

- i. Disease—90% HbS, 8% HbF, 2% HbA₂ (no HbA)
- ii. Trait—55% HbA, 43% HbS, 2% HbA₂

III. HEMOGLOBIN C

- A. Autosomal recessive mutation in β chain of hemoglobin
 - 1. Normal glutamic acid is replaced by lysine.
 - 2. Less common than sickle cell disease
- B. Presents with mild anemia due to extravascular hemolysis
- C. Characteristic HbC crystals are seen in RBCs on blood smear (Fig. 5.10).

NORMOCYTIC ANEMIAS WITH PREDOMINANT INTRAVASCULAR HEMOLYSIS

I. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- A. Acquired defect in myeloid stem cells resulting in absent glycosylphosphatidylinositol (GPI); renders cells susceptible to destruction by complement
 - 1. Blood cells coexist with complement.
 - 2. Decay accelerating factor (DAF) on the surface of blood cells protects against complement-mediated damage by inhibiting C3 convertase.
 - 3. DAF is secured to the cell membrane by GPI (an anchoring protein).
 - 4. Absence of GPI leads to absence of DAF, rendering cells susceptible to complement-mediated damage.
- B. Intravascular hemolysis occurs episodically, often at night during sleep.
 - 1. Mild respiratory acidosis develops with shallow breathing during sleep and activates complement.
 - 2. RBCs, WBCs, and platelets are lysed.
 - 3. Intravascular hemolysis leads to hemoglobinemia and hemoglobinuria (especially in the morning); hemosiderinuria is seen days after hemolysis.
- C. Sucrose test is used to screen for disease; confirmatory test is the acidified serum test or flow cytometry to detect lack of CD55 (DAF) on blood cells.
- D. Main cause of death is thrombosis of the hepatic, portal, or cerebral veins.
 - 1. Destroyed platelets release cytoplasmic contents into circulation, inducing thrombosis.
- E. Complications include iron deficiency anemia (due to chronic loss of hemoglobin in the urine) and acute myeloid leukemia (AML), which develops in 10% of patients.

II. GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

- A. X-linked recessive disorder resulting in reduced half-life of G6PD; renders cells susceptible to oxidative stress
 - 1. RBCs are normally exposed to oxidative stress, in particular H₂O₂.
 - 2. Glutathione (an antioxidant) neutralizes H₂O₂, but becomes oxidized in the process.
 - 3. NADPH, a by-product of G6PD, is needed to regenerate reduced glutathione.
 - 4. $\downarrow$ G6PD $\rightarrow$ $\downarrow$ NADPH $\rightarrow$ $\downarrow$ reduced glutathione $\rightarrow$ oxidative injury by H₂O₂ $\rightarrow$ intravascular hemolysis
- B. G6PD deficiency has two major variants.
 - 1. African variant—mildly reduced half-life of G6PD leading to mild intravascular hemolysis with oxidative stress
 - 2. Mediterranean variant—markedly reduced half-life of G6PD leading to marked intravascular hemolysis with oxidative stress
 - 3. High carrier frequency in both populations is likely due to protective role against falciparum malaria.

- C. Oxidative stress precipitates Hb as Heinz bodies.
 - 1. Causes of oxidative stress include infections, drugs (e.g., primaquine, sulfa drugs, and dapsone), and fava beans.
 - 2. Heinz bodies are removed from RBCs by splenic macrophages, resulting in bite cells (Fig. 5.11).
 - 3. Leads to predominantly intravascular hemolysis
- D. Presents with hemoglobinuria and back pain hours after exposure to oxidative stress
- E. Heinz preparation is used to screen for disease (precipitated hemoglobin can only be seen with a special Heinz stain, Fig. 5.12); enzyme studies confirm deficiency (performed weeks after hemolytic episode resolves).

III. IMMUNE HEMOLYTIC ANEMIA (IHA)

- A. Antibody-mediated (IgG or IgM) destruction of RBCs
- B. IgG-mediated disease usually involves extravascular hemolysis.
 - 1. IgG binds RBCs in the relatively warm temperature of the central body (warm agglutinin); membrane of antibody-coated RBC is consumed by splenic macrophages, resulting in spherocytes.
 - 2. Associated with SLE (most common cause), CLL, and certain drugs (classically, penicillin and cephalosporins)
 - i. Drug may attach to RBC membrane (e.g., penicillin) with subsequent binding of antibody to drug-membrane complex
 - ii. Drug may induce production of autoantibodies (e.g., α -methyl dopa) that bind self antigens on RBCs
 - 3. Treatment involves cessation of the offending drug, steroids, IVIG, and, if necessary, splenectomy.
- C. IgM-mediated disease usually involves intravascular hemolysis.
 - 1. IgM binds RBCs and fixes complement in the relatively cold temperature of the extremities (cold agglutinin).
 - 2. Associated with *Mycoplasma pneumoniae* and infectious mononucleosis
- D. Coombs test is used to diagnose IHA; testing can be direct or indirect.
 - 1. Direct Coombs test confirms the presence of antibody-coated RBCs. Anti-IgG is added to patient RBCs; agglutination occurs if RBCs are already coated with antibody. This is the most important test for IHA.
 - 2. Indirect Coombs test confirms the presence of antibodies in patient serum. Anti-IgG and test RBCs are mixed with the patient serum; agglutination occurs if serum antibodies are present.

IV. MICROANGIOPATHIC HEMOLYTIC ANEMIA

- A. Intravascular hemolysis that results from vascular pathology; RBCs are destroyed as they pass through the circulation.



Fig. 5.11 Bite cell.



Fig. 5.12 Heinz bodies (Heinz preparation).

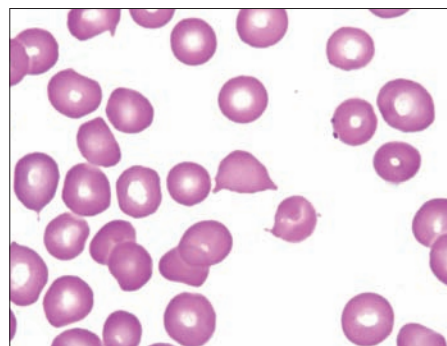


Fig. 5.13 Schistocyte.

1. Iron deficiency anemia occurs with chronic hemolysis.
- B. Occurs with microthrombi (TTP-HUS, DIC, HELLP), prosthetic heart valves, and aortic stenosis; microthrombi produce schistocytes on blood smear (Fig. 5.13).

V. MALARIA

- A. Infection of RBCs and liver with *Plasmodium* (Fig. 5.14); transmitted by the female *Anopheles* mosquito
- B. RBCs rupture as a part of the *Plasmodium* life cycle, resulting in intravascular hemolysis and cyclical fever.
 1. *P falciparum*—daily fever
 2. *P vivax* and *P ovale*—fever every other day
- C. Spleen also consumes some infected RBCs; results in mild extravascular hemolysis with splenomegaly

ANEMIA DUE TO UNDERPRODUCTION

I. BASIC PRINCIPLES

- A. Decreased production of RBCs by bone marrow; characterized by low corrected reticulocyte count
- B. Etiologies include
 1. Causes of microcytic and macrocytic anemia
 2. Renal failure—decreased production of EPO by peritubular interstitial cells
 3. Damage to bone marrow precursor cells (may result in anemia or pancytopenia)

II. PARVOVIRUS B19

- A. Infects progenitor red cells and temporarily halts erythropoiesis; leads to significant anemia in the setting of preexisting marrow stress (e.g., sickle cell anemia).
- B. Treatment is supportive (infection is self-limited).

III. APLASTIC ANEMIA

- A. Damage to hematopoietic stem cells, resulting in pancytopenia (anemia, thrombocytopenia, and leukopenia) with low reticulocyte count
- B. Etiologies include drugs or chemicals, viral infections, and autoimmune damage.
- C. Biopsy reveals an empty, fatty marrow (Fig. 5.15).
- D. Treatment includes cessation of any causative drugs and supportive care with transfusions and marrow-stimulating factors (e.g., erythropoietin, GM-CSF, and G-CSF).
 1. Immunosuppression may be helpful as some idiopathic cases are due to abnormal T-cell activation with release of cytokines.
 2. May require bone marrow transplantation as a last resort

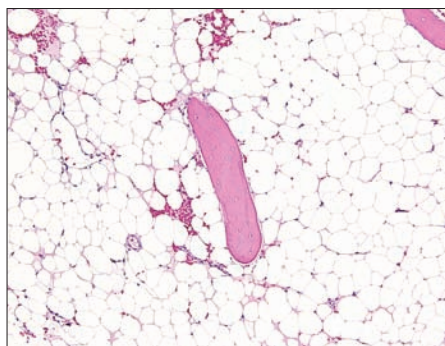
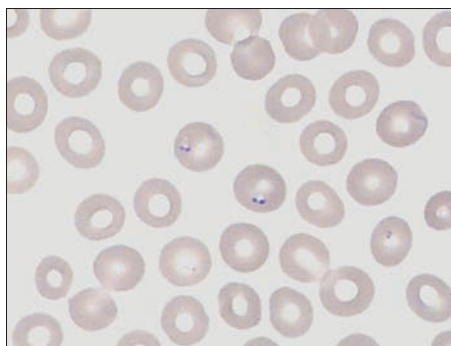


Fig. 5.14 Erythrocytes infected with *P falciparum*. **Fig. 5.15** Aplastic anemia.
(Courtesy of Paulo Mourao, MD)

IV. MYELOPHTHISIC PROCESS

- A. Pathologic process (e.g., metastatic cancer) that replaces bone marrow; hematopoiesis is impaired, resulting in pancytopenia.

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Fundamentals of Pathology: Medical Course and Step 1 Review, First Edition

ISBN 978-0-9832246-0-0

Printed in the United States of America.

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This book is printed on acid-free paper.

Published by Pathoma LLC.

<http://www.pathoma.com>

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Cover and page design by Olaf Nelson, Chinook Design, Inc.

<http://www.chinooktype.com>

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