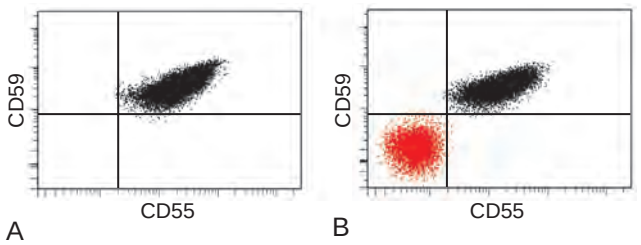

Figure 14-14 Paroxysmal nocturnal hemoglobinuria (PNH). **A,** Flow cytogram of blood from a normal individual shows that the red cells express two phosphatidylinositol glycan (PIG)-linked membrane proteins, CD55 and CD59, on their surfaces. **B,** Flow cytogram of blood from a patient with PNH shows a population of red cells that is deficient in both CD55 and CD59. As is typical of PNH, a second population of CD55+/CD59+ red cells that is derived from residual normal hematopoietic stem cells is also present. (Courtesy Dr. Scott Rodig, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

from venous thrombosis, often involving the hepatic, portal, or cerebral veins. About 5% to 10% of patients eventually develop acute myeloid leukemia or a myelodysplastic syndrome, possibly because hematopoietic stem cells have suffered some type of genetic damage.

PNH is diagnosed by flow cytometry, which provides a sensitive means for detecting red cells that are deficient in GPI-linked proteins such as CD59 (Fig. 14-14). The cardinal role of complement activation in PNH pathogenesis has been proven by therapeutic use of a monoclonal antibody called Eculizumab that prevents the conversion of C5 to C5a. This inhibitor not only reduces the hemolysis and attendant transfusion requirements, but also lowers the risk of thrombosis by up to 90%. How complement activation leads to thrombosis in patients with PNH is not clear; the absorption of NO by free hemoglobin (discussed under sickle cell disease) may be one contributing factor. The drawbacks to C5 inhibitor therapy are its high cost and an increased risk of serious or fatal meningococcal infections (as is true in individuals with inherited complement defects). Immunosuppressive drugs are sometimes beneficial for those with evidence of marrow aplasia. The only cure is hematopoietic stem cell transplantation.

Immunohemolytic Anemias

Hemolytic anemias in this category are caused by antibodies that bind to red cells, leading to their premature destruction. Although these disorders are commonly referred to as *autoimmune hemolytic anemias*, the designation immunohemolytic anemia is preferred because in some instances the immune reaction is initiated by an ingested drug. Immunohemolytic anemia can be classified based on the characteristics of the responsible antibody (Table 14-4).

The diagnosis of immunohemolytic anemia requires the detection of antibodies and/or complement on red cells from the patient. This is done using the *direct Coombs antiglobulin test*, in which the patient's red cells are mixed with sera containing antibodies that are specific for human immunoglobulin or complement. If either immunoglobulin or complement is present on the surface of the red cells, the antibodies cause agglutination, which is easily appreciated visually as clumping. In the *indirect Coombs antiglobulin test*, the patient's serum is tested for its ability to agglutinate commercially available red cells bearing particular defined antigens. This test is used to characterize the antigen target and temperature dependence of the responsible antibody. Quantitative immunologic tests to measure such antibodies directly are also available.

Table 14-4 Classification of Immunohemolytic Anemias

Warm Antibody Type (IgG Antibodies Active at 37°C)
Primary (idiopathic)
Secondary
Autoimmune disorders (particularly systemic lupus erythematosus)
Drugs
Lymphoid neoplasms
Cold Agglutinin Type (IgM Antibodies Active Below 37°C)
Acute (mycoplasmal infection, infectious mononucleosis)
Chronic
Idiopathic
Lymphoid neoplasms
Cold Hemolysin Type (IgG Antibodies Active Below 37°C)
Rare; occurs mainly in children following viral infections

Warm Antibody Type. Warm antibody type is the most common form of immunohemolytic anemia. About 50% of cases are idiopathic (primary); the others are related to a predisposing condition (Table 14-4) or exposure to a drug. Most causative antibodies are of the IgG class; less commonly, IgA antibodies are the culprits. The red cell hemolysis is mostly extravascular. IgG-coated red cells bind to Fc receptors on phagocytes, which remove red cell membrane during "partial" phagocytosis. As in hereditary spherocytosis, the loss of membrane converts the red cells to spherocytes, which are sequestered and destroyed in the spleen. Moderate splenomegaly due to hyperplasia of splenic phagocytes is usually seen.

As with other autoimmune disorders, the cause of primary immunohemolytic anemia is unknown. In many cases, the antibodies are directed against the Rh blood group antigens. The mechanisms of drug-induced immunohemolytic anemia are better understood. Two different mechanisms have been described.

- *Antigenic drugs.* In this setting hemolysis usually follows large, intravenous doses of the offending drug and occurs 1 to 2 weeks after therapy is initiated. These drugs, exemplified by penicillin and cephalosporins, bind to the red cell membrane and are recognized by antidrug antibodies. Sometimes the antibodies bind only to the drug, as in penicillin-induced hemolysis. In other cases, such as in quinidine-induced hemolysis, the antibodies recognize a complex of the drug and a membrane protein. The responsible antibodies sometimes fix complement and cause intravascular hemolysis, but more often they act as opsonins that promote extravascular hemolysis within phagocytes.
- *Tolerance-breaking drugs.* These drugs, of which the antihypertensive agent α-methyldopa is the prototype, induce in some unknown manner the production of antibodies against red cell antigens, particularly the Rh blood group antigens. About 10% of patients taking α-methyldopa develop autoantibodies, as assessed by the direct Coombs test, and roughly 1% develop clinically significant hemolysis.

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