are promptly coated and removed from the maternal circulation by anti-A or anti-B IgM antibodies that do not cross the placenta.
- The antibody response depends on the dose of immunizing antigen; hence, hemolytic disease develops only when the mother has experienced a significant transplacental bleed (>1 mL of Rh-positive fetal red cells).

The incidence of maternal Rh isoimmunization has decreased significantly since the use of Rhesus immune globulin (RhIg) containing anti-D antibodies. Administration of RhIg at 28 weeks and within 72 hours of delivery to Rh-negative mothers significantly decreases the risk for hemolytic disease in Rh-positive neonates and in subsequent pregnancies; RhIg is also administered following abortions, because these too can lead to immunization. Antenatal identification and management of the at-risk fetus have been greatly facilitated by amniocentesis and the advent of chorionic villus and fetal blood sampling. In addition, cloning of the *RHD* gene has resulted in efforts to determine fetal Rh status using maternal serum since it contains fetal DNA. When identified, cases of severe intrauterine hemolysis may be treated by fetal intravascular transfusions via the umbilical cord and early delivery.

The pathogenesis of fetal hemolysis caused by maternal-fetal ABO incompatibility is slightly different from that caused by differences in the Rh antigens. ABO incompatibility occurs in approximately 20% to 25% of pregnancies, but laboratory evidence of hemolytic disease occurs in only 1 in 10 of such infants, and the hemolytic disease is severe enough to require treatment in only 1 in 200 cases. Several factors account for this. First, as mentioned, most anti-A and anti-B antibodies are of the IgM type and hence do not cross the placenta. Second, neonatal red cells express blood group antigens A and B poorly. Third, many cells other than red cells express A and B antigens and thus absorb some of the transferred antibody. ABO hemolytic disease occurs almost exclusively in infants of group A or B who are born of group O mothers. For reasons unknown, certain group O women possess IgG antibodies directed against group A or B antigens (or both) even without prior sensitization. Therefore, the firstborn may be affected. Fortunately, even with transplacentally acquired antibodies, lysis of the infant's red cells is minimal. There is no effective protection against ABO reactions.

There are two consequences of excessive destruction of red cells in the neonate (Fig. 10-10). The severity of these changes varies considerably, depending on the degree of hemolysis and the maturity of the infant.

- *Anemia* is a direct result of red cell loss. If hemolysis is mild, increased red cell production may suffice to maintain near normal levels of red cells. However, with more severe hemolysis, progressive anemia develops and may result in hypoxic injury to the heart and liver. Because of liver injury, plasma protein synthesis decreases, and levels of these proteins may drop to as low as 2 to 2.5 mg/dL. Cardiac hypoxia may lead to cardiac decompensation and failure. The combination of reduced plasma oncotic pressure and increased hydrostatic pressure in the circulation (secondary to cardiac failure) results in generalized edema and anasarca, culminating in hydrops fetalis.
- *Jaundice* develops because hemolysis produces unconjugated bilirubin (Chapter 18). Bilirubin also passes through the infant's poorly developed blood-brain barrier. Being water insoluble, bilirubin blinds to lipids in the brain, and can damage the CNS, causing *kernicterus* (see Fig. 10-13).

Nonimmune Hydrops

The three major causes of nonimmune hydrops include cardiovascular defects, chromosomal anomalies, and fetal anemia (Table 10-3). Both structural and functional cardiovascular defects, such as congenital malformations and arrhythmias, may result in intrauterine cardiac failure and hydrops. Among the chromosomal anomalies, 45,X karyotype (Turner syndrome) and the trisomies 21 and 18 are associated with fetal hydrops because of the accompanying structural cardiac anomalies. In Turner syndrome, abnormalities of lymphatic drainage from the neck may lead to postnuchal fluid accumulation *(cystic hygromas)* as well. Fetal anemia, not caused by Rh- or ABO-associated antibodies, can also result in hydrops. In fact, in some parts of the world (e.g., Southeast Asia), severe fetal anemia due to homozygous α-thalassemia, resulting from deletion of all four α-globin genes, is probably the most common cause of nonimmune hydrops (Chapter 14). Transplacental infection by parvovirus B19 is rapidly emerging as an important cause of hydrops (see earlier). The virus gains preferential entry into erythroid precursors (normoblasts), where it replicates, leading to apoptosis of red cell progenitors and isolated red cell aplasia. Parvoviral intranuclear inclusions can be seen within circulating and marrow erythroid precursors (Fig. 10-9). Approximately 10% of cases of nonimmune hydrops are related to monozygous twin pregnancies and twin-to-twin transfusion occurring through anastomoses between the two circulations.

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The anatomic findings in fetuses with intrauterine fluid accumulation vary with both the severity of the disease and the underlying etiology. As previously noted, hydrops fetalis represents the most severe and generalized manifestation (Fig. 10-11), and lesser degrees of edema such as isolated pleural, peritoneal, or postnuchal fluid collections can occur. Accordingly, infants may be stillborn, die within the first few days, or recover completely. The presence of dysmorphic features suggests a chromosomal abnormality; postmortem examination may reveal an underlying cardiac anomaly.

In hydrops associated with fetal anemia, both fetus and placenta are characteristically pale; in most cases the liver and spleen are enlarged from cardiac failure and congestion. Additionally, the bone marrow demonstrates compensatory hyperplasia of erythroid precursors (parvovirus-associated red cell aplasia being a notable exception), and extramedullary hematopoiesis is present in the liver, spleen, and lymph nodes, and possibly other tissues such as the kidneys, lungs, and even the heart. The increased hematopoietic activity accounts for the presence in the peripheral circulation of large numbers of immature red cells, including reticulocytes, normoblasts, and erythroblasts **(erythroblastosis fetalis)** (Fig. 10-12).