and other malignant and myeloproliferative diseases characterized by thrombocytosis. In these cases, acquired vWD has been successfully treated with IVIG and therapy for the underlying disease.

Another cause of abnormal vWF multimer clearance resulting in acquired vWD is critical aortic stenosis. It is corrected with successful surgical repair.

BLEEDING CAUSED BY COAGULATION FACTOR DISORDERS

Normal platelet hemostasis initiates plugging of vascular lesions and maintains mucosal integrity. Because of abnormalities of coagulation factors, the initial platelet plug is not solidified by secondary hemostasis, and the effects are clot breakdown and bleeding. This bleeding is different from platelet-type bleeding. Coagulation factor deficiencies lead to bleeding in deep tissues and joints, and milder deficiencies result in bleeding in a delayed fashion after surgery.

Most patients with significant factor deficiencies have abnormal screening laboratory test results (E-Table 51-2; see Fig. 51-1), although patients with mild deficiencies can have bleeding and only borderline-abnormal coagulation factor values. Like other hemostasis abnormalities previously discussed, coagulation factor problems can be classified as congenital deficiencies and those acquired from medications or underlying medical conditions.

Congenital Factor Deficiencies

Hemophilia A and B

The X-linked deficiencies of factor VIII (i.e., hemophilia A) and factor IX (i.e., hemophilia B) are the most common factor deficiencies after vWD. Hemophilia A is about six times more common than hemophilia B.

About 50% or more of cases of severe hemophilia A arise as a result of an inversion of a major portion of the gene that results in complete loss of activity. Other mutations tend to result in milder disease. Most patients with hemophilia B have mutations that result in a functionally abnormal factor IX with no activity. The combined results of antigenic and functional assays can resolve whether a deficiency results from a loss of the protein or loss of its normal function.

Both hemophilia A and hemophilia B are categorized by their factor levels. Severe deficiency is characterized by less than 1% of factor VIII or IX, whereas patients with moderate and mild hemophilia have factor levels of 1% to 5% and more than 5%, respectively.

Symptoms and signs of severe hemophilia A and hemophilia B develop in childhood with bleeding into muscles, joints, and soft tissue. Because they are X-linked disorders, they are observed primarily in male patients; the mother of an affected male patient is a carrier, and 50% of maternal uncles have the disease. However, about 25% to 30% of cases of hemophilia result from new mutations and have no relevant family history. In rare instances, a female carrier with extremely skewed X-inactivation may have a mild bleeding disorder with factor levels lower than 30%.

Bleeding in severe hemophilia is often spontaneous and is common after any type of surgery or even mild trauma. Hemorrhage in this condition frequently manifests as hemarthrosis (i.e., bleeding into joints) or retroperitoneal bleeding, or both. Hematuria and mucosal or intracranial bleeding can also occur. Patients with moderate hemophilia have less spontaneous bleeding, but they are still at significant risk for hemorrhagic complications of surgery or trauma. Patients with mild hemophilia may be undiagnosed into adulthood and then only because of bleeding after major surgery.

The complications of hemophilia stem from chronic bleeding into joints and muscles, which leads to severe deformities, arthritis, muscle atrophy, and contractures. These complications require intensive physical therapy and orthopedic care, often culminating in joint replacement. Patients with hemophilia who received pooled-factor concentrates before the era of viral inactivation have complications related to transfusion-transmitted infections, including HIV and hepatitis B and C. Current therapy uses factor concentrates that are virally inactivated or recombinant.

Non–hemophilia A or B Congenital Factor Deficiencies

Inherited bleeding disorders caused by deficiencies of coagulation factors V, VII, X, and XI (see E-Table 51-2) are much less common than hemophilia A and B. Patients with factor V deficiency usually lack plasma factor V and platelet factor V and have joint and muscle bleeding similar to patients with hemophilia. Some patients who are plasma factor V deficient are asymptomatic until they are challenged with the stress of surgery or trauma, and these patients are thought to have normal platelet factor V levels. Rarely, patients inherit factor deficiencies in tandem, such as combined factors V and VIII deficiencies.

Patients with factor XI deficiency usually have a milder bleeding disorder (even with factor XI levels <5%) than patients with hemophilia A or B, whereas factor X deficiency is usually more severe. Factor XI deficiency is an autosomal recessive disorder seen with increased frequency among Ashkenazi Jews, often manifesting late in adulthood and in the clinical settings of increased fibrinolysis, such as after prostate surgery. Acquired factor X deficiency can occur in patients with amyloidosis, a condition in which the abnormal circulating light chains adsorb to and clear factor X, producing low levels and occasional bleeding.

Fibrinogen (factor I) functions as a bridging ligand for the platelet receptor GPIIb/IIIa in the platelet-platelet matrix at sites of vascular damage. Fibrinogen also functions in the final steps of the coagulation cascade to form the fibrin clot. Congenital hypofibrinogenemias and afibrinogenemias are rare. Patients with these disorders produce very low amounts of fibrinogen. Alternatively, some individuals produce an abnormally functioning fibrinogen, which is typically associated with genetic mutations affecting fibrin cross-linking and polymerization. These disorders are referred to as *congenital dysfibrinogenemias*.

Because of fibrinogen's dual role in promoting platelet and coagulation factor hemostasis, patients with congenital fibrinogen disorders can have moderate to severe bleeding problems from early in life. It is not uncommon for patients to have the mucosal membrane bleeding associated with platelet