anemia and reduce the incidence of NTDs, even in countries with fortification of the diet. The levels of fortification provide up to 400 µg daily on average in Chile, but in most countries, it is nearer to 200 µg, so periconceptual folic acid is still needed. Studies in early pregnancy show significant lack of compliance with the folic acid supplements, emphasizing the benefit of food fortification. Supplemental folic acid reduces the incidence of birth defects in babies born to diabetic mothers. In women who have had a previous fetus with an NTD, 5 mg daily is recommended when pregnancy is contemplated and throughout the subsequent pregnancy.

Infancy and Childhood The incidence of folate deficiency is so high in the smallest premature babies during the first 6 weeks of life that folic acid (e.g., 1 mg daily) should be given routinely to those weighing <1500 g at birth and to larger premature babies who require exchange transfusions or develop feeding difficulties, infections, or vomiting and diarrhea.

The World Health Organization currently recommends routine supplementation with iron and folic acid in children in countries where iron deficiency is common and child mortality, largely due to infectious diseases, is high. However, some studies suggest that in areas where malaria rates are high, this approach may increase the incidence of severe illness and death. Even where malaria is rare, there appears to be no survival benefit.

MEGALOBLASTIC ANEMIA NOT DUE TO COBALAMIN OR FOLATE DEFICIENCY OR ALTERED METABOLISM

This may occur with many antimetabolic drugs (e.g., hydroxyurea, cytosine arabinoside, 6-mercaptopurine) that inhibit DNA replication. Antiviral nucleoside analogues used in treatment of HIV infection may also cause macrocytosis and megaloblastic marrow changes. In the rare disease orotic aciduria, two consecutive enzymes in purine synthesis are defective. The condition responds to therapy with uridine, which bypasses the block. In thiamine-responsive megaloblastic anemia, there is a genetic defect in the high-affinity thiamine transport (*SLC19A2*) gene. This causes defective RNA ribose synthesis through impaired activity of transketolase, a thiamine-dependent enzyme in the pentose cycle. This leads to reduced nucleic acid production. It may be associated with diabetes mellitus and deafness and the presence of many ringed sideroblasts in the marrow. The explanation is unclear for megaloblastic changes in the marrow in some patients with acute myeloid leukemia and myelodysplasia.

129 Hemolytic Anemias and Anemia Due to Acute Blood Loss

Lucio Luzzatto

DEFINITIONS

A finite life span is a distinct characteristic of red cells. Hence, a logical, time-honored classification of anemias is in three groups: (1) decreased production of red cells, (2) increased destruction of red cells, and (3) acute blood loss. Decreased production is covered in **Chaps. 126, 128, and 130**; increased destruction and acute blood loss are covered in this chapter.

All patients who are anemic as a result of either increased destruction of red cells or acute blood loss have one important element in common: the anemia results from overconsumption of red cells from the peripheral blood, whereas the supply of cells from the bone marrow is normal (indeed, it is usually increased). On the other hand, these two groups differ in that physical loss of red cells from the bloodstream or *from* the body itself, as in acute hemorrhage, is fundamentally different from destruction of red cells *within* the body, as in hemolytic anemias.

TABLE 129-1 CLASSIFICATION OF HEMOLYTIC ANEMIAS[a]

	Intracorpuscular Defects	Extracorpuscular Factors
Hereditary	Hemoglobinopathies Enzymopathies Membrane-cytoskeletal defects	Familial (atypical) hemolytic-uremic syndrome
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic) Toxic agents Drugs Infectious Autoimmune

[a]Hereditary causes correlate with intracorpuscular defects, because these defects are due to inherited mutations; the one exception is PNH, because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorpuscular factors, because mostly these factors are exogenous; the one exception is familial hemolytic-uremic syndrome (HUS; often referred to as atypical HUS), because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells.

Therefore, the clinical aspects and pathophysiology of anemia in these two groups of patients are quite different, and they will be considered separately.

HEMOLYTIC ANEMIAS

With respect to primary etiology, anemias due to increased destruction of red cells, which we know as hemolytic anemias (HAs), may be *inherited* or *acquired*; from a clinical point of view, they may be more *acute* or more *chronic*, and they may vary from mild to very severe; the site of hemolysis may be predominantly *intravascular* or *extravascular*. With respect to mechanisms, HAs may be due to *intracorpuscular* causes or to *extracorpuscular* causes **(Table 129-1)**. But before reviewing the individual types of HA, it is appropriate to consider what they have in common.

GENERAL CLINICAL AND LABORATORY FEATURES

The clinical presentation of a patient with anemia is greatly influenced in the first place by whether the onset is abrupt or gradual, and HAs are no exception. A patient with autoimmune HA or with favism may be a medical emergency, whereas a patient with mild hereditary spherocytosis or with cold agglutinin disease may be diagnosed after years. This is due in large measure to the remarkable ability of the body to adapt to anemia when it is slowly progressing **(Chap. 77)**.

What differentiates HAs from other anemias is that the patient has signs and symptoms arising directly from hemolysis **(Table 129-2)**. At the clinical level, the main sign is *jaundice*; in addition, the patient may report discoloration of the urine. In many cases of HA, the spleen is enlarged, because it is a preferential site of hemolysis; and in some cases, the liver may be enlarged as well. In all severe congenital forms of HA, there may also be skeletal changes due to overactivity of the bone marrow (although they are never as severe as they are in thalassemia).

TABLE 129-2 FEATURES COMMON TO MOST PATIENTS WITH A HEMOLYTIC DISORDER

General examination	Jaundice, pallor
Other physical findings	Spleen may be enlarged; bossing of skull in severe congenital cases
Hemoglobin level	From normal to severely reduced
MCV, MCH	Usually increased
Reticulocytes	Increased
Bilirubin	Increased (mostly unconjugated)
LDH	Increased (up to 10 time normal with intravascular hemolysis)
Haptoglobin	Reduced to absent (if hemolysis in part intravascular)

Abbreviations: LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.