Blood Composition

Blood: fluid connective tissue composed of

- Plasma
  - 55% in blood volume on average

- Formed elements
  - Erythrocytes (red blood cells - RBCs)
    - Hematocrit (PCV): % RBCs in blood volume
      - 47% ± 5% for males
      - 42% ± 5% for females
        - Aka...Packed cell volume
  - Leukocytes (white blood cells - WBCs)
    - 1% in blood volume on average
  - Platelets
Components of Whole Blood: PCV

1. Withdraw blood and place in tube
2. Centrifuge

- Plasma (55% of whole blood)
- Buffy coat: leukocytes and platelets (<1% of whole blood)
- Erythrocytes (45% of whole blood)

Figure 17.1
Physical Characteristics & Volume

- Sticky, opaque fluid
- Scarlet to dark red
- pH 7.35-7.45
- 38°C (100°F)
- ~ 8% of body weight
- Average volume: 5-6 L for males; 4-5 L for females
Functions of Blood

- Major transport medium
  - Oxygen, CO2, nutrients, wastes, hormones
- Regulate temperature
  - absorbs & distributes heat
- Maintenance of pH and clotting
- Protection against pathogens - Immune response
## Blood Plasma

<table>
<thead>
<tr>
<th>Water (90%)</th>
<th>Protein (8%)</th>
<th>Other (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most of volume of the blood</td>
<td><strong>Albumin</strong>- (most abundant) important carrier molecule (binds and helps carry hormones and other proteins &amp; fats, drugs though the blood), osmotic agent and helps to buffer pH</td>
<td>Electrolytes- like Na and K</td>
</tr>
<tr>
<td>Suspending medium</td>
<td><strong>Globulins</strong>&lt;br&gt;Alpha/beta- transport&lt;br&gt;Gamma - immunoglobulin</td>
<td>Gases- like O2</td>
</tr>
<tr>
<td></td>
<td><strong>Fibrinogen / prothrombin</strong>&lt;br&gt;Proteins for blood coagulation</td>
<td>Hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutrients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wastes</td>
</tr>
</tbody>
</table>

*Diagram showing the percentage of blood plasma components.*
Formed Elements

- **Erythrocytes**
  - Have no nuclei or organelles

- **Leukocytes**
  - Are complete cells

- **Platelets**
  - Cell fragments
Components of Whole Blood

- Platelets
- Erythrocytes
- Monocyte
- Neutrophils
- Lymphocyte

Figure 17.2
Erythrocytes (RBCs)

- Anucleate, essentially no organelles
- Filled with hemoglobin (Hb) for transport of respiratory gases - esp. O2
  - Hb binds reversibly with oxygen
- Life span ~120 days
- Contributes to blood viscosity
- No mitochondria; ATP production is anaerobic
Erythrocytes (RBCs)

Biconcaved  Anucleate
Hemoglobin (Hb)

- Reversibly binds oxygen molecules in blood
  - is composed of the protein **globin** – 2 alpha & 2 beta chains
  - Each chain is bound to a **heme group** – can transport 4 molecules of oxygen - heme is pigmented
    - Every heme has one atom of **iron (Fe)**, which can bind to one oxygen molecule
    - Oxygenated = bright red; deoxygenated = dark red

- Hb levels:
  - 14-20g per 100ml blood in infants
  - 12-18g per 100 ml blood in adults
Structure of Hemoglobin

(a) Hemoglobin consists of globin (two alpha and two beta polypeptide chains) and four heme groups.

(b) Iron-containing heme pigment.

Animation on oxygen transport
Hemoglobin (Hb) terminology

- **Oxyhemoglobin** (ruby red)
  - bound to Oxygen
  - Oxygen loading takes place in the lungs

- **Deoxyhemoglobin** (dark red)
  - low oxygen
  - Oxygen unloading in the tissues

- **Carbaminohemoglobin**
  - bound to carbon dioxide – bound to protein portion not Fe
  - Carbon dioxide loading takes place in the tissues
Blood Cell Formation

- Hematopoiesis (hemopoeisis)
  - Blood cell formation
  - Occurs in red bone marrow
  - Hematopoietic stem cells (hemocytoblasts) > make all formed elements in blood
  - Each type of blood cell is produced in different #s – depending on maturation pathway chosen
    - Once a cell chooses a path, there’s no turning back

- Erythropoiesis : erythrocyte (RBC) production
Production of Erythrocytes: Erythropoiesis

All blood cell formation begins with the same hematopoietic stem cell = hemocytoblast

3 phases:
1. Ribosome synthesis
2. Hemoglobin synthesis
3. Nucleus ejection

Reticulocytes are released into blood

Reticulocyte counts-1-2% used as an index for normal RBC production
Regulation of Erythropoiesis

- Too few RBCs > tissue hypoxia
- Too many RBCs > increased viscosity
- Balance of RBC production and destruction via:
  - Hormonal control
    - Erythropoietin (EPO)
      - Direct stimulus for erythropoiesis
      - Released by kidneys in response to hypoxia
  - Dietary requirements for synthesis
    - Iron, amino acids, B vitamins
Hormonal Control of Erythropoiesis

- **Hypoxia**
  - Drop in RBCs, or Hb
  - Decreased oxygen availability
    - high altitudes/pneumonia/iron deficiency
  - Increased tissue demand for oxygen
    - aerobic exercise

- All related to ability to transport enough oxygen

- Increased erythropoiesis increases the:
  - RBC count in circulating blood
  - Oxygen carrying ability of the blood
Erythropoiesis and EPO

- Rate of erythropoiesis dependant on ability of RBC to transport oxygen, NOT on # of RBCs in circulation

- **Renal failure** can result in low EPO and erythrocyte counts

- **Athletic training**
  - Can be dangerous if coupled to dehydration (inc blood viscosity)

- **Testosterone** -- increases release of EPO – higher RBC counts in males
Erythropoietin Mechanism

1. **Stimulus:** Hypoxia (low blood $O_2$- carrying ability) due to
   - Decreased RBC count
   - Decreased amount of hemoglobin
   - Decreased availability of $O_2$

2. **Kidney** (and liver to a smaller extent) releases erythropoietin.

3. Erythropoietin stimulates red bone marrow.

4. Enhanced erythropoiesis increases RBC count.

5. $O_2$- carrying ability of blood increases.

**Homeostasis:** Normal blood oxygen levels
Dietary Requirements for Erythropoiesis

- **Nutrients:** amino acids, carbohydrates, lipids
  - For basic structural components

- **Iron**
  - stored in Hb (65%), with the rest stored in liver, spleen & bone marrow
  - stored inside the cells as **ferritin & hemosiderin**
  - transported in blood bound to the transport protein **transferrin**

- **Vitamin B12 and Folic Acid**
  - Necessary for DNA synthesis & cell division
Fate and Destruction of Erythrocytes

- Life span: 100 - 120 days
- Old RBCs become fragile; Hb degenerates
  - Heme & globin are separated
    - Heme is degraded into bilirubin (yellow pigment) – secreted into bile
    - Globin is metabolized into amino acids
  - Iron can be re-used
- Dying RBCs are recycled in the spleen and liver by macrophages
Life cycle of red blood cells

1. Low O₂ levels in blood stimulate kidneys to produce erythropoietin.
2. Erythropoietin levels rise in blood.
3. Erythropoietin and necessary raw materials in blood promote erythropoiesis in red bone marrow.
4. New erythrocytes enter bloodstream; function about 120 days.
5. Aged and damaged red blood cells are engulfed by macrophages of liver, spleen, and bone marrow; the hemoglobin is broken down.

- Hemoglobin
  - Heme
  - Globin
- Iron stored as ferritin, hemosiderin
- Amino acids
- Bilirubin
- Iron is bound to transferrin and released to blood from liver as needed for erythropoiesis.
- Bilirubin is picked up from blood by liver, secreted into intestine in bile, metabolized to stercobilin by bacteria, and excreted in feces.

Food nutrients, including amino acids, Fe, B₁₂, and folic acid, are absorbed from intestine and enter blood.

6. Raw materials are made available in blood for erythrocyte synthesis.
1. Low O$_2$ levels in blood stimulate kidneys to produce erythropoietin.

2. Erythropoietin levels rise in blood.

3. Erythropoietin and necessary raw materials in blood promote erythropoiesis in red bone marrow.

4. New erythrocytes enter bloodstream; function about 120 days.
5. Aged and damaged red blood cells are engulfed by macrophages of liver, spleen, and bone marrow; the hemoglobin is broken down.

Hemoglobin → Heme → Iron stored as ferritin, hemosiderin → Amino acids

Bilirubin is picked up from blood by liver, secreted into intestine in bile, metabolized to stercobilin by bacteria, and excreted in feces.

Iron is bound to transferrin and released to blood from liver as needed for erythropoiesis.

Food nutrients, including amino acids, Fe, B₁₂, and folic acid, are absorbed from intestine and enter blood.

6. Raw materials are made available in blood for erythrocyte synthesis.
Erythrocyte Disorders

- **Anemia**
  -blood has abnormally low oxygen-carrying capacity
  -Sign more than a disease itself
  -Blood oxygen levels cannot support metabolism
  -Accompanied by:
    -fatigue, paleness, shortness of breath, and chills
Causes of Anemia

- **Insufficient erythrocytes**
  - Hemorrhagic anemia: acute or chronic blood loss
  - Hemolytic anemia: RBCs rupture prematurely
  - Aplastic anemia: destruction or inhibition of red bone marrow

- **Low Hb content**
  - Iron-deficent anemia
    - Inadequate intake of iron OR
    - Impaired iron absorption OR
    - Secondary to hemorrhagic anemia
  - Pernicious anemia
    - Vitamin B12 deficiency
    - Impaired absorption of B12
Causes of Anemia

- Abnormal Hb
  - Thalassemias: Absent or faulty globin chain
    - RBCs are thin, delicate, Hb deficient
  - Sickle-Cell Anemia
    - Defective gene codes for abnormal Hb (HbS)
    - Causes RBCs to become sickle shaped

- Polycythemia
  - excess RBCs > inc blood viscosity > heart attack or stroke
    - Polycythemias vera: Bone marrow cancer
    - Secondary polycythemia: less O2 available or inc EPO
    - Blood doping (excess blood transfusions)
(a) Normal erythrocyte has normal hemoglobin amino acid sequence in the beta chain.

(b) Sickled erythrocyte results from a single amino acid change in the beta chain of hemoglobin.
Leukocytes (WBCs)

- Make up < 1% of total blood volume
  - Actual count 4,000-11,000/mm³
- Can leave capillaries via diapedesis (squeeze out)
- Two categories of WBCs:
  - Granulocytes
    - Neutrophils, Eosinophils, Basophils
  - Agranulocytes
    - Lymphocytes, Monocytes
- Leukocytosis: WBC count over 11,000 / mm³³
  - Normal response to bacterial or viral invasion
Percentages of Leukocytes

Know the order from most to least the amount of WBCs

Never let monkeys eat bananas

Differential WBC count (All total 4800–10,800/μl)

- Granulocytes
  - Neutrophils (50–70%)
  - Eosinophils (2–4%)
  - Basophils (0.5–1%)

- Agranulocytes
  - Lymphocytes (25–45%)
  - Monocytes (3–8%)

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Granulocytes & Agranulocytes

- **Granulocytes**: neutrophils, eosinophils, and basophils
  - Have cytoplasmic granules (can be seen with Wright’s stain)
  - Larger and shorter-lived than RBCs
  - Have lobed nuclei; Are all phagocytic cells

- **Agranulocytes**: lymphocytes and monocytes
  - Lack visible cytoplasmic granules
  - Have spherical or kidney shaped nuclei
Leukocytes

(a) Neutrophil; multilobed nucleus
(b) Eosinophil; bilobed nucleus, red cytoplasmic granules
(c) Basophil; bilobed nucleus, purplish-black cytoplasmic granules
(d) Small lymphocyte; large spherical nucleus
(e) Monocyte; kidney-shaped nucleus

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Granulocytes: Neutrophils

- Most numerous WBCs
- Multi-lobed nuclei
  - Polymorphonuclear leukocytes (PMNs)
- Respond heavily to bacteria
- Neutrophils are our body’s bacteria slayers
  - Initiate **respiratory bursts** to kill bacteria: oxygen molecule metabolized to bleach or H2O2
  - Also produce antibiotic-like proteins called **defensins**
- **Animation of neutrophil attack**
Granulocytes: Eosinophils

- Red-staining, bi-lobed nuclei
- Red coarse granules
- Digest parasitic worms
- Lessen the severity of allergies by inactivating certain inflammatory chemicals released during allergic reactions
Granulocytes: Basophils

- **Rarest** WBCs
- U- or S-shaped nuclei
- Contain large purplish-black granules - contain histamine
  - Histamine –vasodilator – attracts other WBCs to inflammed site *(bronchoconstriction)*
(a) Neutrophil; multilobed nucleus

(b) Eosinophil; bilobed nucleus, red cytoplasmic granules

(c) Basophil; bilobed nucleus, purplish-black cytoplasmic granules
Agranulocyte: **Lymphocytes**

- Large single, dark purple nuclei
- Mostly in lymph tissue
  - Few in circulation
- Have crucial role in active immunity – Two types
  - T cells: act against virus-infected cells & tumor cells
  - B cells: give rise to plasma cells which produce antibodies
Agranulocytes: Monocytes

- Dark purple kidney- or U-shaped nuclei
- Largest leukocyte
- Leave circulation and enter tissue – turn into macrophages
  - Mobile and Phagocytic
    - Viral
    - Bacterial
    - Clean up
  - Activate lymphocytes for immune response
Hematopoiesis of Leukocytes

All begin with hemocytoblast

Leukopoiesis:
- White blood cell formation
- is stimulated by interleukins and colony-stimulating factors (CSFs)
Leukocyte Disorders

- **Leukopenia**: abnormally low WBC count – drug induced
- **Leukemia**: cancerous conditions of abnormal production
  - Leukemias are named according to the abnormal WBCs involved
    - Myelocytic leukemia – involves myeloblasts
    - Lymphocytic leukemia – involves lymphocytes
  - Acute: quickly developing; primarily affects children
  - Chronic: slow to develop; more prevalent in older people
  - Bone marrow becomes consumed with cancerous WBCs
Leukemia

- Death is caused by internal hemorrhage and overwhelming infections
- Treatments include irradiation, antileukemic drugs, and bone marrow transplants
Platelets (thrombocytes)

- Small fragments of cells called **megakaryocytes**
- Formation is regulated by **thrombopoietin** (produced by liver & kidneys) which stimulates bone marrow
- Contains chemicals for clotting:
  - Serotonin, calcium, enzymes, ADP, PDGF (platelet-derived growth factor)
  - Form a temporary plug to seal vessels
Formation of Platelets

- Platelets arise from megakaryocytes

Stem cell → Hemocytoblast → Megakaryoblast → Promegakaryocyte → Megakaryocyte → Platelets
Hemostasis

- Fast series of reactions to stop bleeding
  - Vascular spasm
    - Vasoconstriction of damaged vessel
    - Triggers direct injury, release of chemicals, pain reflex
  - Platelet plug formation
    - Platelets become sticky and bind to exposed collagen
    - Initiates positive feedback cycle
  - Coagulation (blood clotting)
    - Set of reactions in which blood is transformed from liquid to gel
    - Reinforces platelet plug with fibrin threads
**Step 1** Vascular spasm
- Smooth muscle contracts, causing vasoconstriction.

**Step 2** Platelet plug formation
- Injury to lining of vessel exposes collagen fibers; platelets adhere.
  - Platelets release chemicals that make nearby platelets sticky; platelet plug forms.

**Step 3** Coagulation
- Fibrin forms a mesh that traps red blood cells and platelets, forming the clot.
Platelet Plug Formation

Platelets:
- adhere to collagen
- Stick to exposed collagen fibers and form a platelet plug
- Release chemicals increasing spasms and attracting more platelets
  - Make **Thromboxane A2** increases both these actions
  - **Aspirin** inhibits the formation of thromboxanes and other prostaglandins – inhibiting platelet plug formation
Coagulation

- Two pathways: Intrinsic, extrinsic
- **Vitamin K** is needed for the production of 4 clotting factors
- **Platelet factor 3** (PF3-intrinsic) and **tissue factor** (TF) or **Tissue thromboplastin** (extrinsic) are pivotal players in these pathways
  - Tissue thromboplastin is produced by damaged tissue and is only found in the plasma when tissue has been damaged
- **Prothrombin** $\rightarrow$ thrombin
- **Fibrinogen** $\rightarrow$ fibrin $\rightarrow$ net forms clot
- **Note:** **Calcium (Ca)** is required for this process
Detailed Events of Coagulation

Order of activation:

• **Intrinsic:**
  PF3 → prothrombin → thrombin → fibrinogen → fibrin → clot formation → clot retraction

• **Extrinsic:**
  Tissue factor (thromboplastin) → prothrombin → thrombin → fibrinogen → fibrin → clot formation → clot retraction
Clot Retraction and Repair

- Clot retraction
  - stabilization of the clot squeeze out excess serum

- Repair
  - Platelet-derived growth factor (PDGF) stimulates rebuilding of blood vessel wall
  - Vascular endothelial growth factor (VEGF), stimulates the endothelial cells to multiply and restore the endothelial lining
Fibrinolysis

- removal of unneeded clot after healing
  - Begins within 2 days
- **Plasminogen** in clot is converted to **plasmin** by **tPA** (tissue plasminogen activator), factor XII and thrombin
- **Plasmin** digests fibrin removing the clot after the damage to the vessel is repaired
Hemostasis Disorders: Thromboembolistic Conditions

- Undesirable clot formation

- Thrombus
  - Clot that develops and persists in unbroken blood vessel
    - can block circulation, resulting in tissue death

- Embolus
  - a freely floating clot in bloodstream
    - Can block vessels in the body
      - Pulmonary emboli can impair lungs
      - Cerebral emboli can cause strokes
Prevention of Thromboembolytic Conditions

Prevented by:

- Aspirin (COX inhibitor)
  - Antiprostaplandin that inhibits thromboxane A2
    - thromboxane synthesis needed for platelet plug

- Heparin (anticoagulant)
  - inhibits thrombin (needed to form fibrin net)
  - Used for pre- and post-operative cardiac care

- Warfarin (Coumadin)
  - interferes with action of vitamin K
  - Used for atrial fibrillation
Hemostasis Disorders:

Bleeding Disorders

- Abnormalities that prevent normal clot formation

- **Thrombocytopenia**
  - condition where the number of circulating platelets is deficient
    - Platelet counts less than 50,000/mm³
  - Due to suppression or destruction of bone marrow

- **Impaired liver function** (inability to synthesize procoagulants)
  - Causes include vitamin K deficiency, hepatitis and cirrhosis
  - Inability to absorb fat can lead to vitamin K deficiencies as it is a fat-soluble substance and is absorbed along with fat
  - Liver disease can also prevent the liver from producing bile, which is required for fat and vitamin K absorption
Hemostasis Disorders: Bleeding Disorders

- **Hemophilias**: hereditary bleeding disorders caused by lack of clotting factors
  - Hemophilia A: most common type (77% of all cases) due to a deficiency of factor VIII
  - Hemophilia B: due to a deficiency of factor IX
  - Hemophilia C: mild type, due to a deficiency of factor XI
- Symptoms include prolonged bleeding and painful and disabled joints
- Treatment is with blood transfusions and the injection of missing factors
Blood Transfusions

- Whole blood transfusions are used:
  - When blood loss is substantial
  - In treating thrombocytopenia
- Packed red cells (cells with plasma removed) are used to treat anemia
- Blood Losses of 15-30% result in pallor and weakness
- Losses of 30% or greater result in shock and requires whole blood transfusions
Restoring Blood Volume

- Death from shock may result from low blood volume (low plasma)
- Volume must be immediately replaced to lower blood viscosity with
  - Normal saline or electrolyte solution
    - Mimics plasma electrolyte composition
  - Plasma expanders
    - Mimics properties of albumin
      - Purified human albumin, dextran
Blood Groups

- Humans have 30 varieties of naturally occurring RBC antigens
- The antigens of the ABO and Rh blood groups cause vigorous transfusion reactions when they are improperly transfused
- Other blood groups (M, N, Dufy, Kell, and Lewis) are mainly used for legalities
ABO Blood Groups

- Types: A, B, AB and O
- Based on the presence or absence of:
  - Antigens (agglutinogens - A and B) on the surface of the RBCs
  - Antibodies (agglutinins) in the plasma (anti-A and anti-B)
- Agglutinogens and their corresponding antibodies cannot be mixed without serious hemolytic reactions
## ABO Blood Groups

<table>
<thead>
<tr>
<th>BLOOD GROUP</th>
<th>FREQUENCY (% OF U.S. POPULATION)</th>
<th>RBC ANTIGENS (AGGLUTINOGENS)</th>
<th>ILLUSTRATION</th>
<th>PLASMA ANTIBODIES (AGGLUTININS)</th>
<th>BLOOD THAT CAN BE RECEIVED</th>
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</thead>
<tbody>
<tr>
<td>AB</td>
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<td>A</td>
<td>None</td>
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<td>B, O</td>
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<td>Blood type of RBC</td>
<td>Antigen on RBC</td>
<td>Antibodies produced (anti-sera)</td>
<td>Anti-sera / antibodies that produce clumping (agglutination) of RBCs</td>
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<td>Anti-A and B</td>
<td>Neither Anti-A or B</td>
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</table>
Rh Blood Groups

- Presence of the Rh agglutinogens on RBCs is indicated as Rh⁺
- Anti-Rh antibodies are not spontaneously formed in Rh⁻ individuals
- However, if an Rh⁻ individual receives Rh⁺ blood, anti-Rh antibodies form
- A second exposure to Rh⁺ blood will result in a typical transfusion reaction
Hemolytic disease of the newborn: erythroblastosis fetalis

(a) Rh-positive erythrocytes from fetus enter blood of Rh-negative woman during the birth process.

(b) Anti-Rh antibodies are produced by woman's immune system that remain in the woman's bloodstream.

(c) During succeeding pregnancy, antibodies pass placental barrier and enter fetal blood causing the destruction of fetal erythrocytes.
Hemolytic Disease of the Newborn

- **Rh- mom Rh + fetus.** Usually the first Rh+ fetus all is fine but exposure of blood during birth sensitizes the mother-she begins producing antibodies against Rh. The second Rh+ fetus is in trouble.

- **Hemolytic disease of the newborn-erythroblastosisfetalis** Rh− antibodies of a sensitized Rh− mother cross the placenta and attack and destroy the RBCs of an Rh+ baby
Hemolytic Disease of the Newborn

- The drug **RhoGAM** (anti Rh antibodies) can prevent the Rh- mother from becoming sensitized during the first pregnancy with the a Rh+ fetus

- Treatment of hemolytic disease of the newborn involves pre-birth transfusions and exchange transfusions after birth
Transfusion Reactions

- Transfusion reactions occur when mismatched blood is infused.
- Donor’s cells are attacked by the recipient’s plasma agglutinins causing:
  - Diminished oxygen-carrying capacity
  - Clumped cells that impede blood flow
  - Ruptured RBCs that release free hemoglobin into the bloodstream
- Circulating hemoglobin precipitates in the kidneys and causes renal failure.
Blood Typing

- When serum containing anti-A or anti-B antibodies is added to blood, agglutination will occur between the antibodies and the corresponding antigens.
- Positive reactions indicate agglutination.
Blood being tested

**Type AB** (contains agglutinogens A and B; agglutinates with both sera)

**Type A** (contains agglutinogen A; agglutinates with anti-A)

**Type B** (contains agglutinogen B; agglutinates with anti-B)

**Type O** (contains no agglutinogens; does not agglutinate with either serum)
# ABO and Rh Blood Type Donation Showing Matches Between Donor and Recipient Types

<table>
<thead>
<tr>
<th>Recipients</th>
<th>O+</th>
<th>A+</th>
<th>B+</th>
<th>AB+</th>
<th>O- **</th>
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<th>B-</th>
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</table>
Before birth, blood cell formation takes place in the fetal yolk sac, liver, and spleen.

By the seventh month, red bone marrow is the primary hematopoietic area.

Blood cells develop from mesenchymal cells called blood islands.

The fetus forms HbF, which has a higher affinity for oxygen than adult hemoglobin.
Developmental Aspects

- Age-related blood problems result from disorders of the heart, blood vessels, and the immune system.
- Increased leukemias are thought to be due to the waning deficiency of the immune system.
- Abnormal thrombus and embolus formation reflects the progress of atherosclerosis.