Other helpful assays measure the reticulated platelet count and immature platelet fraction. In principle, RNA-rich immature platelet elements should be readily identifiable in peripheral blood. In the setting of thrombocytopenia, the normal compensatory response of a healthy bone marrow is to increase platelet production, and increased production correlates with increased numbers of immature platelets. However, in the setting of marrow-suppressive drug therapy, immature platelet counts are typically low, indicating hypoproliferative megakaryocytes. A decreased reticulated platelet fraction in the setting of a known offending drug can help to confirm the diagnosis.

Drug-associated thrombocytopenia is usually reversible, and platelet production rebounds as megakaryocytic stem cells eventually recover and regenerate after cessation of the toxic therapy. However, repeated or intensive chemotherapy (e.g., stem cell transplantation) may permanently damage the megakaryocytic stem cells and supporting stromal environment and cause chronic thrombocytopenia. This condition may be accompanied by leukopenia and anemia.

Similar to drug-related marrow suppression, nutritional disorders, especially alcoholism and abnormal folate or cobalamin (vitamin B_{12}) metabolism, are commonly associated with thrombocytopenia. Like destructive drug therapy, the lack of essential nutrients such as vitamin B_{12} or folate paralyzes normal megakaryocyte development, resulting in decreased mature platelet production. The diagnosis of a nutritional deficiency can be confirmed by testing vitamin B_{12} and folate levels in peripheral blood. Platelet counts should respond to abstinence from alcohol and to appropriate multivitamin replacement therapy for deficient nutrients.

Malignancy-Associated Thrombocytopenia

Platelet production is suppressed by intrinsic malignant diseases of the bone marrow (e.g., leukemia, multiple myeloma) and by malignant diseases that secondarily invade the bone marrow (e.g., non-Hodgkin's lymphoma, small cell lung cancer, breast and prostate cancers). The pathophysiology often is attributable to the toxic nature of the bone marrow milieu; normal megakaryocyte development is frequently suppressed by scores of abnormal bone marrow elements or invasive tumors.

The diagnosis of malignancy-associated thrombocytopenia is typically based on a bone marrow aspirate, which characteristically shows decreased megakaryocytes and occasionally shows malignant cells. Bone marrow biopsy has a much higher yield for diagnosing malignant involvement of the marrow. Flow cytometric evaluation for clonal B cells in the marrow aspirate is also highly sensitive for detecting monoclonal B-cell lymphoproliferative disease (e.g., non-Hodgkin's lymphoma). Definitive treatment of the thrombocytopenia relies on aggressively treating the underlying disease process.

Although not strictly an invasive cellular process, myelofibrosis (i.e., increase in reticulin fibers and sometimes collagen) of the marrow may lead to thrombocytopenia or pancytopenia. Myelofibrosis occurs most commonly in myeloproliferative disorders, mastocytosis, and mycobacterial and other infections involving the marrow. It is occasionally seen in patients with myelodysplasia or acute megakaryocytic leukemia and rarely occurs on a congenital basis (i.e., osteogenesis imperfecta).

Like pure malignancy-associated forms of decreased platelet production, myelofibrosis is diagnosed by bone marrow studies. Treating the underlying disorder is the best approach to addressing myelofibrotic thrombocytopenia.

Congenital Thrombocytopenia Syndromes

Thrombocytopenia in children can result from congenital defects of megakaryocyte production, as seen in thrombocytopenia–absent radii syndrome, congenital amegakaryocytic thrombocytopenia (i.e., mutation in the thrombopoietin receptor), and Fanconi's anemia (i.e., congenital aplastic anemia with renal hypoplasia and skin hyperpigmentation). Other disorders that are intrinsic to the bone marrow include the May-Hegglin anomaly and related myosin heavy chain 9 gene *(MYH9)* diseases, characterized by giant platelets and Döhle bodies (i.e., basophilic inclusions in leukocytes and platelets).

Thrombocytopenia with small platelets is characteristic of Wiskott-Aldrich syndrome, an X-linked disorder with eczema and immunodeficiency that can be diagnosed by the lack of CD43 expression on T lymphocytes. When accompanied by nerve deafness and nephritis, congenital hypoproductive thrombocytopenia is called *Alport's syndrome*.

The defects and detailed approaches to the diagnosis of decreased platelet production associated with the previously described conditions are outside the scope of this chapter. Nonetheless, the definitive treatment for many of the congenital thrombocytopenia problems is allogeneic stem cell transplantation, in which the abnormal, endogenous progenitor cell elements are eliminated and replaced by normal precursors capable of producing typical levels of functioning, mature platelets.

Platelet Sequestration

Up to 30% of circulating platelets are normally sequestered within the spleen at any time. Thrombocytopenia due to sequestration is common in advanced liver disease, myeloproliferative disorders accompanied by splenomegaly (e.g., chronic myelogenous leukemia, chronic idiopathic myelofibrosis), and malignant disease involving the spleen. In each of these conditions, increased trapping of platelets in the splenic system decreases platelet counts to between 50,000 and 100,000/μL, athough rarely lower.

The diagnosis of platelet sequestration may be suspected by physical examination findings or imaging studies demonstrating splenomegaly. The reticulated platelet counts or immature platelet fractions may be normal or slightly elevated, and bone marrow studies typically reveal normal megakaryocyte numbers and morphology. Given the lack of specific tests for platelet sequestration, the diagnosis often is one of exclusion of other causes of hypoproliferative and destructive thrombocytopenia.

Treatment of thrombocytopenia due to splenomegaly frequently depends on the underlying cause for increased spleen size. Splenectomy may be indicated in some conditions such as myeloproliferative disease, but it is rarely used to treat thrombocytopenia resulting from portal hypertension. The decision to perform splenectomy for thrombocytopenia in patients with myeloproliferative syndromes must be individualized and weighed against the possibilities of surgical complications, loss of the spleen's extramedullary hematopoietic ability, and rebound thrombocytosis. Medications that help to control underlying disorders (e.g., chemotherapy for malignancy) or actions such as