count in about two thirds of patients, but with the attendant increased risk of bacterial sepsis. Immunomodulatory agents such as intravenous immunoglobulin or anti-CD20 antibody (rituximab) are often effective in patients who relapse after splenectomy or for whom splenectomy is contraindicated. Peptides that mimic the effects of thrombopoietin (so-called *TPO-mimetics*) are also effective in stimulating platelet production and improving platelet counts.

### *Acute Immune Thrombocytopenic Purpura*

Like chronic ITP, this condition is caused by autoantibodies to platelets, but its clinical features and course are distinct. Acute ITP is mainly a disease of childhood occurring with equal frequency in both sexes. Symptoms appear abruptly, often 1 to 2 weeks after a self-limited viral illness, which appears to trigger the development of autoantibodies through uncertain mechanisms. Unlike chronic ITP, acute ITP is self-limited, usually resolving spontaneously within 6 months. Glucocorticoids are given only if the thrombocytopenia is severe. In about 20% of children, usually those without a viral prodrome, thrombocytopenia persists; these less fortunate children have a childhood form of chronic ITP that follows a course similar to the adult disease.

### *Drug-Induced Thrombocytopenia*

Drugs can induce thrombocytopenia through direct effects on platelets and secondary to immunologically mediated platelet destruction. The drugs most commonly implicated are quinine, quinidine, and vancomycin, all of which bind platelet glycoproteins and in one way or another create antigenic determinants that are recognized by antibodies. Much more rarely, drugs induce true autoantibodies through unknown mechanisms. Thrombocytopenia, which may be severe, is also a common consequence of platelet inhibitory drugs that bind glycoprotein IIb/IIIa; it is hypothesized that these drugs induce conformational changes in glycoprotein IIb/IIIa and create an immunogenic epitope.

*Heparin-induced thrombocytopenia (HIT)* has a distinctive pathogenesis and is of particular importance because of its potential for severe clinical consequences. Thrombocytopenia occurs in about 5% of persons receiving heparin and is of two types:

- Type I thrombocytopenia occurs rapidly after the onset of therapy and is of little clinical importance, sometimes resolving despite the continuation of therapy. It most likely results from a direct platelet-aggregating effect of heparin.
- Type II thrombocytopenia is less common but of much greater clinical significance. It occurs 5 to 14 days after therapy begins (or sooner if the person has been sensitized to heparin) and, paradoxically, often leads to life-threatening venous and arterial thrombosis. This severe form of HIT is caused by antibodies that recognize complexes of heparin and platelet factor 4, which is a normal component of platelet granules. Binding of antibody to these complexes activates platelets and promotes thrombosis, even in the setting of thrombocytopenia. Unless therapy is immediately discontinued and an alternative nonheparin anticoagulant instituted, clots within large arteries may lead to vascular insufficiency and limb loss, and emboli from deep venous thrombosis can cause fatal pulmonary thromboembolism. The risk of severe HIT is lowered, but not completely eliminated, by the use of low-molecular-weight heparin preparations. Unfortunately, once severe HIT develops even low-molecular-weight heparins exacerbate the thrombotic tendency and must be avoided.

### *HIV-Associated Thrombocytopenia*

**Thrombocytopenia is one of the most common hematologic manifestations of HIV infection.** Both impaired platelet production and increased destruction contribute. CD4 and CXCR4, the receptor and coreceptor, respectively, for HIV, are found on megakaryocytes, allowing these cells to be infected. HIV-infected megakaryocytes are prone to apoptosis and their ability to produce platelets is impaired. HIV infection also causes B-cell hyperplasia and dysregulation, which predisposes to the development of autoantibodies. In some instances the antibodies are directed against platelet membrane glycoprotein IIb-III complexes. As in other immune cytopenias, the autoantibodies opsonize platelets, promoting their destruction by mononuclear phagocytes in the spleen and elsewhere. The deposition of immune complexes on platelets may also contribute to the accelerated loss of platelets in some patients who are HIV infected.

### *Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic-Uremic Syndrome (HUS)*

The term *thrombotic microangiopathy* encompasses a spectrum of clinical syndromes that includes TTP and HUS. They are caused by insults that lead to excessive activation of platelets, which deposit as thrombi in small blood vessels.

According to its original description, TTP was defined as the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished by the absence of neurologic symptoms, the prominence of acute renal failure, and its frequent occurrence in children. With time, experience, and increased mechanistic insight, however, these distinctions have blurred. Many adult patients with "TTP" lack one or more of the five criteria, and some patients with "HUS" have fever and neurologic dysfunction.

In both conditions, intravascular thrombi cause a *microangiopathic hemolytic anemia* and widespread *organ dysfunction*, and the attendant consumption of platelets leads to thrombocytopenia. It is believed that the varied clinical manifestations of TTP and HUS are related to differing proclivities for thrombus formation in tissues. While disseminated intravascular coagulation (discussed later) and thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenically distinct. In TTP and HUS (unlike in disseminated intravascular coagulation), activation of the coagulation cascade is not of primary importance, and hence laboratory tests of coagulation, such as the PT and PTT, are usually normal.