splicing. The most severe deficiencies result from an inversion involving the X chromosome that completely abolishes the synthesis of factor VIII. Less commonly, severe hemophilia A is associated with point mutations in factor VIII that impair the function of the protein. In such cases factor VIII protein levels may be normal by immunoassay. Mutations permitting some active factor VIII to be synthesized are associated with mild to moderate disease. The disease in such patients may be modified by other genetic factors that influence factor VIII expression levels, which vary widely in normal individuals.

In all symptomatic cases there is a tendency toward easy bruising and massive hemorrhage after trauma or operative procedures. In addition, "spontaneous" hemorrhages frequently occur in regions of the body that are susceptible to trauma, particularly the joints, where they are known as *hemarthroses.* Recurrent bleeding into the joints leads to progressive deformities that can be crippling. Petechiae are characteristically absent.

Patients with hemophilia A have a prolonged PTT and a normal PT, results that point to an abnormality of the intrinsic coagulation pathway. Factor VIII-specific assays are required for diagnosis. As explained in Chapter 4, the bleeding diathesis reflects the pre-eminent role of the factor VIIIa/factor IXa complex in activation of factor X in vivo. The precise explanation for the tendency of hemophiliacs to bleed at particular sites (joints, muscles, and the central nervous system) remains uncertain.

Hemophilia A is treated with infusions of recombinant factor VIII. About 15% of patients with severe hemophilia A develop antibodies that bind and inhibit factor VIII, probably because the protein is perceived as foreign, having never been "seen" by the immune system. These antibody inhibitors can be a very difficult therapeutic challenge. Before the development of recombinant factor VIII therapy, thousands of hemophiliacs received plasma-derived factor VIII concentrates containing HIV, and many developed AIDS (Chapter 6). The risk of HIV transmission has been eliminated but tragically too late for an entire generation of hemophiliacs. Efforts to develop somatic gene therapy for hemophilia are ongoing.

Hemophilia B (Christmas Disease, Factor IX Deficiency)

Severe factor IX deficiency produces a disorder clinically indistinguishable from factor VIII deficiency (hemophilia A). This should not be surprising, given that factors VIII and IX function together to activate factor X. A wide spectrum of mutations involving the gene that encodes factor IX is found in hemophilia B. Like hemophilia A, it is inherited as an X-linked recessive trait and shows variable clinical severity. In about 15% of these patients, factor IX protein is present but is nonfunctional. As with hemophilia A, the PTT is prolonged and the PT is normal. Diagnosis of Christmas disease (named after the first patient identified with this condition, and not the holiday) is possible only by assay of the factor levels. The disease is treated with infusions of recombinant factor IX.

Disseminated Intravascular Coagulation (DIC)

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder characterized by the excessive activation of coagulation and the formation of thrombi in the microvasculature of the body. It occurs as a secondary complication of many different disorders. Sometimes the coagulopathy is localized to a specific organ or tissue. As a consequence of the thrombotic diathesis there is consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolysis. DIC can present with signs and symptoms relating to the tissue hypoxia and infarction caused by the myriad microthrombi; with hemorrhage caused by the depletion of factors required for hemostasis and the activation of fibrinolytic mechanisms; or both.

Etiology and Pathogenesis. At the outset, it must be emphasized that DIC is not a primary disease. It is a coagulopathy that occurs in the course of a variety of clinical conditions. In discussing the general mechanisms underlying DIC, it is useful to briefly review the normal process of blood coagulation and clot removal (Chapter 4).

Clotting in vivo is thought to be initiated by exposure of tissue factor, which combines with factor VII to activate both factor X directly and to activate factor IX. Activation of factor X leads to the generation of *thrombin*, the central player in clotting. At sites where the endothelium is disrupted, thrombin converts fibrinogen to fibrin, feeds back to activate factors IX, VIII, and V, stimulates fibrin cross-linking, inhibits fibrinolysis, and activates platelets, all of which augment the formation of a stable clot. To prevent runaway clotting, this process must be sharply limited to the site of tissue injury. Remarkably, as thrombin is swept away in the bloodstream and encounters uninjured vessels, it is converted to an anticoagulant through binding to *thrombomodulin*, a protein found on the surface of endothelial cells. The thrombin-thrombomodulin complex activates protein C, which is an important inhibitor of factor V and factor VIII. Other activated coagulation factors are removed from the circulation by the liver, and as you will recall, the blood also contains several potent fibrinolytic factors, such as plasmin. These and additional checks and balances normally ensure that just enough clotting occurs at the right place and time.

From this brief review it should be clear that DIC could result from pathologic activation of coagulation or the impairment of clot-inhibiting mechanisms. Because the latter rarely constitute primary mechanisms of DIC, we will focus on the abnormal initiation of clotting.

Two major mechanisms trigger DIC: (1) release of tissue factor or other, poorly characterized procoaagulants, into the circulation, and (2) widespread injury to the endothelial cells. Procoagulants such as tissue factor can be derived from a variety of sources, such as the placenta in obstetric complications or tissues injured by trauma or burns. Mucus released from certain adenocarcinomas may also act as procoagulants by directly activate factor X.

Endothelial injury can initiate DIC in several ways. Injuries that cause endothelial cell necrosis expose the subendothelial matrix, leading to the activation of platelets and the coagulation pathway. However, even subtle endothelial injuries can unleash procoagulant activity. One mediator of endothelial injury is TNF, which is implicated in DIC occurring with sepsis. TNF induces endothelial cells to express tissue factor on their cell surfaces and to decrease the expression of thrombomodulin, shifting the checks and balances that govern hemostasis towards coagulation. In addition, TNF up-regulates the expression of adhesion