

some stage of the disease, the marrow may become hypocellular or even frankly aplastic (see below).

The definitive diagnosis of PNH must be based on the demonstration that a substantial proportion of the patient's red cells have an increased susceptibility to complement (C), due to the deficiency on their surface of proteins (particularly CD59 and CD55) that normally protect the red cells from activated C. The sucrose hemolysis test is unreliable; in contrast, the acidified serum (Ham) test is highly reliable but is carried out only in a few laboratories. The gold standard today is flow cytometry, which can be carried out on granulocytes as well as on red cells and has a very high sensitivity. In PNH, characteristically, one sees a bimodal distribution of cells, with a discrete population that is CD59 and CD55 negative. Although very small populations of CD59(–) cells are of interest in terms of pathophysiology (particularly of aplastic anemia [AA]), no patient should be diagnosed with PNH unless the proportion is substantial: in first approximation at least 5% of the total red cells and at least 20% of the total granulocytes.

PATHOPHYSIOLOGY Hemolysis in PNH is mainly intravascular and is due to an intrinsic abnormality of the red cell, which makes it exquisitely sensitive to activated C, whether C is activated through the alternative pathway or through an antigen-antibody reaction (classic pathway). The former mechanism is mainly responsible for chronic hemolysis in PNH; the latter explains why the hemolysis can be dramatically exacerbated in the course of a viral or bacterial infection. Hypersusceptibility to C is due to deficiency in the red cell membrane of several protective proteins (**Fig. 100-10**), among which CD59 is the most important because it is able to hinder the insertion into the membrane of C9 polymers (the so-called membrane attack complex, or MAC). The molecular basis for the deficiency of these proteins has been pinpointed not to a defect in any of the respective genes, but rather to the shortage of a unique glycolipid molecule, GPI (**Fig. 100-2**), which, through a peptide bond, anchors these proteins to the surface membrane of cells. The shortage of GPI is due in turn to a somatic mutation in an X-linked gene, called *PIGA*, required for an early step in GPI biosynthesis. As a result, the