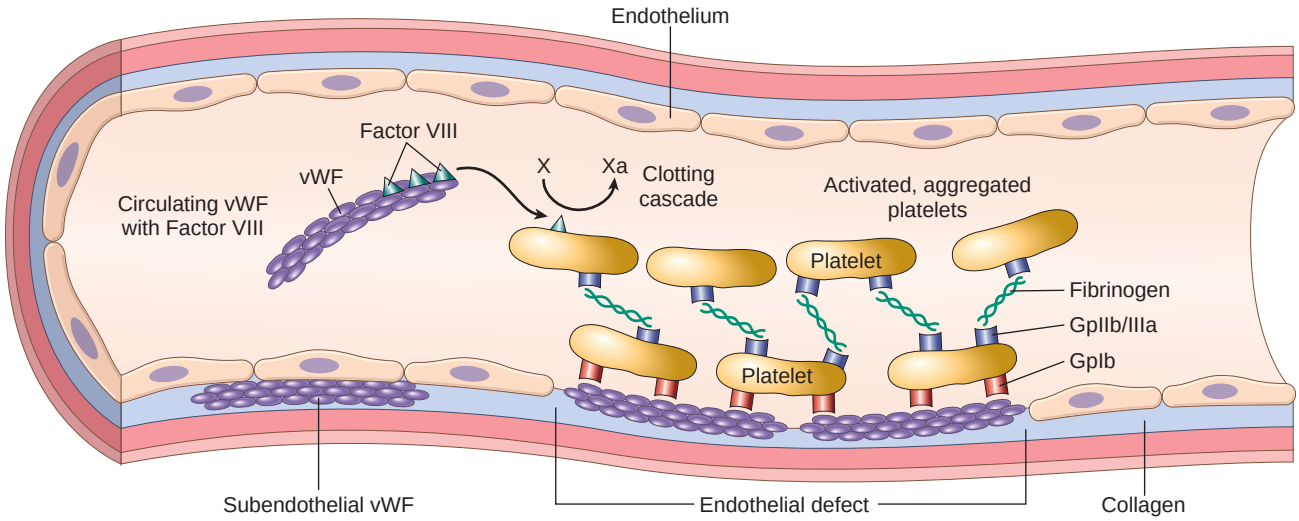

Figure 14-26 Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII is synthesized in the liver and kidney, and vWF is made in endothelial cells and megakaryocytes. The two associate to form a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels and the α-granules of platelets. Following endothelial injury, exposure of subendothelial vWF causes adhesion of platelets, primarily via the glycoprotein Ib (GpIb) platelet receptor. Circulating vWF and vWF released from the α-granules of activated platelets can bind exposed subendothelial matrix, further contributing to platelet adhesion and activation. Activated platelets form hemostatic aggregates; fibrinogen participates in aggregation through bridging interactions with the glycoprotein IIb/IIIa (GpIIb/IIIa) platelet receptor. Factor VIII takes part in the coagulation cascade as a cofactor in the activation of factor X on the surface of activated platelets.