Rhesus antibody anti-e. In patients who have this antigen, the anti-e is a true autoantibody, which then causes an autoimmune HA (see below). Usually this will gradually subside once methyldopa is discontinued.

Severe intravascular hemolysis can be caused by the venom of certain snakes (cobras and vipers), and HA can also follow spider bites.

Paroxysmal Nocturnal Hemoglobinuria (PNH) PNH is an acquired chronic HA characterized by persistent intravascular hemolysis subject to recurrent exacerbations. In addition to hemolysis, there is often pancytopenia and a distinct tendency to venous thrombosis. This triad makes PNH a truly unique clinical condition; however, when not all of these three features are manifest on presentation, the diagnosis is often delayed, although it can always be made by appropriate laboratory investigations (see below).

PNH has about the same frequency in men and women and is encountered in all populations throughout the world, but it is a rare disease; its prevalence is estimated to be approximately 5 per million (it may be somewhat less rare in Southeast Asia and in the Far East). There is no evidence of inherited susceptibility. PNH has never been reported as a congenital disease, but it can present in small children or as late as in the seventies, although most patients are young adults.

CLINICAL FEATURES The patient may seek medical attention because, one morning, she or he passed blood instead of urine **(Fig. 129-9)**. This distressing or frightening event may be regarded as the classical presentation; however, more frequently, this symptom is not noticed or is suppressed. Indeed, the patient often presents simply as a problem in the differential diagnosis of *anemia*, whether symptomatic or discovered incidentally. Sometimes, the anemia is associated from the outset with neutropenia, thrombocytopenia, or both, thus signaling an element of bone marrow failure (see below). Some patients may present with recurrent attacks of severe abdominal pain defying a specific diagnosis and eventually found to be related to thrombosis. When thrombosis affects the hepatic veins, it may produce acute hepatomegaly and ascites, i.e., a full-fledged Budd-Chiari syndrome, which, in the absence of liver disease, ought to raise the suspicion of PNH.

The *natural history* of PNH can extend over decades. Without treatment, the median survival is estimated to be about 8–10 years; in the past, the most common cause of death has been venous thrombosis, followed by infection secondary to severe neutropenia and hemorrhage secondary to severe thrombocytopenia. Rarely (estimated 1–2% of all cases), PNH may terminate in acute myeloid leukemia. On the other hand, full spontaneous recovery from PNH has been documented, albeit rarely.

LABORATORY INVESTIGATIONS AND DIAGNOSIS The most consistent blood finding is anemia, which may range from mild to moderate to very severe. The anemia is usually normomacrocytic, with unremarkable red cell morphology. If the MCV is high, it is usually largely accounted for by reticulocytosis, which may be quite marked (up to 20%, or up to 400,000/μL). The anemia may become microcytic if the patient is allowed to become iron deficient as a result of chronic urinary blood loss through hemoglobinuria. Unconjugated bilirubin is mildly or moderately elevated; LDH is typically markedly elevated (values in the thousands are common); and haptoglobin is usually undetectable. All of these findings make the diagnosis of hemolytic anemia compelling. Hemoglobinuria may be overt in a random urine sample; if it is not, it may be helpful to obtain serial urine samples, because hemoglobinuria can vary dramatically from day to day and even from hour to hour. The bone marrow is usually cellular, with marked to massive erythroid hyperplasia, often with mild to moderate dyserythropoietic features (not to be confused with myelodysplastic syndrome). At 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 labs. The gold standard today is flow cytometry, which can be carried out on granulocytes as well as on red cells. A bimodal distribution of cells, with a discrete population that is CD59 and CD55 negative, is diagnostic of PNH. In PNH patients, this population is 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 it is activated through the alternative pathway or through an antigen-antibody reaction. 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 of several protective membrane proteins **(Fig. 129-10)**, of which CD59 is the most important, because it hinders the insertion into the membrane of C9 polymers. 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. 129-2), which, through a peptide bond, anchors these proteins to the surface membrane of cells. The shortage of GPI is due in turn to a mutation in an X-linked gene, called *PIG-A*, required for an early step in GPI biosynthesis. In virtually each patient, the *PIG-A* mutation is different. This is not surprising, because these mutations are not inherited; rather, each one takes place de novo in a hemopoietic stem cell (i.e., they are somatic mutations). As a result, the patient's marrow is a mosaic of mutant and nonmutant cells, and the peripheral blood always contains both PNH cells and normal (non-PNH) cells. Thrombosis is one of the most immediately life-threatening complications of PNH and yet one of the least understood in its pathogenesis. It could be that deficiency of CD59 on the PNH platelet causes inappropriate platelet activation; however, other mechanisms are possible.

BONE MARROW FAILURE (BMF) AND RELATIONSHIP BETWEEN PNH AND APLASTIC ANEMIA (AA) It is not unusual that patients with firmly established PNH have a previous history of well-documented AA; indeed, BMF preceding overt PNH is probably the rule rather than the exception. On the other hand, sometimes a patient with PNH becomes less hemolytic and more pancytopenic and ultimately has the clinical picture of AA. Because AA is probably an organ-specific autoimmune disease, in which T cells cause damage to hematopoietic stem cells, the same may be true of PNH, with the specific proviso that the damage spares PNH stem cells. *PIG-A* mutations can be demonstrated in normal people, and there is evidence from mouse models that PNH stem cells do not expand when the rest of the bone marrow is normal. Thus, we can visualize PNH as always having two components: failure of normal hematopoiesis and massive expansion of a PNH clone. Findings supporting this notion include skewing of the T cell repertoire and the demonstration of GPI-reactive T cells in patients with PNH.

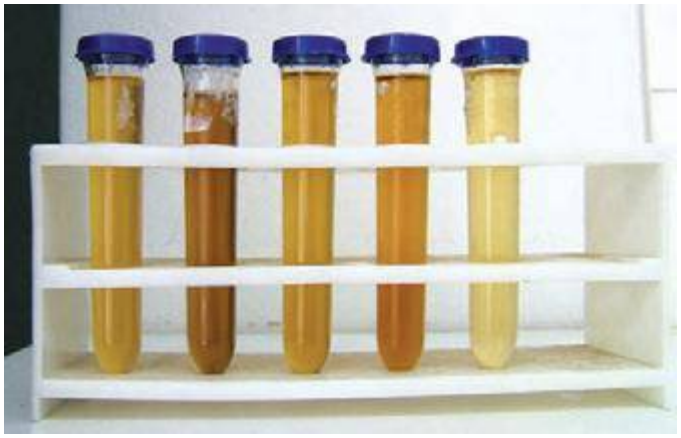

FIGURE 129-9 Consecutive urine samples from a patient with paroxysmal nocturnal hemoglobinuria (PNH). The variation in the severity of hemoglobinuria within hours is probably unique to this condition.