Cold Agglutinin Type. Cold agglutinin type of immunohemolytic anemia is caused by IgM antibodies that bind red cells avidly at low temperatures (0°C to 4°C). It is less common than warm antibody immunohemolytic anemia, accounting for 15% to 30% of cases. Cold agglutinin antibodies sometimes appear transiently following certain infections, such as with *Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus, influenza virus, and human immunodeficiency virus (HIV). In these settings the disorder is self-limited and the antibodies rarely induce clinically important hemolysis. Chronic cold agglutinin immunohemolytic anemia occurs in association with certain B-cell neoplasms or as an idiopathic condition.

Clinical symptoms result from binding of IgM to red cells in vascular beds where the temperature may fall below 30°C, such as in exposed fingers, toes, and ears. IgM binding agglutinates red cells and fixes complement rapidly. As the blood recirculates and warms, IgM is released, usually before complement-mediated hemolysis can occur. However, the transient interaction with IgM is sufficient to deposit sublytic quantities of C3b, an excellent opsonin, which leads to the removal of affected red cells by phagocytes in the spleen, liver, and bone marrow. The hemolysis is of variable severity. Vascular obstruction caused by agglutinated red cells results in pallor, cyanosis, and Raynaud phenomenon (Chapter 11) in body parts exposed to cold temperature.

Cold Hemolysin Type. Cold hemolysins are autoantibodies responsible for an unusual entity known as *paroxysmal cold hemoglobinuria*. This rare disorder causes substantial, sometimes fatal, intravascular hemolysis and hemoglobinuria. The autoantibodies are IgGs that bind to the P blood group antigen on the red cell surface in cool, peripheral regions of the body. Complement-mediated lysis occurs when the cells recirculate to warm central regions, because the complement cascade functions more efficiently at 37°C. Most cases are seen in children following viral infections; in this setting the disorder is transient, and most of those affected recover within 1 month.

Treatment of warm antibody immunohemolytic anemia centers on the removal of initiating factors (i.e., drugs); when this is not feasible, immunosuppressive drugs and splenectomy are the mainstays. Chronic cold agglutinin immunohemolytic anemia caused by IgM antibodies is more difficult to treat.

Hemolytic Anemia Resulting from Trauma to Red Cells

The most significant hemolysis caused by trauma to red cells is seen in individuals with cardiac valve prostheses and microangiopathic disorders. Artificial mechanical cardiac valves are more frequently implicated than are bioprosthetic porcine or bovine valves. The hemolysis stems from shear forces produced by turbulent blood flow and pressure gradients across damaged valves. *Microangiopathic hemolytic anemia* is most commonly seen with disseminated intravascular coagulation, but it also occurs in thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), malignant hypertension, systemic lupus erythematosus, and disseminated cancer. The common pathogenic feature in these disorders is a microvascular lesion that results in luminal narrowing, often due to the deposition of fibrin and platelets. These vascular changes produce shear stresses that mechanically injure passing red cells. Regardless of the cause, traumatic damage leads to the appearance of red cell fragments (*schistocytes*), "burr cells," "helmet cells," and "triangle cells" in blood smears (Fig. 14-15).

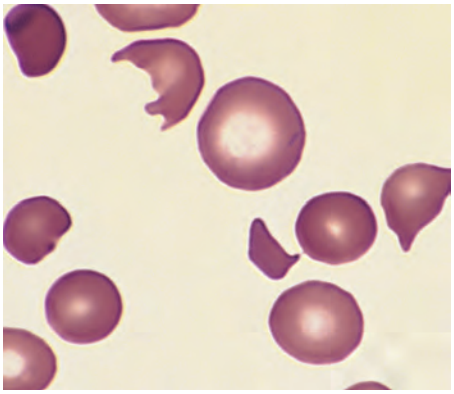

Figure 14-15 Microangiopathic hemolytic anemia. A peripheral blood smear from a person with hemolytic-uremic syndrome shows several fragmented red cells. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

KEY CONCEPTS

Hereditary Spherocytosis

- Autosomal dominant disorder caused by mutations that affect the red cell membrane skeleton, leading to loss of membrane and eventual conversion of red cells to spherocytes, which are phagocytosed and removed in the spleen
- Manifested by anemia, splenomegaly

Thalassemias

- Autosomal codominant disorders caused by mutations in α- or β-globin that reduce hemoglobin synthesis, resulting in a microcytic, hypochromic anemia.
- In β-thalassemia, unpaired α-globin chains form aggregates that damage red cell precursors and further impair erythropoiesis.

Sickle Cell Anemia

- Autosomal recessive disorder resulting from a mutation in β-globin that causes deoxygenated hemoglobin to self-associate into long polymers that distort (sickle) the red cell
- Blockage of vessels by sickled cells causes pain crises and tissue infarction, particularly of the marrow and spleen
- Red cell membrane damage caused by repeated bouts of sickling results in a moderate to severe hemolytic anemia

Glucose-6-Phosphate Dehydrogenase Deficiency

- X-linked disorder caused by mutations that destabilize G6PD, making red cells susceptible to oxidant damage

Immunohemolytic Anemias

- Caused by antibodies against either normal red cell constituents or antigens modified by haptens (e.g., drugs)
- Antibody binding results in either red cell opsonization and extravascular hemolysis or (uncommonly) complement fixation and intravascular hemolysis