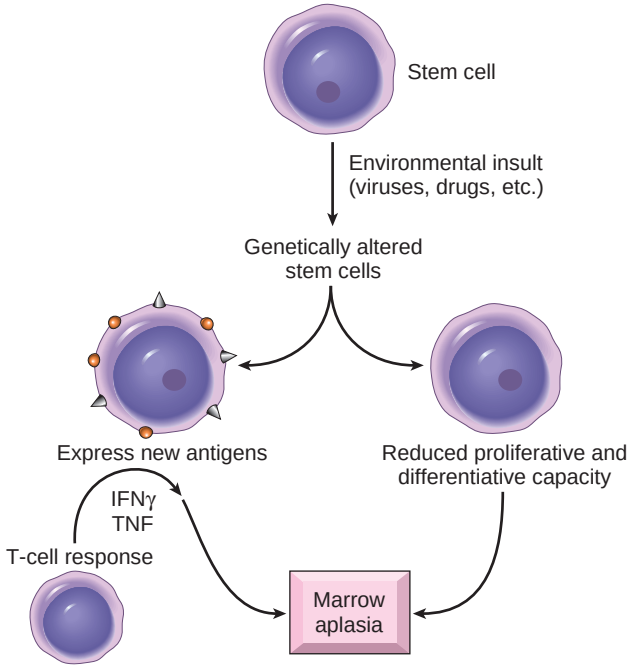

Figure 14-24 Pathophysiology of aplastic anemia. Damaged stem cells can produce progeny expressing neoantigens that evoke an autoimmune reaction, or give rise to a clonal population with reduced proliferative capacity. Either pathway could lead to marrow aplasia. See text for abbreviations.

involved in apoptosis and death pathways are up-regulated; of note, the same genes are up-regulated in normal stem cells exposed to interferon-γ.

- Even more compelling (and clinically relevant) evidence comes from experience with immunosuppressive therapy. Antithymocyte globulin and other immunosuppressive drugs such as cyclosporine produce responses in 60% to 70% of patients. It is proposed that these therapies work by suppressing or killing autoreactive T-cell clones. The antigens recognized by the autoreactive T cells are not well defined. In some instances GPI-linked proteins may be the targets, possibly explaining the previously noted association of aplastic anemia and PNH.

Alternatively, the notion that aplastic anemia results from a fundamental stem cell abnormality is supported by the presence of karyotypic aberrations in many cases; the occasional transformation of aplasias into myeloid neoplasms, typically myelodysplasia or acute myeloid leukemia; and the association with abnormally short telomeres. Some marrow insult (or a predisposition to DNA damage) presumably results in sufficient injury to limit the proliferative and differentiation capacity of stem cells. If the damage is extensive enough, aplastic anemia results. These two mechanisms are not mutually exclusive, because genetically altered stem cells might also express "neoantigens" that could serve as targets for a T-cell attack.

MORPHOLOGY

The markedly hypocellular bone marrow is largely devoid of hematopoietic cells; often only fat cells, fibrous stroma, and scattered lymphocytes and plasma cells remain. Marrow aspirates often yield little material (a "dry tap"); hence, aplasia is best appreciated in marrow biopsies (Fig. 14-25). Other nonspecific pathologic changes are related to granulocytopenia and thrombocytopenia, such as mucocutaneous bacterial infections and abnormal bleeding, respectively. If the anemia necessitates multiple transfusions, systemic hemosiderosis can appear.

Clinical Features

Aplastic anemia can occur at any age and in either sex. The onset is usually insidious. Initial manifestations vary somewhat, depending on which cell line is predominantly affected, but pancytopenia ultimately appears, with the expected consequences. Anemia can cause progressive weakness, pallor, and dyspnea; thrombocytopenia is heralded by petechiae and ecchymoses; and neutropenia manifests as frequent and persistent minor infections or the sudden onset of chills, fever, and prostration. Splenomegaly is characteristically absent; if it is present, the diagnosis of aplastic anemia should be seriously questioned. The red cells are usually slightly macrocytic and normochromic. Reticulocytopenia is the rule.

The diagnosis rests on examination of a bone marrow biopsy. It is important to distinguish aplastic anemia from other causes of pancytopenia, such as "aleukemic"

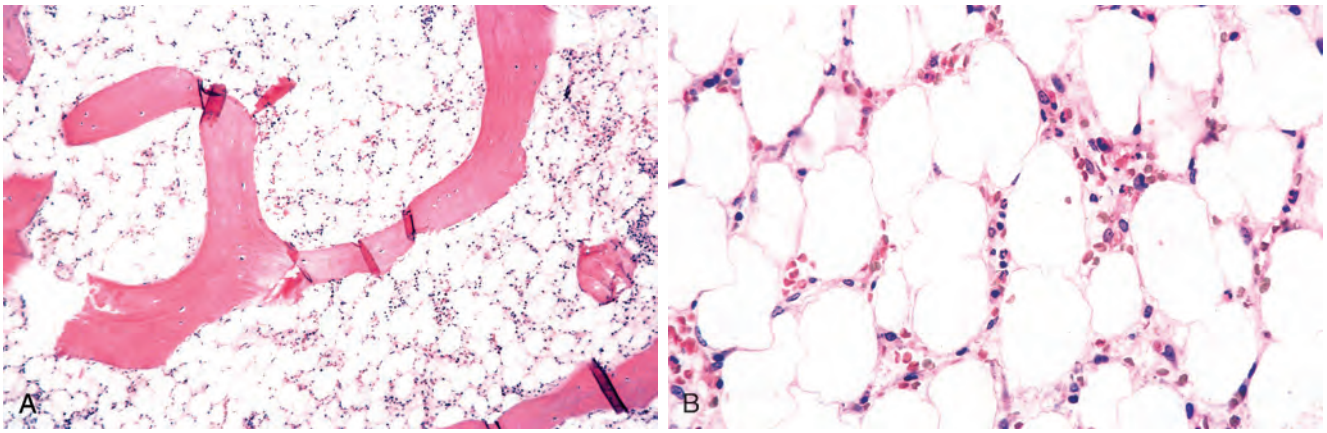

Figure 14-25 Aplastic anemia (bone marrow biopsy). Markedly hypocellular marrow contains mainly fat cells. **A,** Low power. **B,** High power. (Courtesy Dr. Steven Kroft, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)