in many cases the increased output of red cells from the bone marrow can fully balance an increased destruction of red cells. In such cases, we say that hemolysis is *compensated*. The pathophysiology of compensated hemolysis is similar to what we have just described, except there is no anemia. This notion is important from the diagnostic point of view, because a patient with a hemolytic condition, even an inherited one, may present without anemia; and it is also important from the point of view of management, because compensated hemolysis may become "decompensated," i.e., anemia may suddenly appear, in certain circumstances, for instance in pregnancy, folate deficiency, or renal failure interfering with adequate EPO production. Another general feature of chronic HAs is seen when any intercurrent condition, such as an acute infection, depresses erythropoiesis. When this happens, in view of the increased rate of red cell turnover, the effect will be predictably much more marked than in a person who does not have hemolysis. The most dramatic example is infection by parvovirus B19, which may cause a rather precipitous fall in hemoglobin—an occurrence sometimes referred to as *aplastic crisis*.

INHERITED HEMOLYTIC ANEMIAS

There are three essential components in the red cell: (1) hemoglobin, (2) the membrane-cytoskeleton complex, and (3) the metabolic machinery necessary to keep hemoglobin and the membrane-cytoskeleton complex in working order. Diseases caused by abnormalities of hemoglobin, or hemoglobinopathies, are covered in Chap. 127. Here we will deal with diseases of the other two components.

Hemolytic Anemias due to Abnormalities of the Membrane-Cytoskeleton Complex The detailed architecture of the red cell membrane is complex, but its basic design is relatively simple (Fig. 129-2). The lipid bilayer incorporates phospholipids and cholesterol, and it is spanned by a number of proteins that have their hydrophobic transmembrane domain(s) embedded in the membrane; most of these proteins also extend to both the outside (extracellular domains) and the inside of the cell (cytoplasmic domains). Other proteins are tethered to the membrane through a glycosylphosphatidylinositol (GPI) anchor; these have only an extracellular domain, and they include ion channels, receptors for complement components, and receptors for other ligands. The most abundant red cell membrane proteins are glycophorins and the so-called *band 3*, an anion transporter. The extracellular domains of many of these proteins are heavily glycosylated, and they carry antigenic determinants that correspond to blood groups. Underneath the membrane, and tangential to it, is a network of other proteins that make up the cytoskeleton. The main cytoskeletal protein is spectrin, the basic unit of which is a dimer of α-spectrin and β-spectrin. The membrane is physically linked to the cytoskeleton by a third set of proteins (including ankyrin and the so-called *band 4.1* and *band 4.2*), which thus make these two structures intimately connected to each other.

The membrane-cytoskeleton complex is so integrated that, not surprisingly, an abnormality of almost any of its components will be disturbing or disruptive, causing structural failure, which results ultimately in hemolysis. These abnormalities are almost invariably inherited mutations; thus, diseases of the membrane-cytoskeleton complex belong to the category of inherited HAs. Before the red cells lyse, they often exhibit more or less specific morphologic changes that alter the normal biconcave disk shape. Thus, the majority of the diseases in this group have been known for over a century as *hereditary spherocytosis* and *hereditary elliptocytosis*. Over the past 20 years, their molecular basis has been elucidated; it has emerged that both conditions can arise from mutations in several genes with considerable overlap (Fig. 129-3).

HEREDITARY SPHEROCYTOSIS (HS) This is a relatively common type of genetically determined HA, with an estimated frequency of at least 1 in 5000. Its identification is credited to Minkowksy and Chauffard, who, at the end of the nineteenth century, reported families who had the presence of numerous spherocytes in the peripheral blood (Fig 129-4*A*). In vitro studies revealed that the red cells were abnormally susceptible to lysis in hypotonic media; indeed, the presence of *osmotic fragility* became the main diagnostic test for HS. Today we know that HS, thus defined, is genetically heterogeneous; i.e., it can arise from a variety of mutations in one of several genes (Table 129-3). It has been also recognized that the inheritance of HS is not always autosomal dominant (with the patient being heterozygous); indeed, some of the most severe forms are instead autosomal recessive (with the patient being homozygous).

Clinical presentation and diagnosis The spectrum of clinical severity of HS is broad. Severe cases may present in infancy with severe anemia, whereas mild cases may present in young adults or even later in life. The main clinical findings are jaundice, an enlarged spleen, and often gallstones; indeed, it may be the finding of gallstones in a young person that triggers diagnostic investigations.

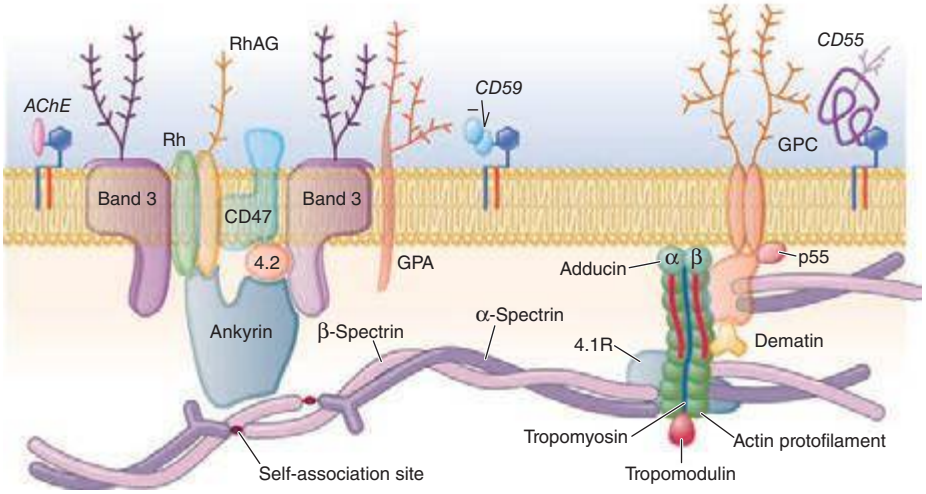

FIGURE 129-2 The red cell membrane. In this figure, one sees, within the lipid bilayer, several membrane proteins, of which band 3 (anion exchanger 1 [AE1]) is the most abundant; the α-β spectrin dimers that associate to form most of the cytoskeleton; and several proteins (e.g., ankyrin) that connect the membrane to the cytoskeleton. In addition, as examples of glycosylphosphatidylinositol (GPI)-linked proteins, one sees acetylcholinesterase (AChE) and the two complement-regulatory proteins CD59 and CD55. The (nonrealistic) shapes of the protein moieties of the GPI-linked proteins are meant to indicate that they can be very different from each other and that, unlike with the other membrane proteins shown, the entire polypeptide chain is extracellular. Branched lines symbolize carbohydrate moiety of proteins. The molecules are obviously not drawn to the same scale. Additional explanations can be found in the text. *(From N Young et al: Clinical Hematology. Copyright Elsevier, 2006; with permission.)*