

Cell Disorders

ANEMIA

I. BASIC PRINCIPLES

- A. [Redacted] in circulating [Redacted] cell (RBC) mass
- B. Presents with signs and symptoms of hypoxia
 - 1. Weakness, fatigue, and dyspnea
 - 2. Pale conjunctiva and skin
 - 3. Headache and light headedness
 - 4. Angina, especially with preexisting [Redacted] artery [Redacted]
- C. [Redacted] (Hb), [Redacted] (Hct), and RBC [Redacted] are used as surrogates for RBC mass, which is difficult to measure.
 - 1. Anemia is defined as Hb < 13.5 g/dL in males [Redacted] 12.5 g/dL in females (normal Hb is 13.5-17.5 g/dL in males and 12.5-16.0 g/dL in females).
- D. Based on [Redacted] [Redacted] (MCV), anemia can be classified as [Redacted] (MCV < 80 μm^3), [Redacted] (MCV = 80-100 μm^3), or [Redacted] (MCV > 100 μm^3).

I. BASIC PRINCIPLES

- A. Anemia with MCV < 80 μm^3
- B. [Redacted] [Redacted] are due to decreased production of [Redacted]
 - 1. RBC progenitor [Redacted] in the bone marrow are large and normally divide multiple times to produce smaller mature [Redacted] (MCV = 80-100 μm^3).
 - 2. Microcytosis is due to an "extra" division which occurs to maintain [Redacted] concentration.
- C. [Redacted] is made of heme and globin; heme is composed of iron and protoporphyrin. A decrease in any of these components leads to [Redacted]
- D. [Redacted] include (1) iron [Redacted] (2) anemia of [Redacted]
 - (3) [Redacted] and (4) [Redacted]

II. IRON [Redacted] ANEMIA

- A. Due to decreased levels of iron
 - 1. \downarrow iron \rightarrow \downarrow heme \rightarrow [Redacted] \rightarrow microcytic anemia
- B. Most common type of anemia
 - 1. Lack of iron is the most common nutritional [Redacted] in the world, affecting roughly 1/3 of world's population.
- C. Iron is consumed in heme (meat-derived) and non-heme (vegetable-derived) forms.
 - 1. Absorption occurs in the duodenum. Enterocytes have heme and non-heme (DMT1) transporters; the heme form is more readily absorbed.
 - 2. Enterocytes transport iron across the cell membrane into [Redacted] via ferroportin.
 - 3. [Redacted] transports iron in the [Redacted] and delivers it to liver and bone marrow macrophages for storage.
 - 4. [Redacted] intracellular iron is bound to [Redacted] which prevents iron from forming free radicals via the Fenton reaction.

- D. Laboratory measurements of iron status
- 1 Serum [redacted] of iron in the [redacted]
 - 2 [redacted] - measure of [redacted] molecules in the [redacted]
 - 3 % saturation - percentage of [redacted] molecules that are bound by iron (normal is 33%)
 - 4 Serum [redacted] - reflects iron stores in macrophages and the liver
- E. Iron [redacted] is usually caused by dietary lack or [redacted] loss.
- 1 Infants - breast-feeding (human milk is low in [redacted])
 - 2 Children-poor diet
 - 3 Adults (20-50 years) - peptic ulcer [redacted] in males and menorrhagia or pregnancy in females
 - 4 Elderly - colon polyps/carcinoma in the Western world; hookworm [redacted] and [redacted] in the developing world
 - 5 Other causes include malnutrition, malabsorption, and gastrectomy [redacted] aids iron absorption by maintaining the Fe^{2+} state, which is more readily absorbed than Fe^{3+} .
- F. Stages of iron [redacted]
- 1 Storage iron is depleted - [redacted]
 - 2 Serum iron is depleted - \downarrow serum [redacted] saturation
 - 3 [redacted] anemia - Bone marrow makes fewer, but normal-sized, RBCs.
 - 4 [redacted] hypochromic anemia - Bone marrow makes smaller and fewer RBCs.
- G. [redacted] of iron [redacted] include [redacted] koilonychia, and pica.
- H. Laboratory findings include
- 1 [redacted] hypochromic RBCs with [redacted] distribution width (RDW, Fig. 51)
 - 2 [redacted] \downarrow serum [redacted] saturation
 - 3 \uparrow Free erythrocyte protoporphyrin (FEP)
- I. Treatment involves supplemental iron (ferrous sulfate).
- J. [redacted] is iron [redacted] anemia with esophageal web and atrophic glossitis; presents as [redacted] dysphagia, and [redacted] tongue

III. ANEMIA OF [redacted]

- A. Anemia associated with [redacted] inflammation (e.g., endocarditis or autoimmune conditions) or cancer; most common type of anemia in hospitalized patients
- B. [redacted] results in production of acute phase reactants from the liver, including
- 1 [redacted] sequesters iron in storage sites by (1) limiting iron transfer from macrophages to [redacted] precursors and (2) suppressing [redacted] (EPO)

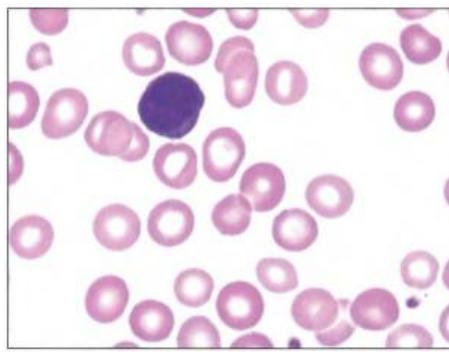


Fig. 5.1 [redacted] hypochromic RBCs of iron

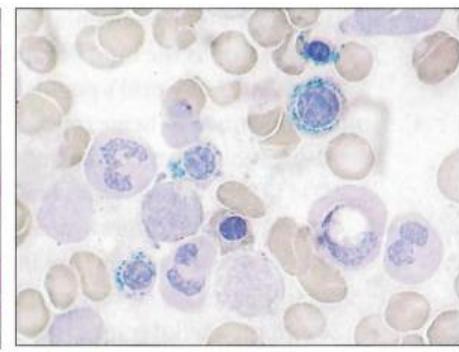


Fig. 5.2 Ringed sideroblasts (Prussian blue stain).

production; aim is to prevent bacteria from accessing [redacted] which is necessary for their survival.

2. available [redacted] | [redacted] anemia
- C. Laboratory findings include
1. [redacted] | [redacted] saturation
 2. ↑ Free erythrocyte protoporphyrin (FEP)
- D. Treatment involves addressing the underlying cause.

IV. [redacted] ANEMIA

- A. Anemia due to defective protoporphyrin synthesis
1. protoporphyrin | heme | [redacted] anemia
- B. Protoporphyrin is synthesized via a series of reactions.
1. [redacted] synthetase (ALAS) converts succinyl CoA to [redacted] (ALA) using [redacted] B₆ as a [redacted] (rate-limiting step).
 2. [redacted] dehydratase (ALAD) converts ALA to porphobilinogen.
 3. Additional reactions convert porphobilinogen to protoporphyrin.
 4. [redacted] attaches protoporphyrin to [redacted] to make heme (final reaction; occurs in the mitochondria).
- C. [redacted] is [redacted] to [redacted] precursors and enters the mitochondria to form heme. If protoporphyrin is deficient, [redacted] remains trapped in mitochondria.
1. [redacted] mitochondria form a ring around the nucleus of [redacted] precursors; these [redacted] are called ringed sideroblasts (hence, the term [redacted] Fig. 5.2).
- D. [redacted] anemia can be congenital or [redacted]
1. Congenital defect most commonly involves ALAS (rate-limiting enzyme).
 2. [redacted] causes include
 - i. Alcoholism - mitochondrial poison
 - ii. Lead poisoning - inhibits ALAD and [redacted]
 - iii. [redacted] B₆ [redacted] - [redacted] for ALAS; most commonly seen as a side effect of [redacted] treatment for tuberculosis
- E. Laboratory findings include [redacted] serum [redacted] and % saturation [redacted] state).

V. [redacted]

- A. Anemia due to decreased synthesis of the globin chains of [redacted]
1. globin [redacted] | [redacted] anemia
- B. Inherited mutation; carriers are protected against *Plasmodium falciparum* malaria.
- C. Divided into α- and [redacted] based on decreased production of alpha or beta globin chains.
1. Normal types of [redacted] are HbF ($\alpha_2\gamma_2$), HbA ($\alpha_2\beta_2$), and HbA₂ ($\alpha_2\delta_2$).

Table 5.1: Laboratory Findings in [redacted] Anemia

STATE	[redacted]	[redacted]	SERUM [redacted]	% SATURATION
Normal	-	300 µg/dL	100 µg/dL	33%
[redacted] Anemia	Low	High	Low	Low
Anemia of [redacted]	High	Low	Low	Low
[redacted] Anemia	High	Low	High	High
Pregnancy and oral contraceptives	-	High	-	Low

- D. [REDACTED] is usually due to gene deletion; normally, 4 alpha genes are present on chromosome 16
1. One gene deleted - asymptomatic
 2. Two genes deleted - mild [REDACTED] with ↑ RBC [REDACTED] cis deletion is associated with an increased risk of severe [REDACTED] in offspring.
 - i. Cis deletion is when both deletions occur on the same chromosome; seen in Asians
 - ii. Trans deletion is when one deletion occurs on each chromosome; seen in Africans, including African Americans
 3. Three genes deleted-severe [REDACTED] β chains form tetramers (HbH) that damage RBCs; HbH is seen on electrophoresis.
 4. Four genes deleted-lethal in utero [REDACTED] γ chains form tetramers (Hb [REDACTED]) that damage RBCs; Hb [REDACTED] is seen on electrophoresis.
- E. [REDACTED] is usually due to gene mutations (point mutations in promoter or splicing sites); seen in individuals of African and Mediterranean descent
1. Two β genes are present on chromosome 11; mutations result in absent (β^0) or diminished (β^+) production of the β -globin chain.
 2. [REDACTED] minor (β/β^+) is the mildest form of [REDACTED] and is usually asymptomatic with an increased RBC [REDACTED]
 - i. [REDACTED] hypochromic RBCs and [REDACTED] are seen on [REDACTED] smear (Fig. 5.3).
 - ii. [REDACTED] electrophoresis shows slightly decreased HbA with increased HbA₂ (5%, normal 2.5%) and HbF (2%, normal 1%).
 3. [REDACTED] major (β^0/β^0) is the most severe form of [REDACTED] and presents with severe [REDACTED] a few months after birth; high HbF ($\alpha_2\gamma_2$) at birth is temporarily protective.
 - i. [REDACTED] α chains precipitate and damage RBC membrane, resulting in ineffective erythropoiesis and [REDACTED] hemolysis (removal of circulating RBCs by the spleen).
 - ii. Massive [REDACTED] ensues resulting in (1) expansion of hematopoiesis into the skull (reactive bone formation leads to 'crewcut' appearance on x-ray, Fig. 5.4) and facial bones ('chipmunk fades'), (2) extramedullary hematopoiesis with hepatosplenomegaly, and (3) risk of aplastic crisis with parvovirus B19 infection of [REDACTED] precursors.
 - iii. [REDACTED] transfusions are often necessary; leads to risk for secondary hemochromatosis
 - iv. Smear shows [REDACTED] hypochromic RBCs with [REDACTED] and nucleated
 - v. Electrophoresis shows HbA₂ and HbF with little or no HbA.

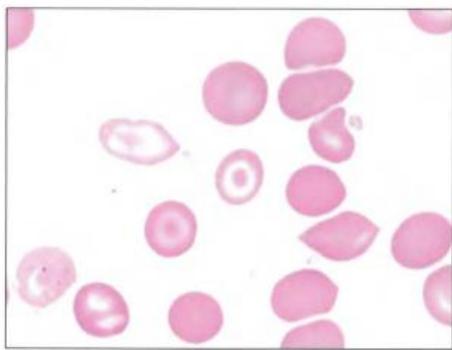


Fig. 5.3 [REDACTED]



Fig. 5.4 'Crewcut' appearance. (Reproduced with permission, www.orthopaedia.com/xgGvAQ)

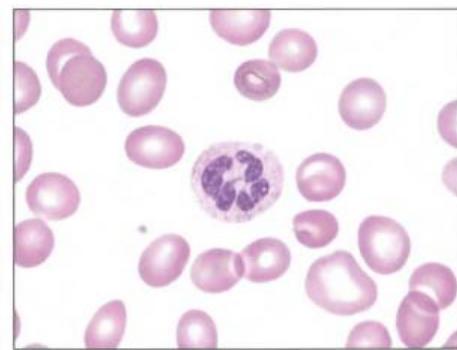


Fig. 5.5 [REDACTED] neutrophil in [REDACTED]

I. BASIC PRINCIPLES

- A. [Redacted] with MCV > 100 μm^3 ; most commonly due to folate or vitamin B12 deficiency [Redacted]
- B. Folate and vitamin B12 are necessary for synthesis of DNA precursors.
1. Folate circulates in the serum as [Redacted] (methyl THF); removal of the methyl group allows for participation in the synthesis of DNA precursors.
 2. Methyl group is [Redacted] to vitamin B12 (cobalamin).
 3. Vitamin B12 then transfers it to [Redacted] producing methionine.
- C. Lack of folate or vitamin B12 impairs synthesis of DNA precursors.
1. [Redacted] division and enlargement of RBC precursors leads to [Redacted]
 2. [Redacted] division of granulocytic precursors leads to [Redacted]
 3. [Redacted] change is also seen in rapidly-dividing (e.g., intestinal) epithelial
- D. Other causes of [Redacted] (without [Redacted] change) include alcoholism, liver [Redacted] and drugs (e.g., 5-FU).

II. FOLATE DEFICIENCY

- A. Dietary folate is obtained from green vegetables and some fruits.
1. Absorbed in the jejunum
- B. Folate deficiency develops within months, as body stores are minimal.
- C. Causes include poor diet (e.g., alcoholics and elderly), increased [Redacted] (e.g., pregnancy, cancer, and hemolytic [Redacted]) and folate antagonists (e.g., [Redacted] which inhibits [Redacted])
- D. [Redacted] and laboratory findings include
1. [Redacted] RBCs and [Redacted] (> 5 lobes, Fig. 5.5)
 2. Glossitis
 3. ↓ serum folate
 4. ↑ serum [Redacted] (increases risk for thrombosis)
 5. Normal [Redacted]

III. VITAMIN B12 DEFICIENCY

- A. Dietary vitamin B12 is complexed to animal-derived proteins.
1. Salivary [Redacted] enzymes (e.g., amylase) liberate vitamin [Redacted] which is then bound by [Redacted] (also from the salivary [Redacted] and carried through the stomach.
 2. Pancreatic proteases in the duodenum detach vitamin B12 from [Redacted]
 3. Vitamin B12 binds [Redacted] (made by gastric parietal [Redacted]) in the small bowel; the [Redacted] B12 complex is absorbed in the ileum.
- B. Vitamin B12 deficiency is less common than folate deficiency and takes years to develop due to large hepatic stores of vitamin [Redacted]
- C. [Redacted] is the most common cause of vitamin B12 [Redacted]
1. Autoimmune destruction of parietal [Redacted] (body of stomach) leads to [Redacted] deficiency
- D. Other causes of vitamin B12 deficiency include pancreatic insufficiency and damage to the terminal ileum (e.g., [Redacted] or [Redacted] [fish tapeworm]); dietary deficiency is rare, except in vegans.
- E. [Redacted] and laboratory findings include
1. [Redacted] RBCs with [Redacted]
 2. Glossitis
 3. Subacute combined degeneration of the spinal [Redacted]

- i. [red] is a [red] for the conversion of [red] to succinyl CoA (important in fatty [red] metabolism).
- ii. [red] results in increased levels of [red] which impairs spinal [red] myelinization.
- iii. Damage results in poor proprioception and vibratory sensation (posterior column) and spastic paresis (lateral [red] tract).
4. ↓ serum [red] (similar to [red] which increases risk for thrombosis)
5. ↑ serum [red] (unlike [red])
6. [red]

[red] [red]

I. BASIC PRINCIPLES

- A. [red] with normal-sized RBCs ($MCV = 80-100 \mu\text{m}^3$)
- B. Due to increased peripheral destruction or underproduction
 1. [red] helps to distinguish between these two etiologies.

II. [red]

- A. Young RBCs released from the bone marrow
 1. Identified on [red] smear as larger [red] with bluish cytoplasm (due to residual RNA, Fig. 5.6)
- B. Normal [red] (RC) is 1-2%.
 1. RBC lifespan is 120 days; each day roughly 1-2% of RBCs are removed from circulation and replaced by [red]
- C. A properly functioning marrow responds to [red] by increasing the RC to > 3%.
- D. RC, however, is falsely elevated in
 1. RC is [red] as percentage of [red] RBCs; decrease in [red] RBCs falsely elevates percentage of [red]
- E. RC is [red] by multiplying [red] by Hct/45.
 1. [red] > 3% indicates good marrow response and suggests peripheral destruction.
 2. [red] < 3% indicates poor marrow response and suggests underproduction.

III. PERIPHERAL RBC DESTRUCTION (HEMOLYSIS)

- A. Divided into [red] and [red] hemolysis; both result in [red] with a good marrow response.
- B. [red] hemolysis involves RBC destruction by the reticuloendothelial system (macrophages of the spleen, liver, and lymph nodes).

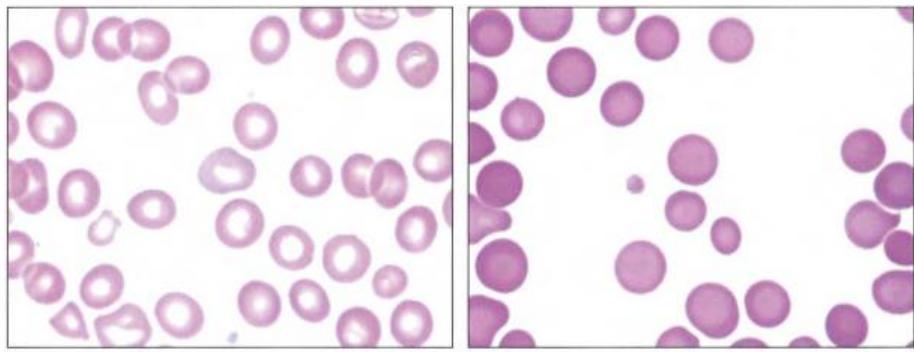


Fig. 5.6 [red]

Fig. 5.7 Spherocytes.

1. Macrophages consume RBCs and break down [REDACTED]
 - i. Globin is broken down into amino [REDACTED]
 - ii. Heme is broken down into [REDACTED] and protoporphyrin; [REDACTED] is recycled.
 - iii. Protoporphyrin is broken down into unconjugated bilirubin, which is bound to serum albumin and [REDACTED] to the liver for conjugation and excretion into bile.
 2. [REDACTED] and laboratory findings include
 - i. [REDACTED] with splenomegaly, jaundice due to unconjugated bilirubin, and increased risk for bilirubin gallstones
 - ii. Marrow [REDACTED] with [REDACTED] > 3%
- C. [REDACTED] hemolysis involves destruction of RBCs within vessels.
1. [REDACTED] and laboratory findings include
 - i. [REDACTED]
 - ii. [REDACTED]
 - iii. Hemosiderinuria - Renal tubular [REDACTED] pick up some of the [REDACTED] that is [REDACTED] into the urine and break it down into [REDACTED] which accumulates as hemosiderin; tubular [REDACTED] are eventually shed resulting in hemosiderinuria.
 - iv. Decreased serum haptoglobin

[REDACTED] WITH [REDACTED] HEMOLYSIS

I. [REDACTED] SPHEROCYTOSIS

- A. Inherited defect of RBC cytoskeleton-membrane tethering proteins
 1. Most commonly involves ankyrin, spectrin, or [REDACTED] 3
- B. Membrane blebs are formed and lost over time.
 1. Loss of membrane renders [REDACTED] round (spherocytes) instead of disc-shaped.
 2. Spherocytes are less able to maneuver through splenic sinusoids and are consumed by splenic macrophages, resulting in [REDACTED]
- C. [REDACTED] and laboratory findings include
 1. Spherocytes with loss of central pallor (Fig. 5.7)
 2. ↑ RDW and ↑ [REDACTED] concentration (MCHC)
 3. Splenomegaly, jaundice with unconjugated bilirubin, and increased risk for bilirubin gallstones [REDACTED] hemolysis)
 4. Increased risk for aplastic crisis with parvovirus B19 infection of [REDACTED] precursors
- D. Diagnosed by osmotic fragility test, which reveals increased spherocyte fragility in hypotonic solution
- E. Treatment is splenectomy; [REDACTED] resolves, but spherocytes persist and Howell-Jolly bodies (fragments of nuclear material in RBCs) emerge on [REDACTED] smear (Fig. 5.8).

II. SICKLE CELL [REDACTED]

- A. Autosomal recessive mutation in β chain of [REDACTED] a single amino [REDACTED] change replaces normal glutamic [REDACTED] (hydrophilic) with valine (hydrophobic).
- B. Gene is carried by 10% of individuals of African descent, likely due to protective role against falciparum malaria.
- C. Sickle cell [REDACTED] arises when two abnormal β genes are present; results in >90% HbS in RBCs
- D. HbS polymerizes when deoxygenated; polymers aggregate into needle-like structures, resulting in sickle [REDACTED] (Fig. 5.9).
 1. Increased risk of sickling occurs with hypoxemia, dehydration, and [REDACTED]
 2. HbF protects against sickling; high HbF at birth is protective for the first few months of life. Treatment with hydroxyurea increases levels of HbF.

- E. [REDACTED] continuously sickle and de-sickle while passing through the microcirculation, resulting in complications related to RBC membrane damage.
1. [REDACTED] hemolysis - Reticuloendothelial system removes RBCs with damaged membranes, leading to [REDACTED] jaundice with unconjugated hyperbilirubinemia, and increased risk for bilirubin gallstones.
 2. [REDACTED] hemolysis - RBCs with damaged membranes dehydrate, leading to hemolysis with decreased haptoglobin and [REDACTED] on [REDACTED] smear.
 3. Massive [REDACTED] ensues resulting in
 - i. Expansion of hematopoiesis into the skull ('crewcut' appearance on x-ray) and facial bones ('chipmunk fades')
 - ii. Extramedullary hematopoiesis with hepatomegaly
 - iii. Risk of aplastic crisis with parvovirus B19 infection of [REDACTED] precursors
- F. Extensive sickling leads to complications of vaso-occlusion.
1. Dactylitis - swollen [REDACTED] and feet due to vaso-occlusive infarcts in bones; common presenting sign in infants
 2. Autosplenectomy - shrunken, fibrotic spleen. Consequences include
 - i. Increased risk of infection with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (most common cause of death in children); affected children should be vaccinated by 5 years of age.
 - ii. Increased risk of *Salmonella paratyphi* osteomyelitis
 - iii. Howell-Jolly bodies on [REDACTED] smear
 3. Acute chest [REDACTED] - vaso-occlusion in pulmonary microcirculation
 - i. Presents with chest pain, shortness of breath, and lung infiltrates
 - ii. Often precipitated by pneumonia
 - iii. Most common cause of death in adult patients
 4. Pain crisis
 5. Renal papillary necrosis - results in gross hematuria and proteinuria
- G. Sickle cell trait is the presence of one mutated and one normal chain; results in < 50% HbS in RBCs (HbA is slightly more efficiently produced than HbS)
1. Generally asymptomatic with no [REDACTED] RBCs with < 50% HbS do not sickle in vivo except in the renal medulla.
 - i. Extreme hypoxia and hypertonicity of the medulla cause sickling, which results in microinfarctions leading to microscopic hematuria [REDACTED] eventually, decreased ability to concentrate urine.
- H. Laboratory findings
1. Sickle [REDACTED] and [REDACTED] are seen on [REDACTED] smear in sickle cell [REDACTED] but not in sickle cell trait.
 2. Metabisulfite screen causes [REDACTED] with any amount of HbS to sickle; positive in both [REDACTED] and trait
 3. Hb electrophoresis confirms the presence and amount of HbS.

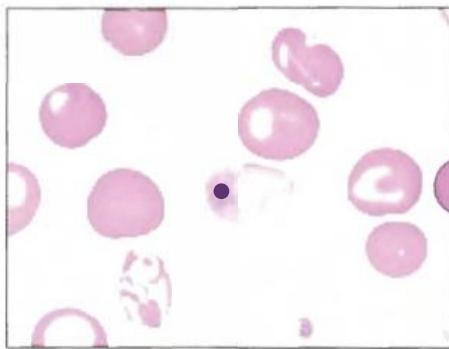


Fig. 5.8 Fragment of nuclear remnant (Howell-Jolly body) within RBC.

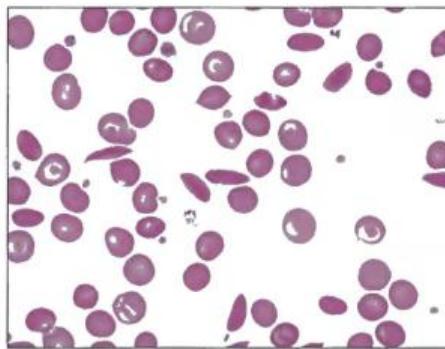


Fig. 5.9 Sickled [REDACTED]

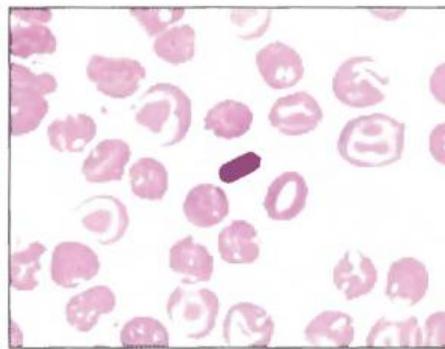


Fig. 5.10 [REDACTED] C crystal.

- i. [Redacted] - 90% HbS, 8% HbF, 2% HbA₂ (no HbA)
- ii. Trait - 55% HbA, 43% HbS, 2% HbA₂

III. [Redacted] C

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

[Redacted] WITH [Redacted]
INTRAVASCULAR HEMOLYSIS

I. PAROXYSMAL NOCTURNAL [Redacted] (PNH)

- A. [Redacted] defect in myeloid stem cells resulting in absent glycosylphosphatidylinositol (GPI); renders cells susceptible to destruction by complement
 - 1. [Redacted] cells coexist with complement.
 - 2. Decay accelerating [Redacted] (DAF) on the surface of [Redacted] cells protects against complement-mediated damage by inhibiting C3 convertase.
 - 3. DAF is [Redacted] to the cell membrane by GPI (an anchoring glycolipid).
 - 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 [Redacted] develops with shallow breathing during sleep [Redacted] activates complement.
 - 2. RBCs, WBCs, [Redacted] platelets are lysed.
 - 3. Intravascular hemolysis leads to [Redacted] (especially in the morning); hemosiderinuria is seen days after hemolysis.
- C. Sucrose test is used to screen for [Redacted]; confirmatory test is the [Redacted] serum test or flow cytometry to detect lack of CD55 (DAF) on [Redacted]
- 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 [Redacted] (due to [Redacted] loss of [Redacted] in the urine) [Redacted] acute myeloid leukemia (AML), which develops in 10% of patients.

II. GLUCOSE-6-PHOSPHATE [Redacted] (G6PD) [Redacted]

- A. X-linked recessive disorder resulting in [Redacted] 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 [Redacted] glutathione.
 - 4. ↓ G6PD ↓ → NADPH ↓ → [Redacted] glutathione → oxidative injury by H₂O₂ → intravascular hemolysis
- B. G6PD [Redacted] has two major variants.
 - 1. African variant - mildly [Redacted] half-life of G6PD leading to mild intravascular hemolysis with oxidative stress
 - 2. Mediterranean variant - markedly [Redacted] 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 [redacted] (Fig. 5.11).
 - 3. Leads to [redacted] hemolysis
- D. Presents with [redacted] and back pain hours after exposure to oxidative stress
- E. Heinz preparation is used to screen for [redacted] (precipitated [redacted] can only be seen with a special Heinz stain, Fig. 5.12); enzyme studies confirm [redacted] (performed weeks after hemolytic episode resolves).

III. IMMUNE HEMOLYTIC [redacted] (IHA)

- A. Antibody-mediated (IgG or IgM) destruction of RBCs
- B. IgG-mediated [redacted] usually involves [redacted] 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 [redacted] of antibody to drug-membrane complex
 - ii. Drug may induce production of autoantibodies (e.g., α -methyldopa) that bind self antigens on RBCs
 - 3. Treatment involves cessation of the offending drug, steroids, IVIG, [redacted] if necessary, splenectomy.
- C. IgM-mediated [redacted] can lead to [redacted] hemolysis.
 - 1. IgM binds RBCs and fixes complement in the relatively cold temperature of the extremities (cold agglutinin).
 - 2. RBCs inactivate complement, but residual C3b serves as an opsonin for splenic macrophages resulting in spherocytes; extreme activation of complement can lead to [redacted] hemolysis.
 - 3. 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- or complement-coated RBCs. When anti-IgG/complement is added to patient RBCs, agglutination occurs if RBCs are already coated with IgG or complement. 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.

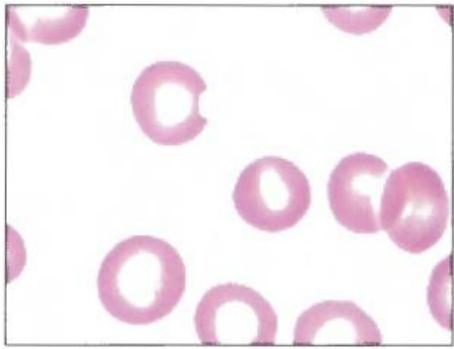


Fig. 5.11 Bite cell.



Fig. 5.12 Heinz bodies (Heinz preparation).

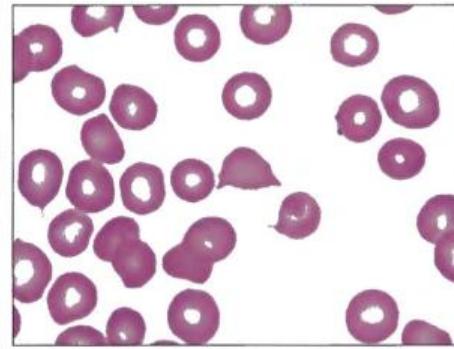


Fig. 5.13 Schistocyte.

IV. MICROANGIOPATHIC HEMOLYTIC ANEMIA

- A. [REDACTED] hemolysis that results from vascular pathology; RBCs are destroyed as they pass through the circulation.
 - 1. [REDACTED] anemia occurs with [REDACTED] hemolysis.
- B. Occurs with microthrombi (TTP-HUS, DIC, HELLp), prosthetic heart valves, and aortic stenosis; when present, microthrombi produce schistocytes on [REDACTED] 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 [REDACTED] 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 [REDACTED] hemolysis with splenomegaly

ANEMIA DUE TO UNDERPRODUCTION

I. BASIC PRINCIPLES

- A. Decreased production of RBCs by bone marrow; characterized by low [REDACTED]
- B. Etiologies include
 - 1. Causes of [REDACTED] and [REDACTED] anemia
 - 2. Renal failure - decreased production of EPO by peritubular interstitial [REDACTED]
 - 3. Damage to bone marrow precursor [REDACTED] (may result in anemia or pancytopenia)

II. PARVOVIRUS B19

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

III. APLASTIC ANEMIA

- A. Damage to hematopoietic stem [REDACTED] resulting in pancytopenia [REDACTED] thrombocytopenia, and leukopenia) with low [REDACTED]
- B. Etiologies include drugs or chemicals, viral infections, and autoimmune damage.
- C. Biopsy reveals an empty, fatty marrow (Fig. 5.15).

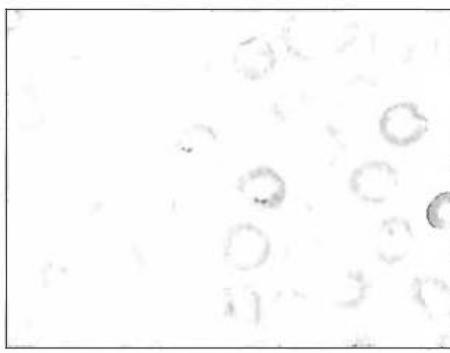


Fig. 5.14 Erythrocytes infected with *Pfalciparum*.
(Courtesy of Paulo Mourao, MD)

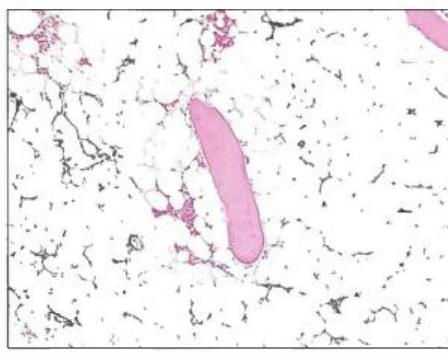


Fig. 5.15 Aplastic [REDACTED]

- D. Treatment includes cessation of any causative drugs [redacted] supportive care with transfusions [redacted] marrow-stimulating [redacted] (e.g., [redacted] GM-CSF, [redacted] 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

IV. MYELOPHTHISIC PROCESS

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

White Cell Disorders

LEUKOPENIA ■ LEUKOCYTOSIS

I BASIC PRINCIPLES

- Hematopoiesis occurs via a stepwise maturation of CD34⁺ hematopoietic stem cells (Fig. 6.1).
- Cells mature [redacted] are released from the bone marrow into the [redacted]
- A normal white [redacted] cell (WBC) [redacted] is approximately 5-10 K/ μ L.
 - A low WBC [redacted] 5 K) is called leukopenia.
 - A high WBC [redacted] (> 10 K) is called leukocytosis.
 - A low or high WBC [redacted] is usually due to a decrease or increase in one particular cell lineage.

II LEUKOPENIA

- Neutropenia refers to a decreased number of circulating [redacted] Causes include
 - Drug toxicity (e.g., chemotherapy with alkylating agents) - Damage to stem cells results in decreased production of WBCs, especially [redacted]
 - Severe infection (e.g., gram-negative sepsis) - Increased movement of [redacted] into tissues results in decreased circulating [redacted]
 - As a treatment, GM-CSF or G-CSF may be used to boost granulocyte production, thereby decreasing risk of infection in neutropenic patients.
- Lymphopenia refers to a decreased number of circulating lymphocytes. Causes include
 - [redacted] (e.g., DiGeorge [redacted] or HIV)
 - High [redacted] state (e.g., exogenous [redacted] or Cushing [redacted]) induces apoptosis of lymphocytes
 - Autoimmune destruction (e.g., systemic lupus erythematosus)
 - Whole body radiation - Lymphocytes are highly sensitive to radiation; lymphopenia is the earliest change to emerge after whole body radiation.

III LEUKOCYTOSIS

- Neutrophilic leukocytosis refers to increased circulating [redacted] Causes include
 - Bacterial infection or tissue necrosis - induces release of marginated pool [redacted] bone marrow [redacted] including immature forms (left shift); immature cells are characterized by decreased Fe receptors (CD16).

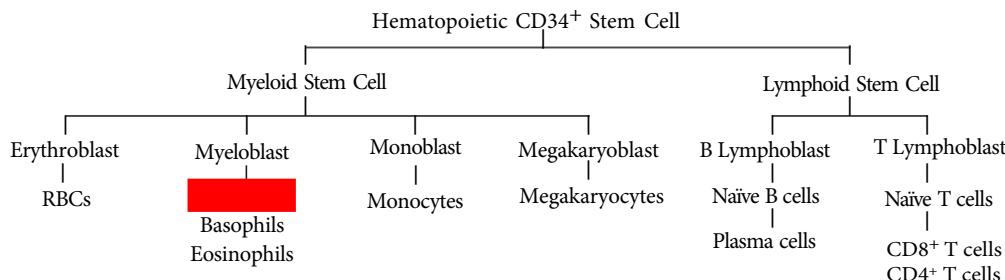


Fig. 6.1 Hematopoiesis.

2. High [redacted] state - impairs leukocyte adhesion, leading to release of marginated pool of [redacted]
- B. Monocytosis refers to increased circulating monocytes. Causes include [redacted] inflammatory states (e.g., autoimmune [redacted] infectious) [redacted] malignancy.
- C. Eosinophilia refers to increased circulating eosinophils. Causes include allergic reactions (type I hypersensitivity), parasitic infections, [redacted] Hodgkin lymphoma. Eosinophilia is driven by increased eosinophil chemotactic [redacted]
- D. Basophilia refers to increased circulating basophils; classically seen in [redacted] myeloid leukemia
- E. Lymphocytic leukocytosis refers to increased circulating lymphocytes. Causes include
1. Viral infections - T lymphocytes undergo [redacted] in response to virally infected [redacted]
 2. *Bordetella pertussis* infection - Bacteria produce lymphocytosis-promoting [redacted] which blocks circulating lymphocytes from leaving the [redacted] to enter the lymph node.

IV. INFECTIOUS MONONUCLEOSIS (IM)

- A. EBV infection that results in a lymphocytic leukocytosis comprised of reactive CD8⁺ T [redacted] CMV is a less common cause.
1. EBV is transmitted by saliva ("kissing" [redacted] classically affects teenagers)
- B. EBV primarily infects
1. Oropharynx, resulting in pharyngitis
 2. Liver, resulting in hepatitis with hepatomegaly [redacted] elevated liver enzymes
 3. B [redacted]
- C. CD8⁺ T-cell response leads to
1. Generalized lymphadenopathy (LAD) due to T-cell [redacted] in the lymph node [redacted]
 2. Splenomegaly due to T-cell [redacted] in the periarterial lymphatic sheath (PALS)
 3. High WBC [redacted] with atypical lymphocytes (reactive CD8⁺ T [redacted] in the [redacted] (Fig. 6.2))
- D. The monospot test is used for screening.
1. Detects IgM antibodies that cross-react with horse or sheep [redacted] [redacted] (heterophile antibodies)
 2. Usually turns positive within 1 week after infection
 3. A negative monospot test suggests CMV as a possible cause of IM.
 4. Definitive diagnosis is made by serologic testing for the EBV viral capsid antigen.

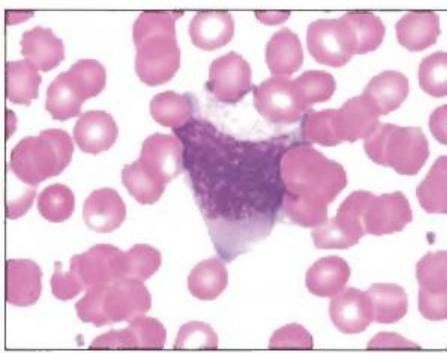


Fig. 6.2 Atypical lymphocyte, infectious mononucleosis.

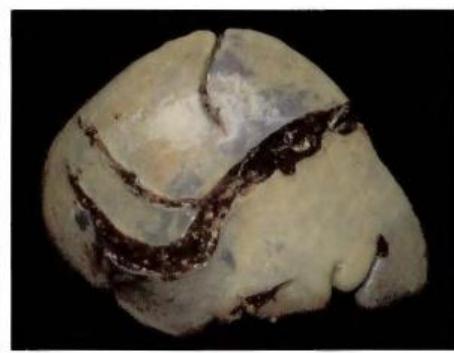


Fig. 6.3 Splenic rupture. (Courtesy of K.V. Santosh, MD)

E. Complications

- 1 Increased risk for splenic rupture (Fig. 6.3); patients are generally advised to avoid contact sports for one month.
- 2 Rash if exposed to ampicillin
- 3 Dormancy of virus in B [redacted] leads to increased risk for both recurrence [redacted] B-cell lymphoma, especially if [redacted] (e.g., HIV) develops.

ACUTE LEUKEMIA

I BASIC PRINCIPLES

- A. Neoplastic proliferation of blasts; defined as the accumulation of > 20% blasts in the bone marrow.
- B. Increased blasts "crowd-out" normal hematopoiesis, resulting in an "acute" presentation with [redacted] (fatigue), thrombocytopenia (bleeding), or neutropenia (infection).
- C. Blasts usually enter the [redacted] stream, resulting in a high WBC [redacted]
 - 1 Blasts are large, immature [redacted] often with punched out nucleoli (Fig. 6.4).
- D. Acute leukemia is subdivided into acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML) based on the phenotype of the blasts.

II ACUTE LYMPHOBLASTIC LEUKEMIA

- A. Neoplastic accumulation of lymphoblasts (> 20%) in the bone marrow
 - 1 Lymphoblasts are characterized by positive nuclear staining for TdT, a DNA polymerase.
 - 2 TdT is absent in myeloid blasts [redacted] mature lymphocytes.
- B. Most commonly arises in children; associated with Down [redacted] (usually arises after the age of 5 years)
- C. Subclassified into B-ALL [redacted] T-ALL based on surface markers
- D. B-ALL is the most common type of ALL.
 - 1 Usually characterized by lymphoblasts (TdT⁺) that express CD10, CD19, [redacted] CD20.
 - 2 Excellent response to chemotherapy; requires prophylaxis to scrotum [redacted] CSF (Fig. 6.5)
 - 3 Prognosis is based on cytogenetic abnormalities.
 - i t(12;21) has a good prognosis; more commonly seen in children
 - ii t(9;22) has a poor prognosis; more commonly seen in adults (Philadelphia⁺ ALL)
- E. T-ALL is characterized by lymphoblasts (TdT⁺) that express markers ranging from CD2 to CD8 (e.g., CD3, CD4, CD7). The blasts do not express CD10.

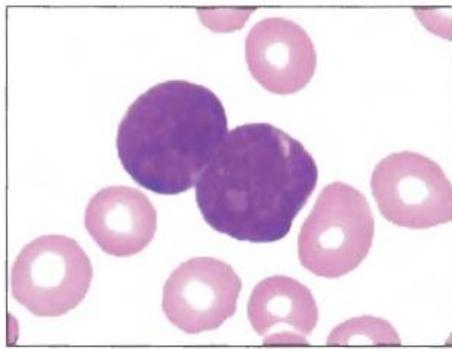


Fig. 6.4 Blasts of acute leukemia.

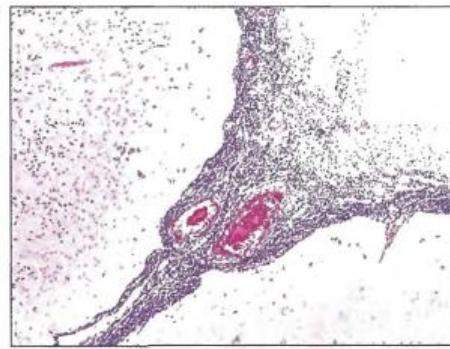


Fig. 6.5 Acute lymphoblastic leukemia involving meninges.

- Usually presents in teenagers as a mediastinal (thymic) mass (called acute lymphoblastic lymphoma because the malignant [redacted] form a mass)

III. ACUTE MYELOID LEUKEMIA

- Neoplastic accumulation of immature myeloid [redacted] (> 20%) in the bone marrow
- Myeloblasts are usually characterized by positive cytoplasmic staining for myeloperoxidase (MPO).
 - Crystal aggregates of MPO may be seen as Auer rods (Fig. 6.6).
- Most commonly arises in older adults (average age is 50-60 years)
- Subclassification based on cytogenetic abnormalities, lineage of immature myeloid [redacted] and surface markers. High-yield subtypes include
 - Acute promyelocytic leukemia (APL)
 - Characterized by t(15;17), which involves translocation of the retinoic [redacted] receptor (RAR) on chromosome 17 to chromosome 15; RAR disruption blocks maturation and promyelocytes (blasts) accumulate.
 - Abnormal promyelocytes contain numerous primary granules that increase the risk for DIC.
 - Treatment is with *all-trans-retinoic acid* (ATRA, a [redacted] A derivative), which binds the [redacted] receptor and causes the blasts to mature [redacted] eventually die).
 - Acute monocytic leukemia
 - Proliferation of monoblasts; usually lack MPO
 - Blasts characteristically infiltrate gums (Fig. 6.7).
 - Acute megakaryoblastic leukemia
 - Proliferation of megakaryoblasts; lack MPO
 - Associated with Down [redacted] (usually arises *before* the age of 5)
- AML may also arise from pre-existing dysplasia (myelodysplastic [redacted] especially with prior exposure to alkylating agents or radiotherapy.
 - Myelodysplastic [redacted] usually present with cytopenias, hypercellular bone marrow, abnormal maturation of [redacted] and increased blasts(< 20%).
 - Most patients die from infection or bleeding, though some progress to acute leukemia.

[redacted] LEUKEMIA

I BASIC PRINCIPLES

- Neoplastic proliferation of mature circulating lymphocytes; characterized by a high WBC [redacted]
- Usually insidious in onset and seen in older adults

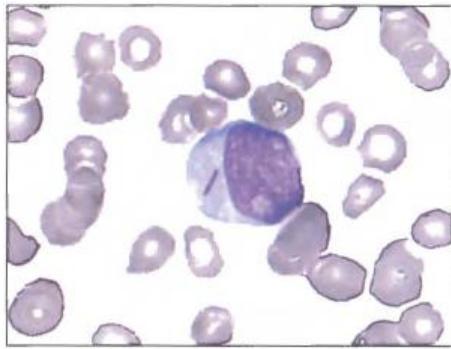


Fig. 6.6 Acute myelogenous leukemia with Auer rod. (Courtesy of Paulo Mourao, MD)



Fig. 6.7 Acute monocytic leukemia. (Courtesy of Drs. H [redacted] and H van Dijk, *Images of Memorable Cases*)

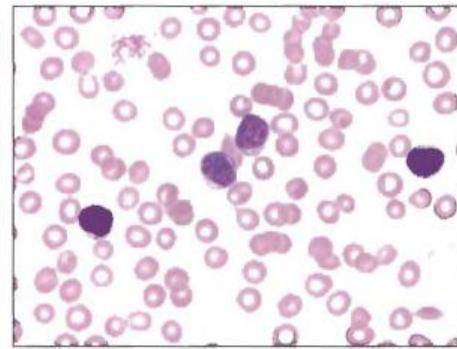


Fig. 6.8 [redacted] lymphocytic leukemia.

