

# 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  $\mu\text{m}^3$ ), [Redacted] (MCV = 80-100  $\mu\text{m}^3$ ), or [Redacted] (MCV > 100  $\mu\text{m}^3$ ).

### I. BASIC PRINCIPLES

- A. Anemia with MCV < 80  $\mu\text{m}^3$
- 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  $\mu\text{m}^3$ ).
  - 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]

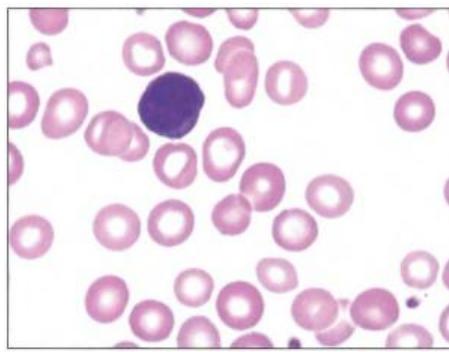
### II. IRON [Redacted] ANEMIA

- 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.

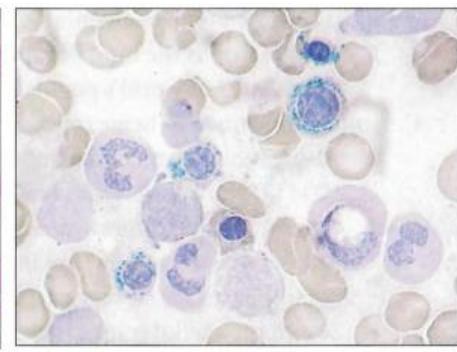
- D. Laboratory measurements of iron status
- 1 Serum [redacted] of iron in the [redacted]
  - 2 [redacted] - measure of [redacted] molecules in the [redacted]
  - 3 % saturation - percentage of [redacted] molecules that are bound by iron (normal is 33%)
  - 4 Serum [redacted] - reflects iron stores 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  $\text{Fe}^{2+}$  state, which is more readily absorbed than  $\text{Fe}^{3+}$ .
- 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] B<sub>6</sub> 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] B<sub>6</sub> [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 HbA<sub>2</sub> ( $\alpha_2\delta_2$ ).

**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]  $\beta$  chains form tetramers (HbH) that damage RBCs; HbH is seen on electrophoresis.
  4. Four genes deleted-lethal in utero [REDACTED]  $\gamma$  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  $\beta$  genes are present on chromosome 11; mutations result in absent ( $\beta^0$ ) or diminished ( $\beta^+$ ) production of the  $\beta$ -globin chain.
  2. [REDACTED] minor ( $\beta/\beta^+$ ) 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 HbA<sub>2</sub> (5%, normal 2.5%) and HbF (2%, normal 1%).
  3. [REDACTED] major ( $\beta^0/\beta^0$ ) 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]  $\alpha$  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 HbA<sub>2</sub> and HbF with little or no HbA.

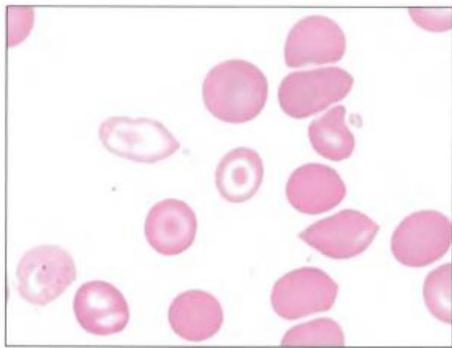


Fig. 5.3 [REDACTED]



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

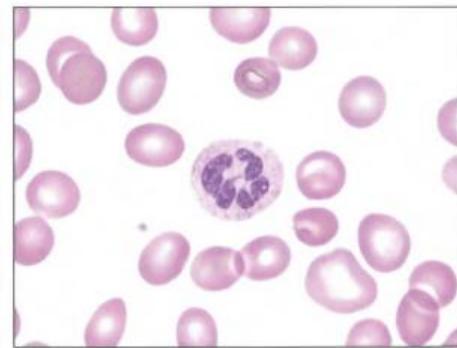


Fig. 5.5 [REDACTED] neutrophil in [REDACTED]

**I. BASIC PRINCIPLES**

- A. [Redacted] with MCV > 100  $\mu\text{m}^3$ ; 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).

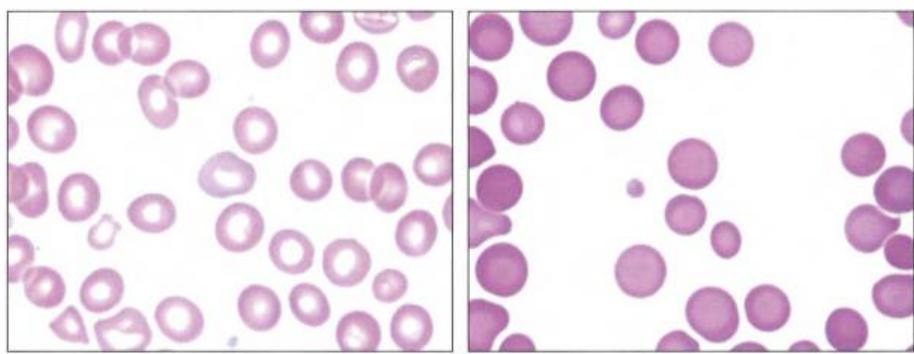


Fig. 5.6 [red]

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

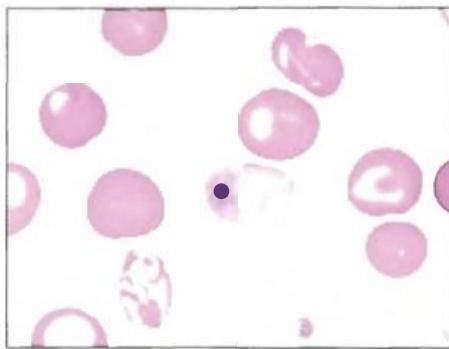
### I. [REDACTED] SPHEROCYTOSIS

- 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).

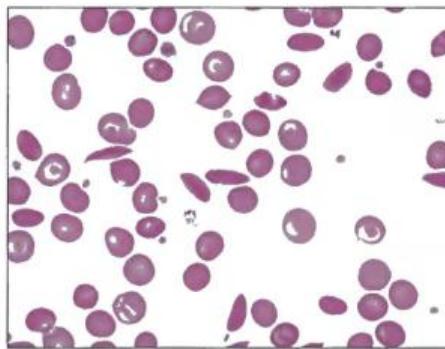
### II. SICKLE CELL [REDACTED]

- A. Autosomal recessive mutation in  $\beta$  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  $\beta$  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.

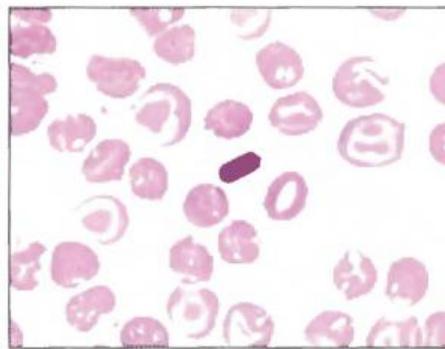
- E. [REDACTED] continuously sickle and de-sickle while passing through the microcirculation, resulting in complications related to RBC membrane damage.
1. [REDACTED] hemolysis - Reticuloendothelial system removes RBCs with damaged membranes, leading to [REDACTED] jaundice with unconjugated hyperbilirubinemia, 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% HbA<sub>2</sub> (no HbA)
- ii. Trait - 55% HbA, 43% HbS, 2% HbA<sub>2</sub>

III. [Redacted] C

- A. Autosomal recessive mutation in  $\beta$  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.

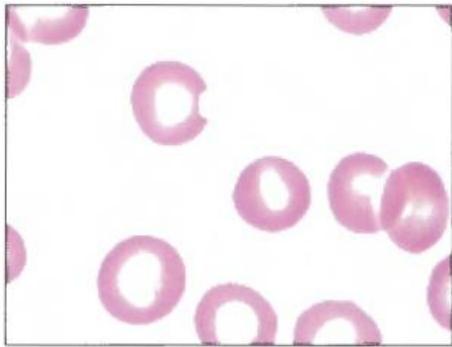
II. GLUCOSE-6-PHOSPHATE [Redacted] (G6PD) [Redacted]

- 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 H<sub>2</sub>O<sub>2</sub>.
  - 2. Glutathione (an antioxidant) neutralizes H<sub>2</sub>O<sub>2</sub>, 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 H<sub>2</sub>O<sub>2</sub> → 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.

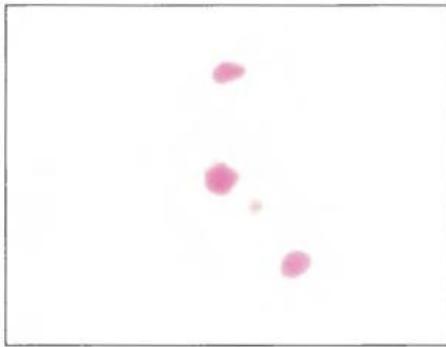
- C. Oxidative stress precipitates Hb as Heinz bodies.
  - 1. Causes of oxidative stress include infections, drugs (e.g., primaquine, sulfa drugs, and dapsone), and fava beans.
  - 2. Heinz bodies are removed from RBCs by splenic macrophages, resulting in bite [redacted] (Fig. 5.11).
  - 3. Leads to [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)

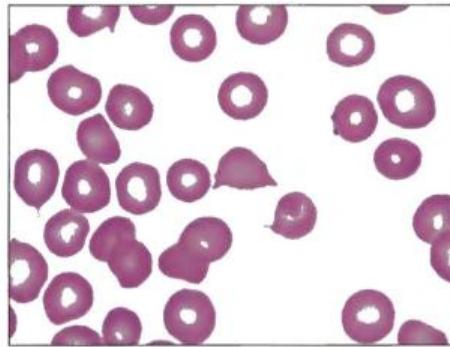
- A. Antibody-mediated (IgG or IgM) destruction of RBCs
- B. IgG-mediated [redacted] usually involves [redacted] hemolysis.
  - 1. IgG binds RBCs in the relatively warm temperature of the central body (warm agglutinin); membrane of antibody-coated RBC is consumed by splenic macrophages, resulting in 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.,  $\alpha$ -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

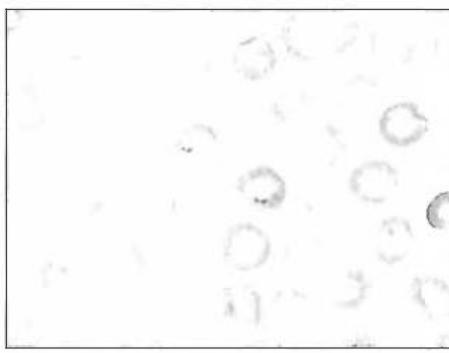
- A. Decreased production of RBCs by bone marrow; characterized by low [REDACTED]
- B. Etiologies include
  - 1. Causes of [REDACTED] and [REDACTED] anemia
  - 2. Renal failure - decreased production of EPO by peritubular interstitial [REDACTED]
  - 3. Damage to bone marrow precursor [REDACTED] (may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

#### II. PARVOVIRUS B19

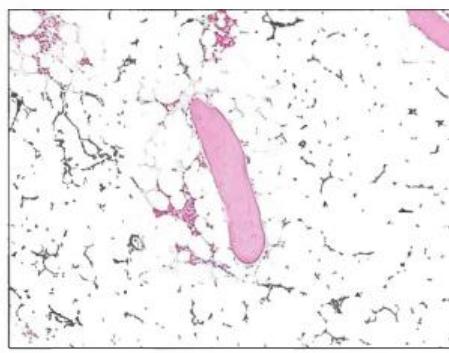
- A. Infects progenitor [REDACTED] and temporarily halts erythropoiesis; leads to significant anemia in the setting of preexisting marrow stress (e.g., sickle cell [REDACTED])
- B. Treatment is supportive (infection is self-limited).

#### 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

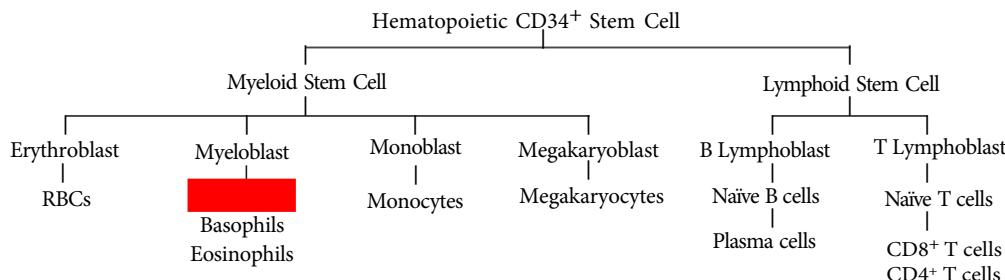
- Hematopoiesis occurs via a stepwise maturation of CD34<sup>+</sup> hematopoietic stem cells (Fig. 6.1).
- Cells mature [redacted] are released from the bone marrow into the [redacted]
- A normal white [redacted] cell (WBC) [redacted] is approximately 5-10 K/ $\mu$ L.
  - A low WBC [redacted] 5 K) is 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).

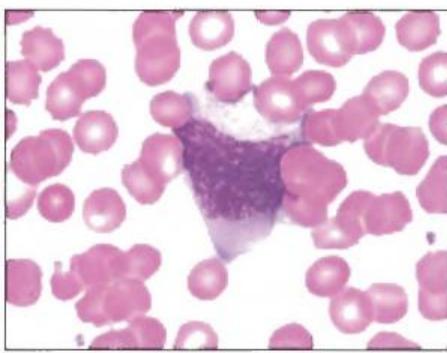


**Fig. 6.1** Hematopoiesis.

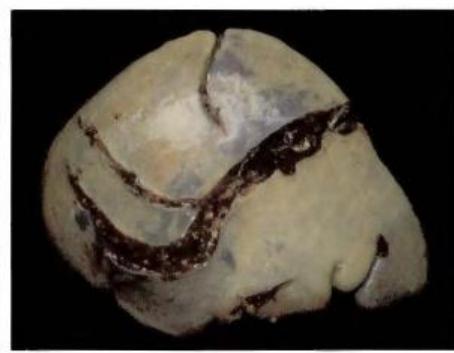
2. High [redacted] state - impairs leukocyte adhesion, leading to release of marginated pool of [redacted]
- B. Monocytosis refers to increased circulating monocytes. Causes include [redacted] inflammatory states (e.g., autoimmune [redacted] infectious) [redacted] malignancy.
- C. Eosinophilia refers 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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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.

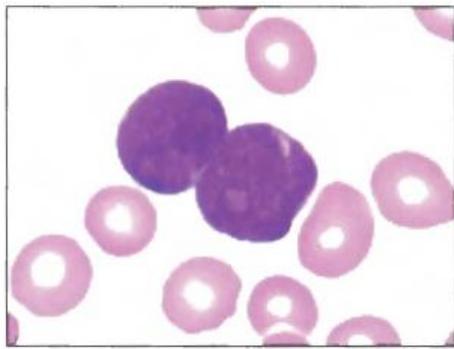
## ACUTE LEUKEMIA

### I BASIC PRINCIPLES

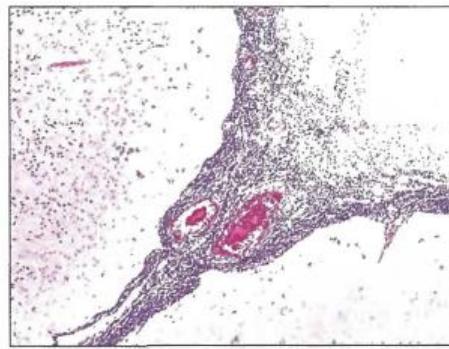
- A. Neoplastic proliferation of blasts; defined as the accumulation of > 20% blasts in the bone marrow.
- B. Increased blasts "crowd-out" normal hematopoiesis, resulting in an "acute" presentation with [redacted] (fatigue), thrombocytopenia (bleeding), or neutropenia (infection).
- C. Blasts usually 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)

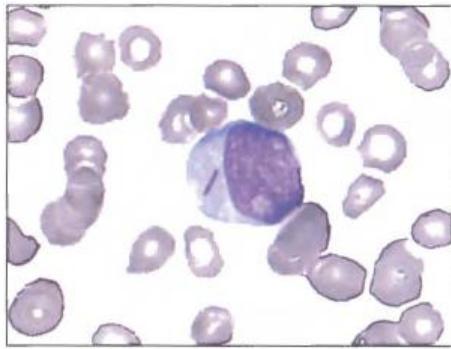
### III. ACUTE MYELOID LEUKEMIA

- 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

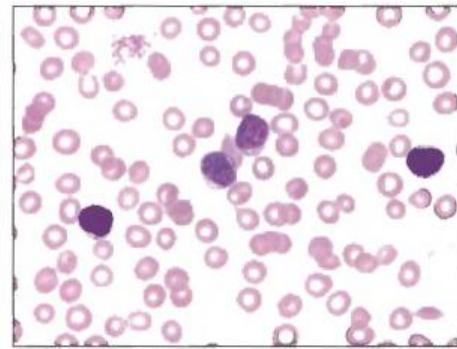
- Neoplastic proliferation of mature circulating lymphocytes; characterized by a high WBC [redacted]
- Usually insidious in onset and seen in older adults



**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.