Overview of Blood Circulation

- Blood leaves the heart via arteries that branch repeatedly until they become capillaries
- Oxygen ($O_2$) and nutrients diffuse across capillary walls and enter tissues
- Carbon dioxide ($CO_2$) and wastes move from tissues into the blood
Overview of Blood Circulation

- Oxygen-deficient blood leaves the capillaries and flows in veins to the heart
- This blood flows to the lungs where it releases CO$_2$ and picks up O$_2$
- The oxygen-rich blood returns to the heart
Composition of Blood

- Blood is the body’s only fluid tissue
- It is composed of liquid plasma and formed elements
  - The fluid matrix is called plasma and lacks collagen and elastic fibers typical of most connective tissues
- Formed elements include:
  - Erythrocytes, or red blood cells (RBCs) (45%)
  - Buffy coat (<1%): Leukocytes, or white blood cells (WBCs)
  - Platelets
  - Plasma (55%)
- Hematocrit – the percentage of RBCs out of the total blood volume
Physical Characteristics and Volume

- Blood is a sticky, opaque fluid with a metallic taste
- Color varies from scarlet to dark red
- The pH of blood is 7.35–7.45
- Temperature is 38°C
- Blood accounts for approximately 8% of body weight
- Average volume: 5–6 L for males, and 4–5 L for females
Functions of Blood

- Blood performs a number of functions dealing with:
  - Substance distribution
  - Regulation of blood levels of particular substances
  - Body protection
Distribution

- Blood transports:
  - Oxygen from the lungs and nutrients from the digestive tract to body cells
  - Metabolic wastes from cells to the lungs (CO2) and kidneys for elimination (urine)
  - Hormones from endocrine glands to target organs
Regulation

- Blood maintains:
  - Appropriate body temperature by absorbing and distributing heat through out the body & skin to encourage or discourage heat loss
  - Normal pH in body tissues using buffer systems thus preventing abrupt changes in blood pH
  - Adequate fluid volume in the circulatory system via salt concentrations
Protection

- Blood prevents blood loss by:
  - Activating plasma proteins and platelets
  - Initiating clot formation when a vessel is broken

- Blood prevents infection by:
  - Synthesizing and utilizing antibodies
  - Activating complement proteins
  - Activating WBCs to defend the body against foreign invaders
Blood Plasma

- Blood plasma contains 90% H2O and over 100 solutes, including:
  - Proteins – albumin, globulins, clotting proteins, and others
  - Lactic acid, urea, creatinine
  - Organic nutrients – glucose, carbohydrates, amino acids
  - Electrolytes – sodium, potassium, calcium, chloride, bicarbonate
  - Respiratory gases – oxygen and carbon dioxide
- 60% of plasma protein is albumin (carrier protein)
- Most plasma proteins are produced by the liver
- Other proteins consist of hormones (endocrine glands and organs) and gamma globulins (antibodies)
Formed Elements

- Erythrocytes, leukocytes, and platelets make up the formed elements
  - Only leukocytes (WBCs) are complete cells
  - Erythrocytes (RBCs) have no nuclei or organelles, and platelets are just cell fragments
- Most formed elements survive in the bloodstream for only a few days
- Most blood cells do not divide but are renewed by cells in bone marrow
Erythrocytes (RBCs)

- Biconcave discs, anucleate, essentially no organelles
- Filled with hemoglobin (Hb), a protein that functions in gas transport
- Contain the plasma membrane protein spectrin and other proteins that:
  - Give erythrocytes their flexibility
  - Allow them to change shape as necessary to twist thru capillaries with diameter smaller than themselves
Erythrocytes (RBCs)

Side view

Top view

2.5 μm

7.5 μm
Components of Whole Blood

- Platelets
- Erythrocytes
- Monocyte
- Neutrophils
- Lymphocyte
Erythrocytes (RBCs)

- Erythrocytes are an example of the complementarity of structure and function
- Structural characteristics contribute to its gas transport function
  - Biconcave shape has a huge surface area relative to volume
  - Erythrocytes are more than 97% hemoglobin
  - ATP is generated anaerobically, so the erythrocytes do not consume the oxygen they transport
- Major factor contributing to blood viscosity
Erythrocyte Function

- RBCs are dedicated to respiratory gas transport
  - Hb reversibly binds with oxygen and most oxygen in the blood is bound to Hb
  - Hb is composed of the protein globin, made up of two alpha and two beta chains, each bound to a heme group
  - Each heme group bears an atom of iron, which can bind to one oxygen molecule
  - Each Hb molecule can transport four molecules of oxygen
  - 1 RBC carries 250 million hemoglobin molecules equalling 1 billion O2 molecules/cell
Structure of Hemoglobin

(a) Hemoglobin
(b) Iron-containing heme group

Figure 17.4
Hemoglobin (Hb)

- Oxyhemoglobin – Hb bound to oxygen (bright red)
  - Oxygen loading takes place in the lungs
- Deoxyhemoglobin – Hb after oxygen diffuses into tissues (reduced Hb) (dark red)
- Carbaminohemoglobin – Hb bound to carbon dioxide (CO2 binds to Hb’s amino acids, not to heme group and occurs more readily when Hb is in its reduced state)
  - Carbon dioxide loading takes place in the tissues
Production of Erythrocytes

- Hematopoiesis – blood cell formation
- Hematopoiesis occurs in the red bone marrow of the:
  - Axial skeleton and girdles
  - Epiphyses of the humerus and femur
- Hemocytoblasts give rise to all formed elements
Production of Erythrocytes: Erythropoiesis

- A hemocytoblast is transformed into a proerythroblast
- Proerythroblasts develop into early erythroblasts
- The developmental pathway consists of three phases
  - 1 – ribosome synthesis in early erythroblasts
  - 2 – Hb accumulation in late erythroblasts and normoblasts
  - 3 – ejection of the nucleus from normoblasts and formation of reticulocytes
- Reticulocytes then become mature erythrocytes
As cells mature they migrate through the thin walls of the sinusoids (blood capillaries) & enter the bloodstream.

Marrow produces 100 billion new cells daily.

All erythrocytes arise from a single type of stem cell, the pluripotent hematopoietic stem cell (hemocytoblast) in the red bone marrow.

They mature along different paths. Once committed to that path there is no going back.

This change is signaled by membrane surface receptors that respond to specific hormones & growth factors assisting in the cell’s specialization.
Production of Erythrocytes: Erythropoiesis

- A hemocytoblast is transformed into a proerythroblast
- Proerythroblasts develop into early erythroblasts
Production of Erythrocytes: Erythropoiesis

- The developmental pathway consists of three phases
  - 1 – ribosome synthesis in early erythroblasts
  - 2 – Hb synthesis and iron accumulation in late erythroblasts and normoblasts
  - 3 – ejection of the organelles from normoblasts and formation of reticulocytes (young erythrocytes). Nucleus degenerates and the cell takes on a donut shape

- Reticulocytes enter the blood stream and begin their task. 2 days later they are fully mature erythrocytes as their ribosomes are degraded
Production of Erythrocytes: Erythropoiesis

Figure 17.5

- Stem cell: Hemocytoblast
- Committed cell: Proerythroblast
- Developmental pathway:
  - Phase 1: Ribosome synthesis
  - Phase 2: Hemoglobin accumulation
  - Phase 3: Ejection of nucleus

- Early erythroblast
- Late erythroblast
- Normoblast
- Reticulocyte
- Erythrocyte
Regulation and Requirements for Erythropoiesis

- Circulating erythrocytes – the number remains constant and reflects a balance between RBC production and destruction
  - Too few RBCs leads to tissue hypoxia
  - Too many RBCs causes undesirable blood viscosity
- Erythropoiesis is hormonally controlled and depends on adequate supplies of iron, amino acids, and B vitamins
Hormonal Control of Erythropoiesis

- Stimulus for erythrocyte formation is erythropoietin (EPO), a glycoprotein hormone
- Erythropoietin (EPO) release by the kidneys is triggered by:
  - Hypoxia due to decreased RBCs
  - Decreased oxygen availability
  - Increased tissue demand for oxygen
- Enhanced erythropoiesis increases the:
  - RBC count in circulating blood
  - Oxygen carrying ability of the blood
Erythropoietin Mechanism

Testosterone can also enhance EPO production.

Stimulus: Hypoxia due to decreased RBC count, decreased amount of hemoglobin, or decreased availability of O₂

Enhanced erythropoiesis increases RBC count

Erythropoietin stimulates red bone marrow

Kidney (and liver to a smaller extent) releases erythropoietin

Enzyme activated by Imbalance

Start

Imbalance

Homeostasis: Normal blood oxygen levels

Increases O₂-carrying ability of blood

Reduces O₂ levels in blood
EPO and Athletes

July 23, 2006

Floyd Landis wins the Tour de France
Dietary Requirements of Erythropoiesis

- Erythropoiesis requires:
  - Proteins, lipids, and carbohydrates
  - Iron, vitamin $\text{B}_{12}$, and folic acid
- The body stores iron in Hb (65%), the liver, spleen, and bone marrow
- Intracellular iron is stored in protein-iron complexes such as ferritin and hemosiderin
- Circulating iron is loosely bound to the transport protein transferrin
- Iron is lost daily in feces, urine, and perspiration. Women’s menstrual flow accounts for greater loss of iron compared to that of men (1.7 mg vs. 0.9 mg daily)
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.

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

7. Raw materials are made available in blood for erythrocyte synthesis.

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Fate and Destruction of Erythrocytes

- RBCs are anucleate
- They are unable to synthesize protein, grow, and divide
- Proteins in RBCs become damaged & cannot be replaced
- The life span of an erythrocyte is 100–120 days
- Eventually they become trapped and fragmented in the smaller capillaries of the spleen
- Dying RBCs are engulfed by macrophages
- Heme and globin are separated and the iron is salvaged for reuse
Fate and Destruction of Erythrocytes

- Heme is degraded to a yellow pigment called bilirubin that binds to albumin for transport
- The liver secretes bilirubin into the intestines as bile
- This degraded pigment leaves the body in feces
Erythropoietin levels rise in blood.

Erythropoietin levels rise in blood.

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

New erythrocytes enter bloodstream; function about 120 days.

Aged and damaged red blood cells are engulfed by macrophages of liver, spleen, and bone marrow; the hemoglobin is broken down.

Low $O_2$ levels in blood stimulate kidneys to produce erythropoietin.

Figure 17.7
Hemoglobin

Amino acids

Globin

Raw materials are made available in blood for erythrocyte synthesis.

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.

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

Bilirubin

Heme

Globin

Amino acids

Iron stored as ferritin, hemosiderin

Circulation

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

Figure 17.7
Erythrocyte Disorders

- Anemia – blood has abnormally low oxygen-carrying capacity
  - It is a symptom rather than a disease itself
  - Blood oxygen levels cannot support normal metabolism
  - Signs/symptoms include fatigue, paleness, shortness of breath, and chills
Anemia: Insufficient Erythrocytes

- Hemorrhagic anemia – result of acute or chronic loss of blood
- Hemolytic anemia – prematurely ruptured RBCs
- Aplastic anemia – destruction or inhibition of red bone marrow
Anemia: Decreased Hemoglobin Content

- Iron-deficiency anemia results from:
  - A secondary result of hemorrhagic anemia
  - Inadequate intake of iron-containing foods
  - Impaired iron absorption

- Pernicious anemia results from:
  - Deficiency of vitamin $B_{12}$
  - Lack of intrinsic factor needed for absorption of $B_{12}$
  - Treatment is intramuscular injection of $B_{12}$; application of Nascobal
Anemia: Abnormal Hemoglobin

- Thalassemias – absent or faulty globin chain in Hb
  - RBCs are thin, delicate, and deficient in Hb
- Sickle-cell anemia – results from a defective gene coding for an abnormal Hb called hemoglobin S (HbS)
  - HbS has a single amino acid substitution in the beta chain
  - This defect causes RBCs to become sickle-shaped in low oxygen situations
Leukocytes (WBCs)

- Leukocytes, the only blood components that are complete cells (w/ nuclei & organelles):
  - Are less numerous than RBCs
  - Make up 1% of the total blood volume
Leukocytes (WBCs)

- Function in disease defense against bacteria, viruses, parasites, toxins, and tumors
  - RBCs are confined to the blood stream and function only in blood
  - WBCs can leave capillaries via diapedesis w/ the circulatory system acting as their means of transport
- Move through tissue spaces
Leukocytes (WBCs)

- Leukocytes are signalled to leave the bloodstream by adhesion molecules (selectins) displayed by endothelial cells forming the capillary walls at sites of inflammation.

- They then move by amoeba motion and follow a chemical trail of molecules released by damaged cells (positive chemotaxis).

- WBCs then gather and destroy damaged tissue or foreign substances.
Granulocytes

- Granulocytes – neutrophils, eosinophils, and basophils
  - Contain cytoplasmic granules that stain specifically (acidic, basic, or both) with Wright’s stain
  - Are larger and usually shorter-lived than RBCs
  - Have lobed nuclei
  - Are all phagocytic cells
Neutrophils

- Most numerous WBC
- Neutrophils have two types of granules that:
  - Take up both acidic and basic dyes ("neutro")
  - Contain peroxidases, hydrolytic enzymes, and defensins (antibiotic-like proteins)
- Respiratory Burst: O2 is metabolized to produce a potent oxidizing substance and lysis occurs in a phagosome
  - Neutrophils are our body’s bacteria slayers
Eosinophils

- Eosinophils account for 1–4% of WBCs
  - Have red-staining, bilobed nuclei connected via a broad band of nuclear material
  - Have red to crimson (acidophilic) large, coarse, lysosome-like granules
  - Lead the body’s counterattack against parasitic worms that are too large to phagocytize
  - Lessen the severity of allergies by phagocytizing immune complexes
Basophils

- Account for 0.5% of WBCs and:
  - Have U- or S-shaped nuclei with two or three conspicuous constrictions
  - Are functionally similar to mast cells
  - Have large, purplish-black (basophilic) granules that contain histamine
    - Histamine – inflammatory chemical that acts as a vasodilator and attracts other WBCs (antihistamines counter this effect)
    - Both basophils and mast cells bind to IgE causing the cells to release histamine, e.g. a runny nose
Agranulocytes

- Agranulocytes – lymphocytes and monocytes:
  - Lack visible cytoplasmic granules
  - Are similar structurally, but are functionally distinct and unrelated cell types
  - Have spherical (lymphocytes) or kidney-shaped (monocytes) nuclei
Lymphocytes

- Account for 25% or more of WBCs and:
  - Have large, dark-purple, circular nuclei that occupies most of the cytoplasm
  - Are found mostly enmeshed in lymphoid tissue (lymph nodes & spleen) but some circulate in the blood
  - Major role is in immunity
- There are two types of lymphocytes: T cells and B cells
  - T cells function in the immune response and act directly against virus infected cells and tumor cells
  - B cells give rise to plasma cells which produce antibodies (immunoglobulins, Igs) that are released to the blood (Chapt. 21)
Monocytes

- Monocytes account for 4–8% of leukocytes
  - They are the largest leukocytes
  - They have abundant pale-blue cytoplasms
  - They have purple-staining, U- or kidney-shaped nuclei
  - They leave the circulation, enter tissue, and differentiate into highly mobile macrophages which “eat” viruses, bacteria, and parasites
Leukocytes

(a) Neutrophil  (b) Eosinophil  (c) Basophil

(d) Lymphocyte  (e) Monocyte
KU GAME DAY!!
## Summary of Formed Elements

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>ILLUSTRATION</th>
<th>DESCRIPTION*</th>
<th>CELLS/μL (mm³) OF BLOOD</th>
<th>DURATION OF DEVELOPMENT (D) AND LIFE SPAN (LS)</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythrocytes</strong> (red blood cells, RBCs)</td>
<td>![Illustration]</td>
<td>Biconcave, anucleate disc; salmon-colored; diameter 7–8 μm</td>
<td>4–6 million</td>
<td>D: about 15 days LS: 100–120 days</td>
<td>Transport oxygen and carbon dioxide</td>
</tr>
<tr>
<td><strong>Leukocytes</strong> (white blood cells, WBCs)</td>
<td>![Illustration]</td>
<td>Spherical, nucleated cells</td>
<td>4800–10,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Neutrophil</td>
<td>![Illustration]</td>
<td>Nucleus multilobed; inconspicuous cytoplasmic granules; diameter 10–12 μm</td>
<td>3000–7000</td>
<td>D: about 14 days LS: 6 hours to a few days</td>
<td>Phagocytize bacteria</td>
</tr>
<tr>
<td>- Eosinophil</td>
<td>![Illustration]</td>
<td>Nucleus bilobed; red cytoplasmic granules; diameter 10–14 μm</td>
<td>100–400</td>
<td>D: about 14 days LS: about 5 days</td>
<td>Kill parasitic worms; destroy antigen-antibody complexes; inactivate some inflammatory chemicals of allergy</td>
</tr>
<tr>
<td>- Basophil</td>
<td>![Illustration]</td>
<td>Nucleus lobed; large purplish-black cytoplasmic granules; diameter 10–14 μm</td>
<td>20–50</td>
<td>D: 1–7 days LS: a few hours to a few days</td>
<td>Release histamine and other mediators of inflammation; contain heparin, an anticoagulant</td>
</tr>
</tbody>
</table>

*Appearance when stained with Wright's stain.
## Summary of Formed Elements

### Table 17.2.2

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>ILLUSTRATION</th>
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<th>CELLS/μl (mm³) OF BLOOD</th>
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<td></td>
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<td>4800–10,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agranulocytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lymphocyte</td>
<td><img src="image" alt="Lymphocyte Illustration" /></td>
<td>Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 μm</td>
<td>1500–3000</td>
<td>D: days to weeks LS: hours to years</td>
<td>Mount immune response by direct cell attack or via antibodies</td>
</tr>
<tr>
<td>• Monocyte</td>
<td><img src="image" alt="Monocyte Illustration" /></td>
<td>Nucleus U or kidney shaped; gray-blue cytoplasm; diameter 14–24 μm</td>
<td>100–700</td>
<td>D: 2–3 days LS: months</td>
<td>Phagocytosis; develop into macrophages in the tissues</td>
</tr>
<tr>
<td>Platelets</td>
<td><img src="image" alt="Platelets Illustration" /></td>
<td>Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 μm</td>
<td>150,000–400,000</td>
<td>D: 4–5 days LS: 5–10 days</td>
<td>Seal small tears in blood vessels; instrumental in blood clotting</td>
</tr>
</tbody>
</table>

*Appearance when stained with Wright’s stain.
Production of Leukocytes

- Leukopoiesis is stimulated by interleukins and colony-stimulating factors (CSFs)
  - Interleukins are numbered (e.g., IL-1, IL-2), whereas CSFs are named for the WBCs they stimulate (e.g., granulocyte-CSF stimulates granulocytes)
  - The ILs have been cloned

- Macrophages and T cells are the most important sources of cytokines
- Many hematopoietic hormones are used clinically to stimulate bone marrow
Formation of Leukocytes

- All leukocytes originate from hemocytoblasts
- Develop along one-way paths, committed
- Granules appear in the myelocyte stage & then cell division stops
- Nuclei bend in the band cell stage
- Nuclear segmentation occurs just prior to release into the circulation
- Bone marrow stores mature granulocytes
- Monocytes diverge from a myeloblast that can become either a neutrophil or monocyte
Hemocytoblast

Myeloid stem cell

Lymphoid stem cell

Myeloblast

Myeloblast

Myeloblast

Lymphoblast

Stem cells

Committed cells

Promyelocyte

Promyelocyte

Promyelocyte

Promonocyte

Prolymphocyte

Developmental pathway

Eosinophilic myelocyte

Basophilic myelocyte

Neutrophilic myelocyte

Eosinophilic band cells

Basophilic band cells

Neutrophilic band cells

Eosinophils

(a)

Granular leukocytes

Basophils

(b)

(d)

Monocytes

Agranular leukocytes

Lymphocytes

(c)

Eosinophils

(basophils)

(c)

(d)

(e)

Some become

Macrophages (tissues)

Some become

Plasma cells

Figure 17.11
Leukocytes Disorders: Leukopenia & Leukemias

- Leukopenia is an abnormally low WBC count
- Leukemia refers to cancerous conditions involving WBCs
- A single clone (original cell) remains unspecialized and divides out of control impairing normal bone marrow function
- Leukemias are named according to the abnormal WBCs involved
  - Myelocytic leukemia – involves myeloblasts
  - Lymphocytic leukemia – involves lymphocytes
- Acute leukemia involves blast-type cells and primarily affects children
- Chronic leukemia is more prevalent in older people
Leukemia

- Immature WBCs are found in the bloodstream in all leukemias
- Bone marrow becomes totally occupied with cancerous leukocytes
- The WBCs produced, though numerous, are not functional
- Results in severe anemia and bleeding via exclusion of RBCs and platelets
- Death is caused by internal hemorrhage and overwhelming infections
- Treatments include irradiation, antileukemic drugs, and bone marrow transplants
Mono: The Kissing Disease

- Viral disease occurring usually in young adults
- Caused by Epstein-Barr virus
- Results in an excessive number of agranulocytes
- Symptoms: tired, achy, chronic sore throat, low-grade fever
- Only cure is 3 weeks rest
Platelets

- Platelets are fragments of megakaryocytes with a blue-staining outer region and a purple granular center.

- Their granules contain serotonin, Ca$^{2+}$, enzymes, ADP, and platelet-derived growth factor (PDGF).

- Platelets function in the clotting mechanism by forming a temporary plug that helps seal breaks in blood vessels.

- Platelets not involved in clotting are kept inactive by nitric oxide (NO) and prostacyclin.
Genesis of Platelets

- The hormone thrombopoietin regulates platelet development
- The stem cell for platelets is the hemocytoblast
- Repeated mitosis w/o cytokinesis of the megakaryoblast
- Presses against synusoid sending cytoplasmic extensions thru and into the bloodstream
- Cytoplasmic extensions rupture releasing platelet fragments into the bloodstream
Hemostasis

- A series of reactions for stoppage of bleeding
- During hemostasis, three phases occur in rapid sequence
  - Vascular spasms – immediate vasoconstriction in response to injury
  - Platelet plug formation
  - Coagulation (blood clotting)
Vascular spasm

- Immediate response is constricting of the damaged blood vessel (vasoconstriction)

- Initiated by injury to vascular smooth muscle, chemicals released by endothelial cells & platelets, reflexes initiated by local pain receptors

- Functions to reduce blood loss
Platelet Plug Formation

- Platelets do not stick to each other or to blood vessels
- Upon damage to blood vessel endothelium platelets:
  - With the help of von Willebrand factor (VWF) adhere to collagen
  - Release serotonin and ADP, which attract still more platelets
  - Positive F.B. that attracts & activates more platelets
  - Functions to reduce further blood loss
- The platelet plug is limited to the immediate area of injury by prostaglandin (PGI2) released by intact endothelial cells inhibiting platelet aggregation
- Platelet plug is reinforced by fibrin
Coagulation: Blood Clotting

- A set of reactions in which blood is transformed from a liquid to a gel
- Coagulation follows intrinsic and extrinsic pathways
- The final three steps of this series of reactions are:
  - Prothrombin activator is formed
  - Prothrombin (found in plasma) is converted into the enzyme thrombin
  - Thrombin catalyzes the joining of fibrinogen (found in plasma) into a fibrin mesh
Coagulation

Figure 17.13a
Detailed Events of Coagulation
Coagulation Phase 1: Two Pathways to Prothrombin Activator

- May be initiated by either the intrinsic or extrinsic pathway

- Clotting outside of the body is initiated only by the intrinsic mechanism (a slower mechanism)

- In the intrinsic mechanism, all clotting factors are found intrinsic to the blood

- In tissue where additional clotting factors are found, the short-cut extrinsic clotting mechanism occurs
Coagulation Phase 2: Pathway to Thrombin

- Prothrombin activator catalyzes the transformation of prothrombin to the active enzyme thrombin
Coagulation Phase 3: Common Pathways to the Fibrin Mesh

- Thrombin catalyzes the polymerization of fibrinogen into fibrin
- Insoluble fibrin strands form the structural basis of a clot
- Fibrin causes plasma to become a gel-like trap
- Fibrin in the presence of calcium ions activates factor XIII that:
  - Cross-links fibrin
  - Strengthens and stabilizes the clot
Clot Retraction and Repair

- Platelets possess actin & myosin and contract much like a muscle fiber
- Contraction pulls on the fibrin strands squeezing serum out of the mass & compacting the clot
- Platelet Derived GF: stimulates smooth muscle & fibroblasts to divide and rebuild the wall
- Endothelial cells stimulated by VEGF (vascular endothelial growth factor) multiply and restore the endothelial lining
Factors Limiting Clot Growth or Formation

- Two homeostatic mechanisms prevent clots from becoming large
  - Swift removal of clotting factors
  - Inhibition of activated clotting factors
Inhibition of Clotting Factors

- Fibrin acts as an anticoagulant by binding thrombin and preventing its:
  - Positive feedback effects of coagulation
  - Ability to speed up the production of prothrombin activator via factor V
  - Acceleration of the intrinsic pathway by activating platelets
  - Heparin is a natural anticoagulant found in basophil and mast cell granules, as well as endothelial cells, and inhibits thrombin
Factors Preventing Undesirable Clotting

- Unnecessary clotting is prevented by endothelial lining the blood vessels

- Platelet adhesion is prevented by:
  - The smooth endothelial lining of blood vessels
  - Heparin and PGI$_2$ secreted by endothelial cells
  - Vitamin E quinone, a potent anticoagulant
Hemostasis Disorders: Thromboembolytic Conditions

- Thrombus – a clot that develops and persists in an unbroken blood vessel
  - Thrombi can block circulation, resulting in tissue death
  - Coronary thrombosis – thrombus in blood vessel of the heart
Hemostasis Disorders: Thromboembolysis Conditions

- Embolus – a thrombus freely floating in the bloodstream
  - Pulmonary emboli can impair the ability of the body to obtain oxygen
  - Cerebral emboli can cause strokes
Hemostasis Disorders

- Artherosclerosis cause thromboembolic disease by roughening vessel walls and allowing platelets to get a foot hold
Prevention of Undesirable Clots

- Substances used to prevent undesirable clots:
  - Aspirin – helps prevent undesired clotting by inhibiting the formation of thromboxane A$_2$
  - Heparin – an anticoagulant used clinically for pre- and postoperative cardiac care
  - Warfarin (e.g. Coumadin) – used for those prone to atrial fibrillation (pooling of blood in the heart) to reduce the risk of stroke
Hemostasis Disorders: Bleeding Disorders

- Hemophilias – hereditary bleeding disorders caused by lack of clotting factors
  - Hemophilia A – most common type (83% 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
Hemostasis Disorders: Bleeding Disorders

- X-linked condition in males (usually)
- 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
- Shelf life of blood is a month at 4 C
Human Blood Groups

- RBC membranes have glycoprotein antigens on their external surfaces

- These antigens are:
  - Unique to the individual
  - Recognized as foreign if transfused into another individual
  - Promoters of agglutination and are referred to as agglutinogens

- Presence or absence of these antigens is used to classify blood groups

- If transfused with an incompatible blood type, cells will be agglutinated (clumped) and removed
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

- The ABO blood groups consists of:
  - Two antigens (A and B) on the surface of the RBCs
  - Two antibodies in the plasma (anti-A and anti-B)
- ABO blood groups may have various types of antigens and preformed antibodies
- Agglutinogens and their corresponding antibodies cannot be mixed without serious hemolytic reactions
## ABO Blood Groups

<table>
<thead>
<tr>
<th>BLOOD GROUP</th>
<th>FREQUENCY (% U.S. POPULATION)</th>
<th>RBC ANTIGENS (AGGLUTINOGENS)</th>
<th>PLASMA ANTIBODIES (AGGLUTININS)</th>
<th>BLOOD THAT CAN BE RECEIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>4  4  5  &lt;1</td>
<td>A  B</td>
<td>None</td>
<td>A, B, AB, O (Universal recipient)</td>
</tr>
<tr>
<td>B</td>
<td>11 20 27 4</td>
<td>B</td>
<td>Anti-A (a)</td>
<td>B, O</td>
</tr>
<tr>
<td>A</td>
<td>40 27 28 16</td>
<td>A</td>
<td>Anti-B (b)</td>
<td>A, O</td>
</tr>
<tr>
<td>O</td>
<td>45 49 40 79</td>
<td>None</td>
<td>Anti-A (a)</td>
<td>O (Universal donor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-B (b)</td>
<td></td>
</tr>
</tbody>
</table>

Table 17.4
Rh Blood Groups

- There are 45 different Rh agglutinogens, three of which (C, D, and E) are common.
- “Rh” comes from rhesus monkey.
- 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, but no agglutination and removal (takes time to form antibodies).
- A second exposure to Rh⁺ blood will result in a typical transfusion reaction where anti-Rh antibodies attack and kill the Rh⁺ RBCs.
Blood Typing

- When serum containing anti-A or anti-B agglutinins is added to blood, agglutination will occur between the agglutinin and the corresponding agglutinogens

- Positive reactions indicate agglutination
## Blood Typing

<table>
<thead>
<tr>
<th>Blood type being tested</th>
<th>RBC agglutinogens</th>
<th>Serum Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>–</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
<td>–</td>
</tr>
</tbody>
</table>
**Figure 29.9 Blood typing of ABO blood types.** When serum containing anti-A or anti-B agglutinins is added to a blood sample, agglutination will occur between the agglutinin and the corresponding agglutinogen (A or B). As illustrated, agglutination occurs with both sera in blood group AB, with anti-B serum in blood group B, with anti-A serum in blood group A, and with neither serum in blood group O.