**Cells of the Blood**
- Blood and bone marrow help maintain homeostasis
- Blood consists of water, proteins, and specialized cells
- Most prevalent cells are erythrocytes (red blood cells (RBC)) which transport oxygen to tissues and contribute to buffering of the blood (see Chapter 4)
- Leukocytes (white blood cells) defend against infection
- Thrombocytes (platelets) contain organelles, but no nucleus; involved in control of bleeding by continuing to normal thrombus (clot) formation in blood vessels

**Classification and Functions of Leukocytes and Thrombocytes**
- The Granulocytes
  - Polymorphonuclear leukocytes with multi-lobed nucleus; secretory granules visible when stained
  - When activated in response to chemical stimuli, they release granules that contain cell-signaling molecules that mediate inflammatory processes
  - Neutrophils: stain pink; phagocytic, migrate to area of infection/tissue damage -> engulf foreign bodies and destroy them by respiratory burst (see Chapter 24); respiratory burst creates oxygen radicals that rapidly destroy foreign material found at infection site
  - Eosinophils: stain red; fight viral infection by releasing RNase from their granules; remove fibrin during inflammation; protect against parasites (worms) by releasing granules containing hydrolytic enzymes and cationic proteins which are toxic to parasites; implicated in asthma, allergic responses and antigen presentation to T cells
  - Basophils: stain blue; least abundant leukocyte; participate in hypersensitivity (allergic) reaction; granules store histamine, produced by decarboxylation of histidine; release of histamine -> smooth muscle cells contract -> vascular permeability increases; granules contain enzymes (proteases, betaglucuronidase, lyso phospholipase) -> degrade microbial structures and assist in remodeling of damaged tissue
- Mononuclear Leukocytes
  - Lymphocytes: rounded nucleus; small round cells in lymph fluid; cells have high nuclear volume:cytoplasmic volume; primary antigen (foreign body)-recognizing cells; 3 major types:
    - T cells: precursors produced in bone marrow -> migrate to thymus -> mature, then enter circulation; several subclasses exist -> different surface membrane proteins determine function
    - B cells: mature in bone marrow; secrete antibodies in response to antigen binding
    - NK cells: target virally-infected and malignant cells for destruction
  - Monocytes: rounded nucleus; circulatory monocytes -> tissue macrophages; macrophages are phagocytic -> enter inflammatory sites and consume microorganisms and necrotic host cell debris left after granulocyte attack; macrophages in spleen remove damaged RBCs -> maintain oxygen-delivering capabilities of blood
- The Thrombocytes: heavily granulated, disc-like cells; aid in intravascular clotting; lack a nucleus -> arise by budding in the cytoplasm of megakaryocytes (multinucleated cells in bone marrow) (see Chapter 45)
  - Anemia
    - RBCs deliver oxygen to tissue due to [hemoglobin (Hb)] in RBCs
    - [Hb] < normal = anemia (Table 44.2)
    - Anemias categorized based on RBC size and [Hb] (Table 44.3), used to Dx/treat
      - Size: normal = normocytic; small = microcytic; large = macrocytic
      - [Hb]: normal = normochromic; decreased = hypochromic
    - Also classified using mean corpuscle volume (MCV - average volume of RBC) and mean corpuscular hemoglobin concentration (MCHC - average concentration of hemoglobin in each RBC)

**Erythrocyte Metabolism**
- The Mature Erythrocyte
  - Mature RBCs contain no intracellular organelles -> enzymes limited to those in cytoplasm -> necessary for prevention/repair of damage by oxygen radicals (see Chapter 24) and generation of energy
  - RBCs can only generate ATP by glycolysis (see Chapter 22) -> ATP used for ion transport across cell
membrane (Na+, K+, Ca+), phosphorylation of membrane proteins, and priming reactions of glycolysis
- Glycolysis uses Rapoport-Luebering shunt to generate 2,3-bisphosphoglycerate (2,3-BPG)
- 2,3-BPG used for phosphoglycerate mutase reaction of glycolysis in other cells; also modulates oxygen binding to hemoglobin that stabilized the deoxy form of hemoglobin -> facilitates release of O2 to tissues
- To bind O2, iron of hemoglobin must be in ferrous (+2) state; reactive oxygen can oxidize iron to ferric (+3) state, producing methemoglobin
- Some NADH produced in glycolysis regenerates hemoglobin from methemoglobin by the NADH-cytochrome b5 methemoglobin reductase system
- 5-10% of glucose metabolized in RBCs generates NADPH via hexose monophosphate shunt; NADPH used to maintain glutathione in reduced state -> glutathione cycle is RBCs main defense against protein/lipid damage by reactive oxygen (see Chapter 24)
- Glucose-6-phosphate dehydrogenase (G6PD) catalyzes the first step of the hexose monophosphate shunt -> lifespan of RBC correlates with G6PD activity
- G6PD cannot be synthesized in RBCs (no ribosomes) -> as G6PD activity decreases, oxidative damage accumulates -> RBC lysis -> when RBC lysis exceeds normal rate of RBC production, number of RBCs in blood drops below normal -> hemolytic anemia

- The Erythrocyte Precursor Cells and Heme Synthesis
  - **Heme Structure**
    - Porphyrin ring (made of 4 pyrrole rings joined by methenyl bridges (-CH-) coordinated with atom of iron
    - 8 side chains are substituents on porphyrin ring (2 per pyrrole); may be acetyl (A), propionyl (P); methyl (M); or vinyl (V) groups
    - Most abundant porphyrin is type III: M V M V M P M
    - Heme is most common porphyrin in body; complexed with proteins to form hemoglobin, myoglobin, and cytochromes (see Chapters 7, 21, 24)
  - **Synthesis of Heme** (Figure 44.3)
  - **Source of Iron** (Figure 44.6)
    - Iron is rarely deficient in diet, but only 10-50% is normally absorbed, so body deficiency is common
    - Iron in meats is in form of heme -> readily absorbed
    - Nonheme iron in plants is not readily absorbed because it contains oxalates, phytates, tannins, and other phenolic compounds that chelate or form insoluble precipitates with iron
    - Vitamin C (ascorbic acid) increase uptake of nonheme iron from digestive tract
    - Iron uptake is also increased during times of need - process unknown
    - Iron is absorbed in ferrous state (2+), but is oxidized to ferric state (3+) by ferroxidase (AKA ceruloplasmin - copper-containing enzyme) for transport through body
    - Free iron is toxic, so transported bound to protein: apotransferrin + Fe3+ = transferrin
    - Transferrin is usually only 1/3 saturated with iron -> binds to transferrin receptor on cell surface and internalized into cell as slightly acidic endosome
  - **Regulation of Heme Synthesis**
    - Heme regulates the synthesis of delta-ALA synthase (needed for first step of heme synthesis) and inhibits the activity of the enzyme (allosteric modifier)
    - Heme levels fall -> heme is synthesized, heme levels rise -> rate of heme synthesis decreases
- Heme also regulates synthesis of hemoglobin by stimulating synthesis of protein globin by maintaining ribosomal initiation complex in an active state (see Chapter 15)

- **Degradation of Heme**
  - Heme degraded -> bilirubin -> conjugated with glucuronic acid -> excreted in bile; occurs for all types of heme, but most comes from hemoglobin
  - RBCs at end of life span (~120 days) -> phagocytosed by cells of reticuloendothelial system -> globin cleaved to amino acids and iron returned to body stores -> heme oxidized and cleaved -> produces CO and biliverdin -> biliverdin reduced to bilirubin -> transported to liver with complexed with serum albumin
  - In liver, bilirubin + UDP-glucuronate -> water-soluble bilirubin monoglucuronide -> converted to diglucuronide -> excreted into bile
  - In intestine, bacteria deconjugate bilirubin diglucuronide -> urobilinogens -> some absorbed into blood and excreted in urine, most oxidized to urobilins (like stercobilin) and excreted in feces, giving it brown color

- **The Red Blood Cell Membrane**
  - Red, biconcave disc facilitates gas exchange across the cell membrane -> membrane proteins that maintain shape allow RBC to transverse small capillaries (by folding) to deliver O2 to tissues
  - When passing through kidneys, RBCs traverse hypertonic (6x more than normal) -> cells shrink and expand
  - In sphen, viability of RBCs is determined (RBCs pass through sphen 120 times/day) -> small passages test deformability of RBC -> no longer deformable, become trapped -> destroyed by macrophages
  - Proteins (spectrin, actin, band 4.1, band 4.2, and ankyrin) form 2D lattice that gives RBC flexibility; when RBC is subjected to stress, spectrin rearranges (uncoil/extend and compress) -> shape changes, but not surface area
  - Mature RBC cannot synthesize new membrane proteins or lipids, but lipids can be exchanged with circulating lipoprotein lipids -> glutathione system protects proteins and lipids from oxidative damage

- **Agents that Affect Oxygen Binding**
  - **2,3-Bisphosphoglycerate**
    - Formed in RBC from 1,3-bisphosphoglycerate
    - Binds to globin in central cavity formed by 4 subunit -> increasing energy required for conformational changes that facilitate binding or O2 -> lowers affinity of hemoglobin for O2
  - **Proton Binding (Bohr Effect)**
    - Binding of H+ by hemoglobin lowers its affinity for O2 -> contributes to Bohr Effect
    - CO2 produced by metabolism -> catalyzed by carbonic anhydrase in RBCs to form carbonic acid -> dissociation produces H+ -> pH of blood decreases as it enters tissues -> H+ reacts with amino acid residues in hemoglobin -> conformational changes promote release of O2
    - In lungs, process is reversed: O2 binds to hemoglobin -> H+ released -> H+ combines with bicarbonate -> forms carbonic acid -> decrease in H+ causes pH of blood to rise -> carbonic anhydrase cleaves carbonic acid to CO2 and H2O -> CO2 is exhaled
  - **Carbon Dioxide**
    - Most CO2 produced in tissues by metabolism is carried to lungs as bicarbonate, some CO2 is covalently bound to hemoglobin
    - In tissues, CO2 forms carbamate adducts with the N-terminal amino groups of deoxyhemoglobin -> stabilizes deoxy conformation
    - In lungs, PO2 is high -> O2 binds to hemoglobin -> bound CO2 is released

- **Hematopoiesis**
  - In presence of signals, hematopoietic stem cells proliferate, differentiate and mature into any of the types of cells that make up the blood
  - Hematopoietic differentiation is hierarchical (Figure 44.15), fates of a specific cell become progressively restricted
  - Progenitors are designated colony-forming unit-lineage (AKA colony-forming unit-erythroid (CFU-E)); progenitors that form very large colonies are “burst-forming” units
  - **Cytokines and Hematopoiesis**
    - Developing progenitor cells in marrow grow in close proximity to marrow stromal cells (fibroblasts, endothelial cells, adipocytes, macrophages), which form extracellular matrix and secrete growth factors that
Hematopoiesis
- In presence of signals, hematopoietic stem cells proliferate, differentiate and mature into any of the types of cells that make up the blood
- Hematopoietic differentiation is hierarchical (Figure 44.15), fates of a specific cell become progressively restricted
- Progenitors are designated colony-forming unit-lineage (AKA colony-forming unit-erythroid (CFU-E)); progenitors that form very large colonies are “burst-forming” units
- Cytokines and Hematopoiesis
  - Developing progenitor cells in marrow grow in close proximity to marrow stromal cells (fibroblasts, endothelial cells, adipocytes, macrophages), which form extracellular matrix and secrete growth factors that regulate hematopoietic development
  - Hematopoietic growth factors stimulate proliferation, differentiation, and maturation and prevent apoptosis; most recognized by receptors in cytokine receptor superfamily
  - Binding of ligand to receptor -> receptor aggregation -> phosphorylation of Janus kinases (JAKs) (see Chapter 11)
    - Activated JAKs phosphorylate the cytokine receptor -> creates docking regions where signal transducer and activator of transcription (STAT) transcription factors bind -> JAKs phosphorylate STATs -> STATs dimerize and translocate to nucleus -> activate target genes; additional proteins bind to cytokine receptor -> activate Ras/Raf/MAP kinase pathway; other pathways activated -> inhibit apoptosis (see Chapter 18)
  - Response to cytokine binding transient because cell contains negative regulators such as silencer of cytokine signaling (SOCS) proteins that prevent the docking of signal transduction proteins; other SOCS bind to JAKs and inhibit them
  - SHP-1 is tyrosine phosphatase necessary for proper development of myeloid and lymphoid lineages by dephosphorylating JAK2, inactivating it
  - STATs are inactivated by protein inhibitors of activated STAT (PIAS); PIAS bind to phosphorylated STATs and prevent dimerization/promote dissociation
- Erythropoiesis
  - Production of RBCs regulated by demands of O2 delivery to tissues
  - Tissue oxidation reduced -> kidney releases hormone erythropoietin (EPO) -> stimulates multiplication/maturation of RBC progenitors -> stem cell -> CFU-GEMM -> BFU-E -> CFU-E -> normoblast -> 4 more cycles of division where nucleus becomes smaller/more condensed -> nucleus is extruded forming reticulocyte (have ribosomes and mRNA, can synthesize hemoglobin) -> released from bone marrow and circulated for 1-2 days -> end up in spleen and mature, losing ribosomes and mRNA
- Nutritional Anemias
  - Daily RBC production ~10^12 cells/day -> large numbers of RBC production may lead to nutritional deficiencies in iron, vitamin B12, and folate -> appearance of resulting RBCs indicates type of deficiency
    - Iron deficiency: pale, microcytic (small) anemia -> decreased heme synthesis, affects globin synthesis
    - Folate/B12 deficiency: megaloblastic (large) anemia -> DNA replication/nuclear division do not keep pace with maturation of cytoplasm -> nucleus is extruded before required number of division -> greater cell volume, fewer RBCs
- Hemoglobinopathies, Hereditary Persistence of Fetal Hemoglobin, and Hemoglobin Switching
  - Hemoglobinopathies: Disorders in the Structure or Amount of the Globin Chains
    - 700+ mutant hemoglobins discovered, most resulting from single base substitution -> single amino acid replacement; most are not clinically significant
    - Hemoglobin S (HbS, sickle cell anemia): most common mutation, devastating effect on homozygote (see Will Sichel, Chapter 6)
    - Hemoglobin C (HbC, mild hemolytic anemia in heterozygotes only): results from glu-to-lys replacement in same position as HbS mutation; promotes water loss from the cell by activating K+ transporter -> higher than normal [Hb] in cell; lowers Hg solubility in the homozygote -> Hg tends to precipitate in the cell, but does not deform the cell
- **Thalassemias**
  - To function optimally, hemoglobin alpha- and beta-globin chains must have proper structure and 1:1 ratio.
  - Large excess of one over the other -> thalassemia disease (heterogeneous class of anemias that can arise by multiple mechanisms).
  - Like sickle cell anemia, thalassemias provide resistance to malaria in heterozygous individual.
  - **Mechanisms:**
    - Single amino acid replacement mutations -> globin subunit has decreased stability.
    - Decreased synthesis of one subunit (more common):
      - Alpha-thalassemias: arise from complete gene deletions; 2x alpha-globin gene found on each copy of chromosome 16, resulting in 4 copies total per progenitor cell -> 1 copy deleted = Hb concentration minimally reduced, 2 copies deleted = asymptomatic with microcytic, hypochromic cells, 3 copies deleted = moderately severe microcytic hypochromic anemia with splenomegaly, 4 copies deleted = fatal in utero; alpha chains precipitate at every developmental stage -> ineffective erythropoiesis.
      - Beta-thalassemias: heterogeneous genetic disease (see Chapter 14); can result from deletions, promoter mutations, and splice-junction mutations; heterozygous for beta+ (some globin chain synthesis) or beta-null (no globin chain synthesis) = asymptomatic with microcytic, hypochromic cells (may have mild anemia); beta+ homozygous = anemia of variable severity; beta-positive/beta-null heterozygous = more severely affected; beta-null homozygous = severe anemia; excess beta chains are ineffective at delivering O\(_2\) to tissues because of high O\(_2\) affinity -> over time HbH precipitates in cells -> form inclusion bodies -> trapped/destroyed in spleen.

- **Hereditary Persistence of Fetal Hemoglobin**
  - Fetal hemoglobin (HbF) = 2xalpha-chains and 2xgamma-chains vs. adult Hb (HbA) (2xalpha, 2xbeta).
  - Hemoglobin switching: process that regulates conversion of HbF -> HbA (not 100% normally).
  - Hereditary Persistence of Fetal Hemoglobin (HPFH): continue to produce up to 100% of HbF in place of HbA people with beta-thalassemia or sickle cell anemia have less severe illnesses with elevated HbF.
  - **Nondeletion Forms of Hereditary Persistence of Fetal Hemoglobin:** derive from point mutations in A-gamma and G-gamma promoters; have ameliorating effect on sickle cell and beta-thalassemia because of increased production of gamma-chains.
  - **Deletion Forms of Hereditary Persistence of Fetal Hemoglobin:** both delta- and beta-genes are deleted from one copy of chromosome 11; only HbF is produced; if fetal globins remain activated after birth, person is clinically normal; if enough HgF is not produced to compensate, person has delta-0, beta-0-thalassemia.

- **Hemoglobin Switching: A Developmental Process Controlled by Transcription Factors**
  - Embryonic megaloblasts (large, retaining nucleus) are produced in yolk sac ~15 days after fertilization.
  - After 6 weeks, erythropoiesis shifts to liver (and a little bit to spleen).
  - In last few weeks in utero, bone marrow begins producing RBCs.
  - 8-10 weeks after birth, all RBCs produces in bone marrow and HbA is produced.

- **Structure and Transcriptional Regulation of Alpha/Beta-Globin Gene Loci**
  - HbF is alpha-2, G-gamma-2; HbA is predominately alpha-2, beta-2; some HbA is alpha-2, delta-2 (HgA2).
  - HbF in adult cells is alpha-2, A-gamma-2.
  - Timing of hemoglobin switching is controlled by developmental clock, relatively unaffected by environmental conditions.
Key Concepts

- The blood contains a wide variety of distinct cell types, each of whose function is necessary for maintaining the body’s internal environment.
- Erythrocytes transport oxygen throughout the body and return carbon dioxide back to the lung.
  - Erythrocytes lack nuclei and carry out limited metabolic reactions.
  - Glycolysis provides energy and NADH.
  - The NADH maintains the iron in hemoglobin in the ferrous state.
  - The HMP shunt provides NADPH to regenerate reduced glutathione to protect the membrane from oxidative damage.
  - 1,3-Bisphosphoglycerate is converted to 2,3-bisphosphoglycerate as a by-product of glycolysis to regulate oxygen binding to hemoglobin.
  - Heme synthesis occurs in the erythrocyte precursor, using succinyl-CoA and glycine. Inherited defects in heme synthesis lead to porphyrias.
  - Iron, a critical part of heme, is carried throughout the body on protein carriers because free iron is toxic.
  - The erythrocyte membrane is flexible as a result of its unique cytoskeletal structure, which allows erythrocytes to deform in order to travel through narrow capillaries.
  - Oxygen binding to hemoglobin in the erythrocyte is modulated by a variety of factors.
    - 2,3-Bisphosphoglycerate stabilizes the deoxy form of hemoglobin.
    - Proton binding to hemoglobin stabilizes the deoxy form of hemoglobin (the Bohr effect).
    - Carbon dioxide links covalently to the amino termini of the four globin chains in a hemoglobin molecule, further stabilizing the deoxy form of hemoglobin.
  - Hematopoiesis is the generation of the unique blood cell types from a single precursor stem cell in the bone marrow.
  - Polymorphonuclear leukocytes consist of a variety of cell types that release chemical signals when activated (granulocytes), phagocytose foreign bodies (neutrophils), destroy parasites (eosinophils), and are involved in the allergic response (basophils).
  - Mononuclear leukocytes include the lymphocytes (necessary for the immune response) and monocytes (which develop into macrophages, which engulf debris left behind after granulocytes attack foreign material).
  - A wide variety of mutations can lead to alterations in hemoglobin function (hemoglobinopathies):
    - Sickle cell anemia
    - Thalassemias
    - Hereditary persistence of fetal hemoglobin (hemoglobin switching and its regulation)

Table 44.4 Diseases Discussed in Chapter 44

<table>
<thead>
<tr>
<th>Disease or Disorder</th>
<th>Environmental or Genetic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemias</td>
<td>Genetic</td>
<td>Unbalanced synthesis of alpha and beta chains of hemoglobin, leading to anemia. Red cell hemolysis, leading to fewer red cells. An increase in 2,3-BPG levels often masks the effects of the anemia.</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency</td>
<td>Genetic</td>
<td>Oxidation of the iron in hemoglobin to the ferric state, which will not bind oxygen, although many individuals with this disorder are asymptomatic.</td>
</tr>
<tr>
<td>Congenital methemoglobinemia</td>
<td>Genetic</td>
<td>Affects red blood cell membrane stability through an inability to protect membrane proteins and lipids against oxidation. Inherited defects in almost any step of heme synthesis leading to a series of diseases with different symptoms and outcomes.</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase defect</td>
<td>Genetic</td>
<td>Reduced iron leads to reduced heme synthesis and reduced oxygen delivery to the tissues.</td>
</tr>
<tr>
<td>Porphyrias</td>
<td>Genetic</td>
<td>Reduced iron leads to reduced heme synthesis and reduced oxygen delivery to the tissues. Loss of a cytokine receptor subunit, leading to a complete loss of B- and T-cell maturation and proliferation, and no functional immune system.</td>
</tr>
<tr>
<td>Hemoglobin C</td>
<td>Genetic</td>
<td>A point mutation in hemoglobin leading to a lysine for a glutamic acid at position 6 of the beta chain, leading to hemolytic anemia in the homozygous state.</td>
</tr>
<tr>
<td>Hereditary persistence of fetal hemoglobin</td>
<td>Genetic</td>
<td>Mutations in promoters and enhancer regions leading to misexpression of the globin gamma gene, and constant expression of the gene Mutations in any of several red blood cell membrane proteins (such as spectrin), leading to instability of the red cells, destruction of the red blood cells, and an anemia.</td>
</tr>
</tbody>
</table>

2,3-BPG, 2,3-bisphosphoglycerate.

All known glucose-6-phosphate dehydrogenase (G6PD) variant genes contain small in-frame deletions or missense mutations. The corresponding proteins, therefore, have decreased stability or lowered activity, leading to a reduced half-life or life span for the red cell. No mutations have been found that result in complete absence of G6PD. Based on studies with knockout mice, those mutations would be expected to result in embryonic lethality.

An inherited deficiency in pyruvate kinase leads to hemolytic anemia (an anemia caused by the destruction of red blood cells; hemoglobin values typically drop to 4 to 10 g/dL in this condition, with normal values being 13.5 to 17.5 in males, or 11.5 to 15.5 in females). Because the amount of adenosine triphosphate (ATP) formed from glycolysis is decreased by 50%, red blood cell ion transporters cannot function effectively. The red blood cells tend to gain Ca²⁺ and lose K⁺ and water. The water loss increases the intracellular hemoglobin concentration. With the increase in intracellular hemoglobin concentration, the internal viscosity of the cell is increased to the point that the cell becomes rigid and, therefore, more susceptible to damage by shear forces in the circulation. Once they are damaged, the red blood cells are removed from circulation, leading to the anemia. However, the effects of the anemia are frequently moderated by the twofold to threefold elevation in 2,3-bisphosphoglycerate (2,3-BPG) concentration that results from the blockade of the conversion of phosphoenolpyruvate to pyruvate. Because 2,3-BPG binding to hemoglobin decreases the affinity of hemoglobin for oxygen, the red blood cells that remain in circulation are highly efficient in releasing their bound oxygen to the tissues.

Congenital methemoglobinemia, the presence of excess methemoglobin, is found in people with an enzymatic deficiency in cytochrome b₅ reductase or in people who have inherited hemoglobin M. In hemoglobin M, a single amino acid substitution in the heme-binding pocket stabilizes the ferric (Fe³⁺) oxygen. Individuals with congenital methemoglobinemia appear cyanotic but have few clinical problems. Methemoglobinemia can be acquired by ingestion of certain oxidants such as nitrates, quinones, aniline, and sulfonamides. Acquired methemoglobinemia can be treated by the administration of reducing agents, such as ascorbic acid or methylene blue.
A complete blood count (CBC) is ordered when a physician suspects a problem in the cellular composition of a patient's blood. The cells within the collected blood are counted and typed using an automated analyzer based on flow cytometry (counting cells one at a time as they flow through a detector). As each cell flows through the machine, a laser shines light at the cell, which leads to predictable light scattering and absorbance depending on the cell type. Based on the light-scattering and absorption pattern, the machine keeps track of the results of each cell that flows through the machine, leading to a very accurate count of each cell type present in the sample. The data from this analysis will include the total number of red blood cells per liter, the amount of hemoglobin in the red blood cells (in grams per liter), the hematocrit (the fraction of whole blood that consists of red blood cells), the mean corpuscular volume, the total number of white blood cells, as well as a count of the different types of white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

In X-linked severe combined immunodeficiency (SCID) disease, the most common form of SCID, circulating T lymphocytes are not formed, and B lymphocytes are not active. The affected gene encodes the γ-chain of the interleukin-2 receptor. Mutant receptors are unable to activate Janus kinase 3 (JAK3), and the cells are unresponsive to the cytokines that stimulate growth and differentiation. Recall also that adenosine deaminase deficiency (see Chapter 41), which is not X-linked, also leads to a form of SCID, but for different reasons.

The difference in amino acid composition between the β-chains of HbA and the γ-chains of fetal hemoglobin (HbF) results in structural changes that cause HbF to have a lower affinity for 2,3-biphosphoglycerate (2,3-BPG) than adult hemoglobin (HbA) and thus a greater affinity for oxygen. Therefore, the oxygen released from the mother's hemoglobin (HbA) is readily bound by HbF in the fetus. Thus, the transfer of oxygen from the mother to the fetus is facilitated by the structural difference between the hemoglobin molecule of the mother and that of the fetus.

Hemoglobin C (Hbc) is found in high frequency in West Africa, in regions with a high frequency of hemoglobin S (Hbs). Consequently, compound heterozygotes for Hbs and Hbc are not uncommon in some African regions and among African Americans. HbS/Hbc individuals have significantly more hemopathology than individuals with sickle cell trait (adult hemoglobin [HbA]/Hbs). Polymerization of deoxygenated Hbs is dependent on the Hbs concentration within the cell. The presence of Hbc in the compound heterozygote increases the Hbs concentration by stimulating K⁺ and water efflux from the cell. Because the Hbc globin tends to precipitate, the proportion of Hbs tends to be higher in Hbs/Hbc cells than in the cells of individuals with sickle cell trait (Hbs/HbA). The way in which multiple mutations ameliorate or exacerbate hemopathologic diseases has provided insights into the molecular mechanisms of hemoglobin function and developmental regulation.

A complication of sickle cell disease is an increased formation of gallstones. A sickle cell crisis accompanied by the intravascular destruction of red blood cells (hemolysis) experienced by patients with sickle cell disease, such as Wil Sichel, increases the amount of unconjugated bilirubin that is transported to the liver. If the concentration of this unconjugated bilirubin exceeds the capacity of the hepatocytes to conjugate it to the more soluble diglucuronide through interaction with hepatic UDP-glucuronate, both the total and the unconjugated bilirubin levels in the blood increase. More unconjugated bilirubin is then secreted by the liver into the biliary tree. The increase in unconjugated bilirubin (which is not very water-soluble) results in its precipitation within the gallbladder lumen, leading to the formation of pigmented (calcium bilirubinate) gallstones.

Perturbed JAK/STAT signaling is associated with development of lymphoid and myeloid leukemias, severe congenital neutropenia (a condition in which levels of circulating neutrophils are severely reduced), and Fanconi anemia, which is characterized by bone marrow failure and increased susceptibility to malignancy.

Families have been identified whose members have a mutant erythropoietin (EPO) receptor that is unable to bind SHP-1. Erythropoietin is the hematopoietic cytokine that stimulates production of red blood cells. Individuals with the mutant EPO receptor have a higher than normal percentage of red blood cells in the circulation because the mutant EPO receptor cannot be deactivated by SHP-1. Erythropoietin causes sustained activation of Janus kinase 2 (JAK2) and STAT 5 in these cases.

Populations of hematopoietic cells enriched with stem cells can be isolated by fluorescence-activated cell sorting, based on the expression of specific cell-surface markers. Increasing the population of stem cells in cells used for a bone marrow transplantation increases the chances of success of the transplantation.

There are two ways in which an individual might have two α-globin genes deleted. In one case, one copy of chromosome 16 might have both α-globin genes deleted, whereas the other copy had two functional α-globin genes. In the second case, both chromosomes might have lost one of their two copies of the α-globin gene. The former possibility is more common among Asians, the latter among Africans.

Defects in erythrocyte cytoskeletal proteins lead to hemolytic anemia. Shear stresses in the circulation result in the loss of pieces of the red cell membrane. As the membrane is lost, the red blood cell becomes more spherical and loses its deformability. As these cells become more spherical, they are more likely to lyse in response to mechanical stresses in the circulation, or to be trapped and destroyed in the spleen.

Drugs, such as phenobarbital, induce enzymes of the drug-metabolizing systems of the endoplasmic reticulum that contain cytochrome P450. Because heme is used for synthesis of cytochrome P450, free heme levels fall and δ-aminolevulinic acid (δ-ALA) synthesis is induced to increase the
(5-ALA) synthase is induced to increase the rate of heme synthesis.