Table 14-2 Adult Reference Ranges for Red Cells*

Measurement (units)	Men	Women
Hemoglobin (gm/dL)	13.6-17.2	12.0-15.0
Hematocrit (%)	39-49	33-43
Red cell count ($\times 10^6/\mu L$)	4.3-5.9	3.5-5.0
Reticulocyte count (%)	0.5-1.5	
Mean cell volume (fL)	82-96	
Mean cell hemoglobin (pg)	27-33	
Mean cell hemoglobin concentration (gm/dL)	33-37	
Red cell distribution width	11.5-14.5	

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used in interpreting test results.

oliguria and anuria can develop as a result of renal hypoperfusion. Central nervous system hypoxia can cause headache, dimness of vision, and faintness.

Anemias of Blood Loss

Acute Blood Loss

The effects of acute blood loss are mainly due to the loss of intravascular volume, which if massive can lead to cardiovascular collapse, shock, and death. The clinical features depend on the rate of hemorrhage and whether the bleeding is external or internal. If the patient survives, the blood volume is rapidly restored by the intravascular shift of water from the interstitial fluid compartment. This fluid shift results in hemodilution and a lowering of the hematocrit. The reduction in oxygenation triggers increased secretion of erythropoietin from the kidney, which stimulates the proliferation of committed erythroid progenitors (CFU-E) in the marrow (see Fig. 13-1). It takes about 5 days for the progeny of these CFU-Es to mature and appear as newly released red cells (reticulocytes) in the peripheral blood. The iron in hemoglobin is recaptured if red cells extravasate into tissues, whereas bleeding into the gut or out of the body leads to iron loss and possible iron deficiency, which can hamper the restoration of normal red cell counts.

Significant bleeding results in predictable changes in the blood involving not only red cells, but also white cells and platelets. If the bleeding is sufficiently massive to cause a decrease in blood pressure, the compensatory release of adrenergic hormones mobilizes granulocytes from the intravascular marginal pool and results in *leukocytosis* (see Fig. 13-2). Initially, red cells appear normal in size and color (normocytic, normochromic). However, as marrow production increases there is a striking increase in the reticulocyte count (*reticulocytosis*), which reaches 10% to 15% after 7 days. Reticulocytes are larger in size than normal red cells (macrocytes) and have a blue-red polychromatophilic cytoplasm. Early recovery from blood loss is also often accompanied by *thrombocytosis*, which results from an increase in platelet production.

Chronic Blood Loss

Chronic blood loss induces anemia only when the rate of loss exceeds the regenerative capacity of the marrow or when iron reserves are depleted and iron deficiency anemia appears (see later).

Hemolytic Anemias

Hemolytic anemias share the following features:

- A shortened red cell life span below the normal 120 days
- Elevated erythropoietin levels and a compensatory increase in erythropoiesis
- Accumulation of hemoglobin degradation products that are created as part of the process of red cell hemolysis

The physiologic destruction of senescent red cells takes place within macrophages, which are abundant in the spleen, liver, and bone marrow. This process appears to be triggered by age-dependent changes in red cell surface proteins, which lead to their recognition and phagocytosis. In the great majority of hemolytic anemias the premature destruction of red cells also occurs within phagocytes, an event that is referred to as *extravascular hemolysis*. If persistent, extravascular hemolysis leads to a hyperplasia of phagocytes manifested by varying degrees of *splenomegaly*.

Extravascular hemolysis is generally caused by alterations that render the red cell less deformable. Extreme changes in shape are required for red cells to navigate the splenic sinusoids successfully. Reduced deformability makes this passage difficult, leading to red cell sequestration and phagocytosis by macrophages located within the splenic cords. Regardless of the cause, the principal clinical features of extravascular hemolysis are *anemia, splenomegaly, and jaundice.* Some hemoglobin inevitably escapes from phagocytes, which leads to variable decreases in plasma *haptoglobin*, an α_2-globulin that binds free hemoglobin and prevents its excretion in the urine. Because much of the pathologic destruction of red cells occurs in the spleen, individuals with extravascular hemolysis often benefit from splenectomy.

Less commonly, *intravascular hemolysis* predominates. Intravascular hemolysis of red cells may be caused by mechanical injury, complement fixation, intracellular parasites (e.g., falciparum malaria, Chapter 8), or exogenous toxic factors. Causes of mechanical injury include trauma caused by cardiac valves, thrombotic narrowing of the microcirculation, or repetitive physical trauma (e.g., marathon running and bongo drum beating). Complement fixation occurs in a variety of situations in which antibodies recognize and bind red cell antigens. Toxic injury is exemplified by clostridial sepsis, which results in the release of enzymes that digest the red cell membrane.

Whatever the mechanism, intravascular hemolysis is manifested by *anemia, hemoglobinemia, hemoglobinuria, hemosiderinuria, and jaundice.* The large amounts of free hemoglobin released from lysed red cells are promptly bound by haptoglobin, producing a complex that is rapidly cleared by mononuclear phagocytes. As serum haptoglobin is depleted, free hemoglobin oxidizes to *methemoglobin*, which is brown in color. The renal proximal tubular cells reabsorb and catabolize much of the filtered hemoglobin and methemoglobin, but some passes out in the urine, imparting a red-brown color. Iron released from hemoglobin can accumulate within tubular cells, giving rise to *renal hemosiderosis*. Concomitantly, heme groups derived from hemoglobin-haptoglobin complexes are catabolized to bilirubin within mononuclear phagocytes, leading to jaundice. Unlike in extravascular hemolysis, splenomegaly is not seen.