- *Decreased platelet survival.* This important mechanism of thrombocytopenia can have an immunological or nonimmunologic basis. In *immune thrombocytopenia*, destruction is caused by the deposition of antibodies or immune complexes on platelets. Antibodies to platelets can recognize self-antigens (autoantibodies) or non-self antigens (alloantibodies). Autoimmune thrombocytopenia is discussed in the following section. *Alloantibodies* can arise when platelets are transfused or cross the placenta from the fetus into the pregnant mother. In the latter case, IgG antibodies made in the mother can cause clinically significant thrombocytopenia in the fetus. This is reminiscent of hemolytic disease of the newborn, in which red cells are the target (Chapter 10). The most important nonimmunologic causes are *disseminated intravascular coagulation* and the *thrombotic microangiopathies*, in which unbridled, often systemic, platelet activation reduces platelet life span. Nonimmunologic destruction of platelets may also be caused by *mechanical injury*, such as in individuals with prosthetic heart valves.
- *Sequestration.* The spleen normally sequesters 30% to 35% of the body's platelets, but this can rise to 80% to 90% when the spleen is enlarged, producing moderate degrees of thrombocytopenia.
- *Dilution.* Massive transfusions can produce a dilutional thrombocytopenia. With prolonged blood storage the number of viable platelets decreases; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

Chronic Immune Thrombocytopenic Purpura (ITP)

Chronic ITP is caused by autoantibody mediated destruction of platelets. It can occur in the setting of a variety of predisposing conditions and exposures (secondary) or in the absence of any known risk factors (primary or idiopathic). The contexts in which chronic ITP occurs secondarily are numerous and include individuals with systemic lupus erythematosus (Chapter 6), HIV infection, and B-cell neoplasms such as chronic lymphocytic leukemia (Chapter 13). The diagnosis of primary chronic ITP is made only after secondary causes are excluded.

Pathogenesis. The autoantibodies, most often directed against platelet membrane glycoproteins IIb-IIIa or Ib-IX, can be demonstrated in the plasma and bound to the platelet surface in about 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IgG class.

As in autoimmune hemolytic anemias, antiplatelet antibodies act as opsonins that are recognized by IgG Fc receptors expressed on phagocytes (Chapter 6), leading to increased platelet destruction. The thrombocytopenia is usually markedly improved by splenectomy, indicating that the spleen is the major site of removal of opsonized platelets. The splenic red pulp is also rich in plasma cells, and part of the benefit of splenectomy (a frequent treatment for chronic ITP) may stem from the removal of a source of autoantibodies. In some instances the autoantibodies may also bind to and damage megakaryocytes, leading to decreases in platelet production that further exacerbate the thrombocytopenia.

MORPHOLOGY

The principal changes of thrombocytopenic purpura are found in the spleen, bone marrow, and blood, but they are not specific. Secondary changes related to the bleeding diathesis may be found in any tissue or structure in the body.

The spleen is of normal size. Typically, there is congestion of the sinusoids and enlargement of the splenic follicles, often associated with prominent reactive germinal centers. In many instances scattered megakaryocytes are found within the sinuses, possibly representing a mild form of extramedullary hematopoiesis driven by elevated levels of thrombopoietin. **The marrow reveals a modestly increased number of megakaryocytes**. Some are apparently immature, with large, nonlobulated, single nuclei. These findings are not specific but merely reflect accelerated thrombopoiesis, being found in most forms of thrombocytopenia resulting from increased platelet destruction. The importance of bone marrow examination is to rule out thrombocytopenias resulting from bone marrow failure or other primary bone marrow disorders. The secondary changes relate to the hemorrhages that are dispersed throughout the body. The **peripheral blood often reveals abnormally large platelets** (megathrombocytes), which are a sign of accelerated thrombopoiesis.

Clinical Features

Chronic ITP occurs most commonly in adult women younger than 40 years of age. The female-to-male ratio is 3:1. It is often insidious in onset and is characterized by bleeding into the skin and mucosal surfaces. Cutaneous bleeding is seen in the form of pinpoint hemorrhages (*petechiae*), which are especially prominent in the dependent areas where the capillary pressure is higher. Petechiae can become confluent, giving rise to *ecchymoses.* Often there is a history of easy bruising, nosebleeds, bleeding from the gums, and hemorrhages into soft tissues from relatively minor trauma. The disease may manifest first with melena, hematuria, or excessive menstrual flow. Subarachnoid hemorrhage and intracerebral hemorrhage are serious and sometimes fatal complications, but fortunately they are rare in treated patients. Splenomegaly and lymphadenopathy are uncommon in primary disease, and their presence should lead one to consider other diagnoses, such as ITP secondary to a B-cell neoplasm.

The clinical signs and symptoms are not specific but rather reflective of the thrombocytopenia. The findings of a low platelet count, normal or increased megakaryocytes in the bone marrow, and large platelets in the peripheral blood are taken as presumptive evidence of accelerated platelet destruction. The PT and PTT are normal. Tests for platelet autoantibodies are not widely available. Therefore, the diagnosis is one of exclusion and can be made only after other causes of thrombocytopenia (such as those listed in Table 14-9) have been ruled out.

Almost all patients respond to glucocorticoids (which inhibit phagocyte function), but many eventually relapse. Those with moderately severe thrombocytopenia (platelet counts > 30,000/mL) can be followed carefully, and some of these individuals may have spontaneous remissions over a period of a year or more. In individuals with severe thrombocytopenia, splenectomy normalizes the platelet