the formation of membrane attack complex (MAC). In an international, placebo-controlled, randomized trial of 87 patients (so far the only controlled therapeutic trial in PNH) who had been selected on grounds of having severe hemolysis making them transfusion-dependent, eculizumab proved effective and was licensed in 2007. Eculizumab, by abrogating complement-dependent intravascular hemolysis, significantly improves the quality of life of PNH patients. One would expect that the need for blood transfusion would also be abrogated; indeed, this is the case in about one-half of patients, in many of whom there is also a rise in hemoglobin levels. In the remaining patients, however, the anemia remains sufficiently severe to require blood transfusion. One reason for this is that, once the distal complement pathway is blocked, red cells no longer destroyed by the MAC become opsonized by complement (C3) fragments and undergo extravascular hemolysis (Fig. 129-10). The extent to which this happens depends in part on a genetic polymorphism of the complement receptor CR1. Based on its half-life, eculizumab must be administered intravenously every 14 days. The only form of treatment that currently can provide a definitive cure for PNH is allogeneic BMT. When an HLA-identical sibling is available, BMT should be offered to any young patient with severe PNH; the availability of eculizumab has decreased significantly the proportion of patients receiving BMT.

For patients with the PNH-AA syndrome, immunosuppressive treatment with antithymocyte globulin and cyclosporine A may be indicated, especially in order to relieve severe thrombocytopenia and/or neutropenia in patients in whom these were the main problem(s); of course, this treatment will have little or no effect on hemolysis. Any patient who has had venous thrombosis or who has a genetically determined thrombophilic state in addition to PNH should be on regular anticoagulant prophylaxis. With thrombotic complications that do not resolve otherwise, thrombolytic treatment with tissue plasminogen activator may be indicated.

ANEMIA DUE TO ACUTE BLOOD LOSS

Blood loss causes anemia by two main mechanisms: (1) by the direct loss of red cells; and (2) if the loss of blood is protracted, it will gradually deplete iron stores, eventually resulting in iron deficiency. The latter type of anemia is covered in **Chap. 126**; here we are concerned with the former type, i.e., *posthemorrhagic anemia*, which follows *acute* blood loss. This can be *external* (e.g., after trauma or obstetric hemorrhage) or *internal* (e.g., from bleeding in the gastrointestinal tract, rupture of the spleen, rupture of an ectopic pregnancy, subarachnoid hemorrhage). In any of these cases, after the sudden loss of a large amount of blood, there are three clinical/pathophysiologic stages. (1) At first, the dominant feature is hypovolemia, which poses a threat particularly to organs that normally have a high blood supply, like the brain and the kidneys; therefore, loss of consciousness and acute renal failure are major threats. It is important to note that at this stage an ordinary blood count will not show anemia, because the hemoglobin concentration is not affected. (2) Next, as an emergency response, baroreceptors and stretch receptors will cause release of vasopressin and other peptides, and the body will shift fluid from the extravascular to the intravascular compartment, producing hemodilution; thus, the hypovolemia gradually converts to anemia. The degree of anemia will reflect the amount of blood lost. If after 3 days the hemoglobin is, for example, 7 g/dL, it means that about half of the entire blood has been lost. (3) Provided bleeding does not continue, the bone marrow response will gradually ameliorate the anemia.

The diagnosis of acute posthemorrhagic anemia (APHA) is usually straightforward, although sometimes internal bleeding episodes (e.g., after a traumatic injury), even when large, may not be immediately obvious. Whenever an abrupt fall in hemoglobin has taken place, whatever history is given by the patient, APHA should be suspected. Supplementary history may have to be obtained by asking the appropriate questions, and appropriate investigations (e.g., a sonogram or an endoscopy) may have to be carried out.

TREATMENT ANEMIA DUE TO ACUTE BLOOD LOSS

With respect to treatment, a two-pronged approach is imperative. (1) In many cases, the blood lost needs to be replaced promptly. Unlike with many chronic anemias, when finding and correcting the cause of the anemia is the first priority and blood transfusion may not be even necessary because the body is adapted to the anemia, with acute blood loss the reverse is true; because the body is not adapted to the anemia, blood transfusion takes priority. (1) While the emergency is being confronted, it is imperative to stop the hemorrhage and to eliminate its source.

A special type of APHA is blood loss during and immediately after surgery, which can be substantial (e.g., up to 2 L in the case of a radical prostatectomy). Of course with elective surgical procedures, the patient's own stored blood may be available (through preoperative autologous blood donation), and in any case, blood loss ought to have been carefully monitored/measured. The fact that this blood loss is iatrogenic dictates that ever more effort should be invested in optimizing its management.

A Holy Grail of emergency medicine for a long time has been the idea of a blood substitute that would be universally available, suitable for all recipients, easy to store and to transport, safe, and as effective as blood itself. Two main paths have been pursued: (1) fluorocarbon synthetic chemicals that bind oxygen reversibly, and (2) artificially modified hemoglobins, known as hemoglobin-based oxygen carriers (HBOCs). Although there are numerous anecdotal reports of the use of both approaches in humans, and although HBOCs have reached the stage of phase 2–3 clinical trials, no "blood substitute" has yet become standard treatment.

130 Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia

Neal S. Young

The hypoproliferative anemias are normochromic, normocytic, or macrocytic and are characterized by a low reticulocyte count. Hypoproliferative anemia is also a prominent feature of hematologic diseases that are described as bone marrow failure states; these include aplastic anemia, myelodysplastic syndrome (MDS), pure red cell aplasia (PRCA), and myelophthisis. Anemia in these disorders is often not a solitary or even the major hematologic finding. More frequent in bone marrow failure is *pancytopenia*: anemia, leukopenia, and thrombocytopenia. Low blood counts in the marrow failure diseases result from deficient hematopoiesis, as distinguished from blood count depression due to peripheral destruction of red cells (hemolytic anemias), platelets (idiopathic thrombocytopenic purpura [ITP] or due to splenomegaly), and granulocytes (as in the immune leukopenias). Marrow damage and dysfunction also may be secondary to infection, inflammation, or cancer.

Hematopoietic failure syndromes are classified by dominant morphologic features of the bone marrow **(Table 130-1)**. Although practical distinction among these syndromes usually is clear, some processes are so closely related that the diagnosis may be complex. Patients may seem to suffer from two or three related diseases simultaneously, or one diagnosis may appear to evolve into another. Many of these syndromes share an immune-mediated mechanism of marrow destruction and some element of genomic instability resulting in a higher rate of malignant transformation.

It is important that the internist and general practitioner recognize the marrow failure syndromes, as their prognosis may be poor if the