N3 The Hematologic System

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N3

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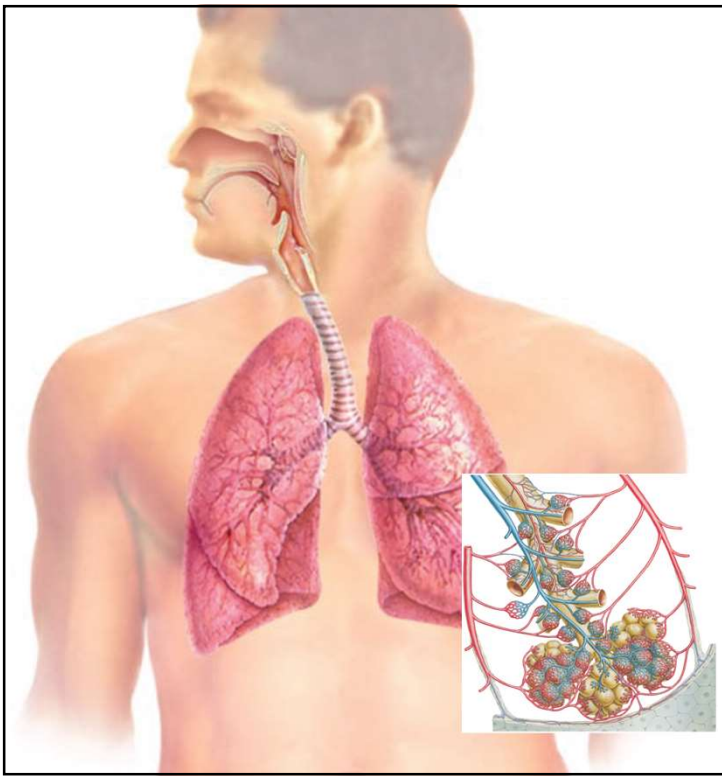

Mechanical Respiration

- Pulmonary Ventilation: inhalation and exhalation
- Cleaning, warming, and moistening of air
- External respiration

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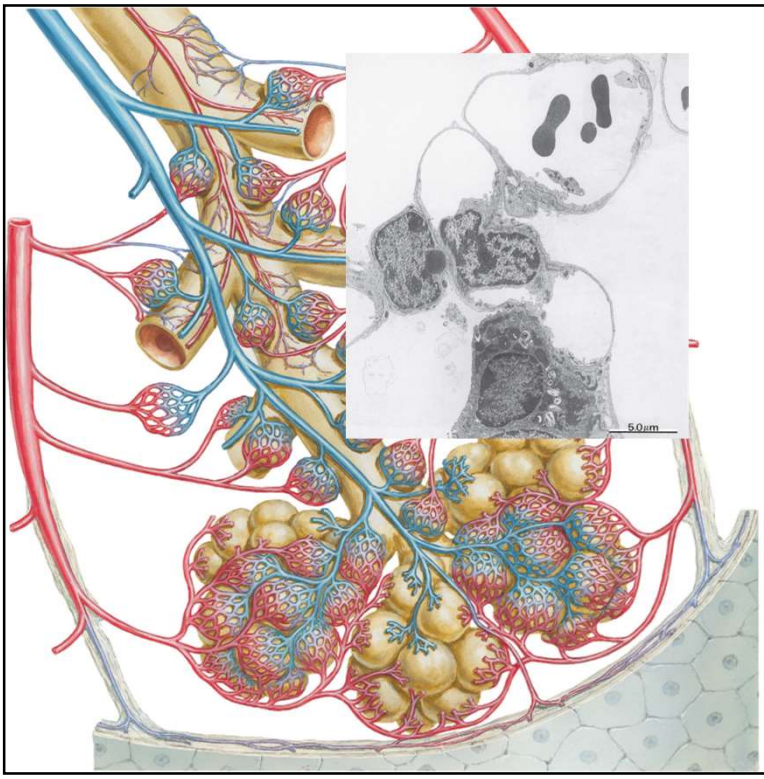

External respiration:

- exchange of gases between the alveoli of the lungs and the blood in pulmonary capillaries across the respiratory membrane

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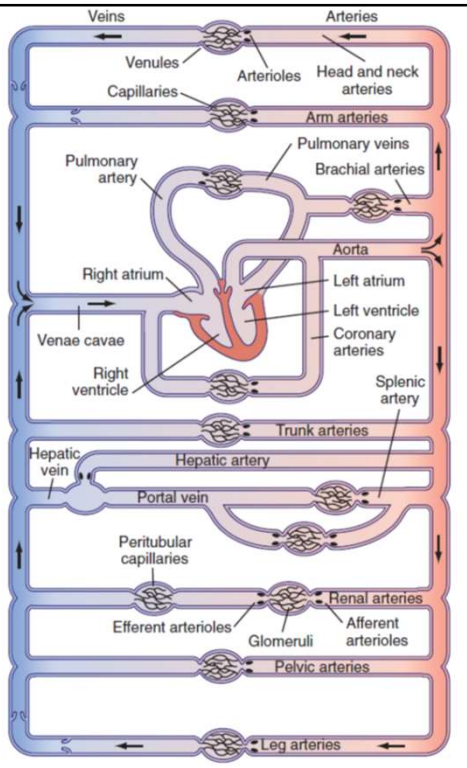

Circulatory System

- Transports and distributes essential substances to tissues
- Removes metabolic byproducts
- Other functions:
  - Regulate body temperature
  - Maintenance of fluid balance
  - Adjustment of 02 and nutrient supply

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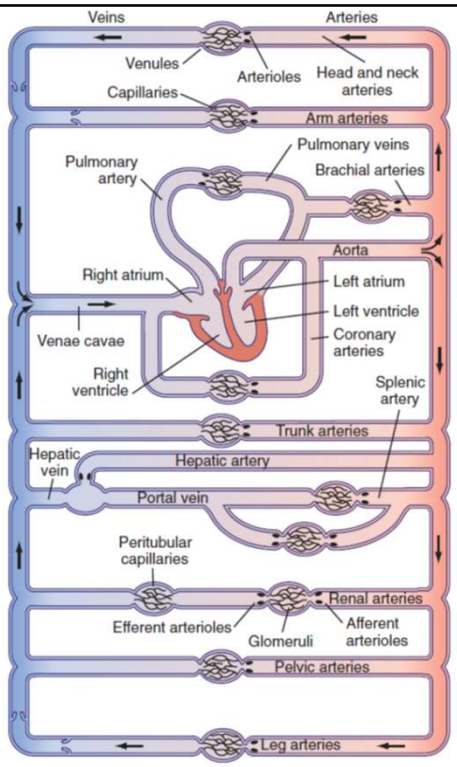

Circulatory System

Through:

- Heart:pump
- Blood vessels: distributing and collecting tubes
- Capillaries: thin vessels that permit rapid exchange between tissues and vascular channels
- Blood – heterogenous fluid composed of cells that serves as a transport vehicle for the gases, nutrients, waste products, cells, and hormones

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Objectives:

- Describe the functions of the parts of the hematopoietic system
- Describe the function of blood
- Describe the physical characteristics of blood
- Describe the principal components of blood
- Explain the process of the formation of blood components
- Describe the structure, functions, life cycle, and production of red blood cells
- Describe how the blood transports oxygen and carbon dioxide
- Describe the structure, functions, and production of white blood cells
- Describe the structure, function, and origin of thrombocytes
- Describe three mechanisms that contribute to hemostasis
- Identify the stages of blood clotting
- Explain the various factors that promote and inhibit blood clotting
- Explain the significance of blood groups and types

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Parts of the Hematologic System

1. Bone Marrow - the site of hematopoeisis or blood cell formation
2. Blood
   a. Blood cells
      i. Erythrocytes
      ii. Leukocytes
      iii. Thrombocytes
   b. Plasma - fluid component (90% water, 8% protein, 1% inorganic salts, 0.5% lipids, 0.1% glucose)
3. Reticuloendothelial System- neutrophils, special tissue macrophages and the network of fibers that support the functions of phagocytic cells

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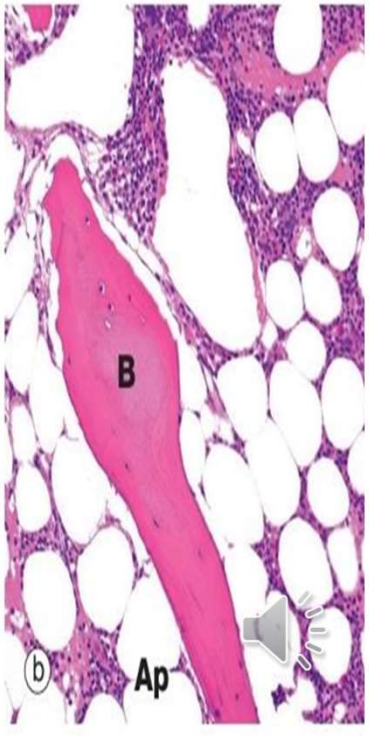
Bone Marrow

- highy vascular connective tissue
- Between trabeculae of spongy bone
- composed of
  - **stem cells** - self-replicate and differentiate into myeloid or lymphoid cells
  - **stroma** - produce colony-stimulating factors
    - yellow marrow
    - fibroblasts, osteoclasts, osteoblasts, and endothelial cells



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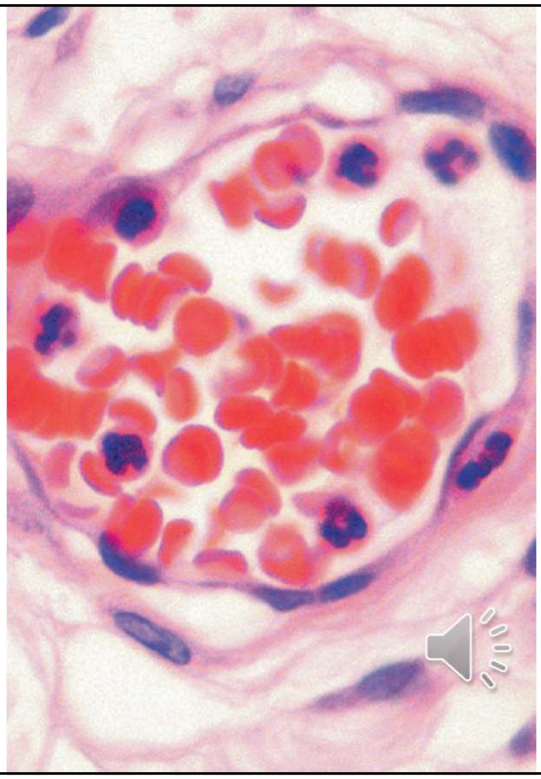
Blood

- A liquid connective tissue that consists of cells surrounded by a liquid extracellular matrix (plasma)

- General functions:

1. Transportation
2. Regulation: pH, body temperature, blood osmotic pressure
3. Protection: hemostasis and defense (transit of leukocytes)



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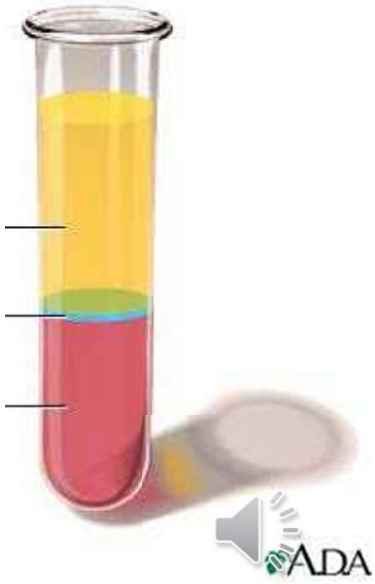
Physical Characteristics of Blood

- Denser and more viscous than water
- 38 degrees C
- pH 7.35-7.45 (slightly alkaline)
- Color varies with oxygen content
  - Bright red: saturated with oxygen
  - Dark red: unsaturated
- Constitutes 20% of extracellular fluid (8% of body mass)
  - 5-6 L in adult males
  - 4-5 L in adult females



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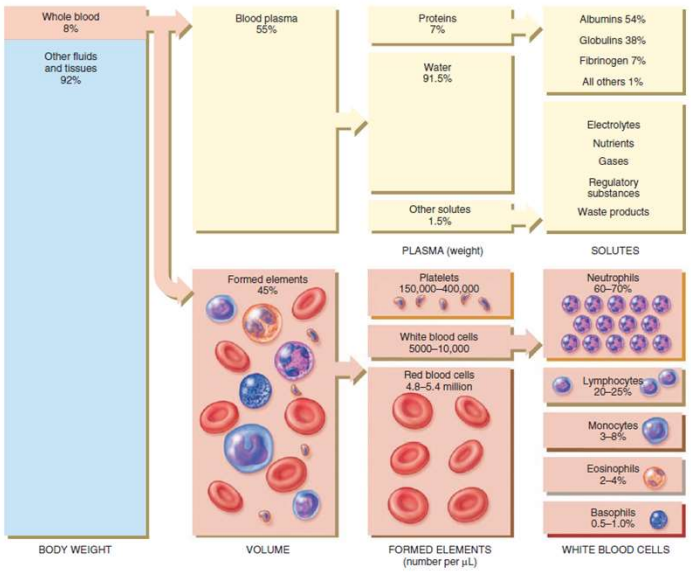
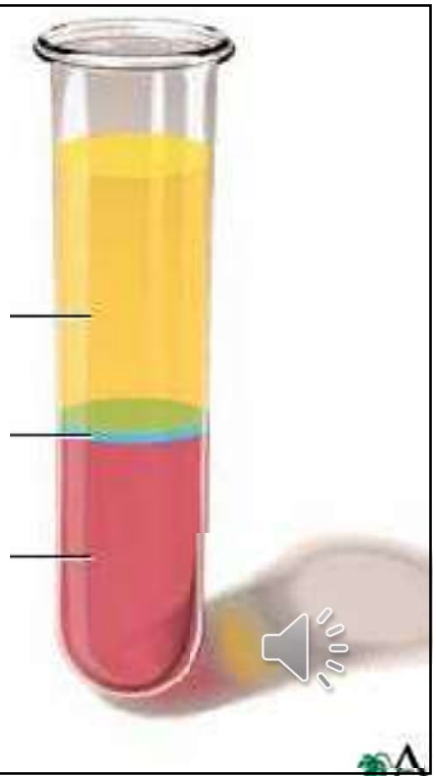
Components of Blood





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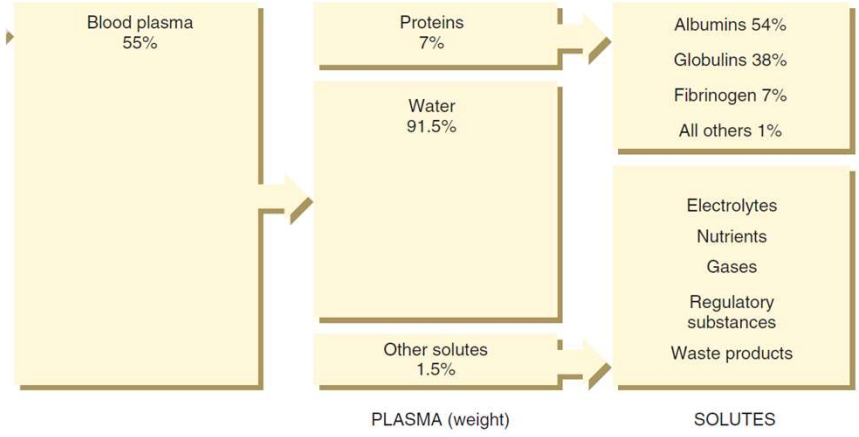
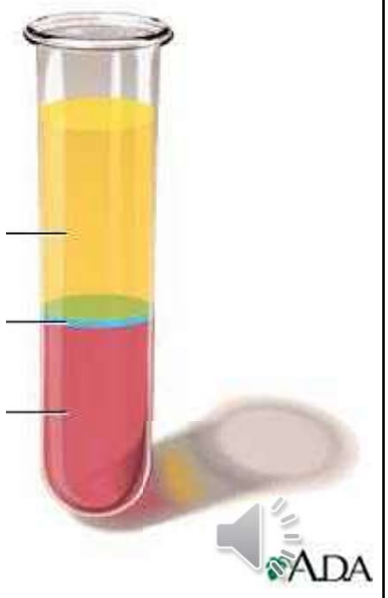
Components of Blood

Plasma – 55% of blood; straw-colored watery liquid





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Components of Blood (Substances in Blood Plasma)

CONSTITUENT	DESCRIPTION / FUNCTION
Water	Solvent and suspending medium. Absorbs, transports, and releases heat
Plasma Proteins – mostly produced by the liver	Colloid osmotic pressure; blood viscosity; transport of hormones, fatty acids, and calcium,; regulation of pH
• Albumin	
• Globulins	• Immunoglobulins: help attack pathogens (viruses and bacteria) • Alpha and beta: transport of iron, lipids, and fat-soluble vitamins
• Fibrinogen	Blood clotting

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Components of Blood (Substances in Blood Plasma)

CONSTITUENT	DESCRIPTION / FUNCTION
Other Solutes	
Electrolytes	Maintain osmotic pressure and essential roles in cell functions
Nutrients	Cell function, growth, and development
Gases	• Oxygen: needed for cellular respiration and energy production • Carbon dioxide: blood pH regulation
Regulatory substances	• Enzymes: catalyze chemical reactions • Hormones: regulate metabolism, growth, and development • Vitamins: cofactors for enzymatic reactions
Waste Products	Mostly breakdown products of protein metabolism (urea, uric acid, creatinine, bilirubin, ammonia)

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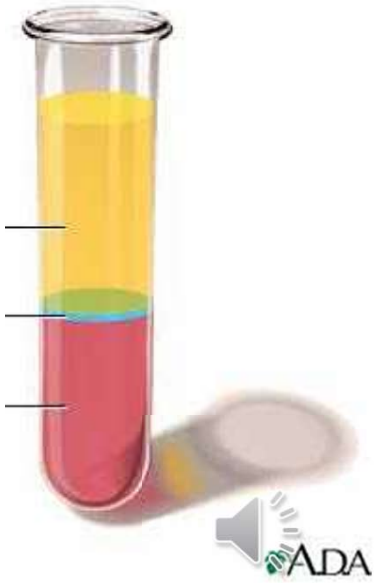
Components of Blood

Formed Elements – cells and cell fragments**:**

- **Buffy Coat**:
  - white blood cells
  - platelets
- **Red Blood Cells**
  - *Hematocrit* – percentage blood volume occupied by RBCs
    - Adult males: 40-54% (testosterone stimulates EPO production)
    - Adult females: 38-46%



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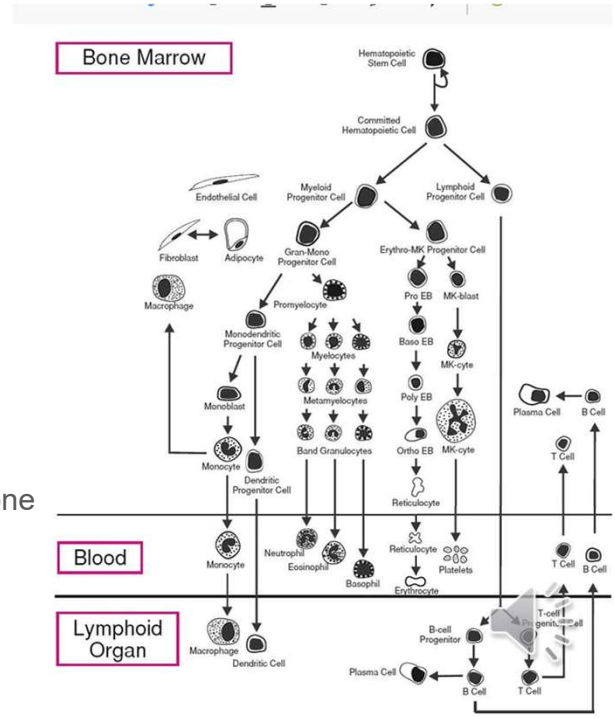
Hematopoeisis

- production of mature blood cells from precursors
- Happens in:
  - Embryo – yolk sac
  - Fetus – liver, spleen, thymus, lymph nodes
  - 3 months before birth onwards: red bone marrow



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Hematopoeisis

- pluripotent stem cells → hematopoeitic stem cells → progenitor cells (including colony or burst-forming units) → precursor cells/blasts
  - ***Pluripotent stem cells*** – cells derived from the mesenchyme that have the capacity to develop into many different types of cells
  - ***Hematopoietic cells***: Myeloid and lympoid stem cells
  - ***Progenitor cells*** – no longer capable of reproducing themselves and are committed to giving rise to more specific elements of blood
  - ***Precursor cells*** - undergo cell division to develop actual formed elements of blood

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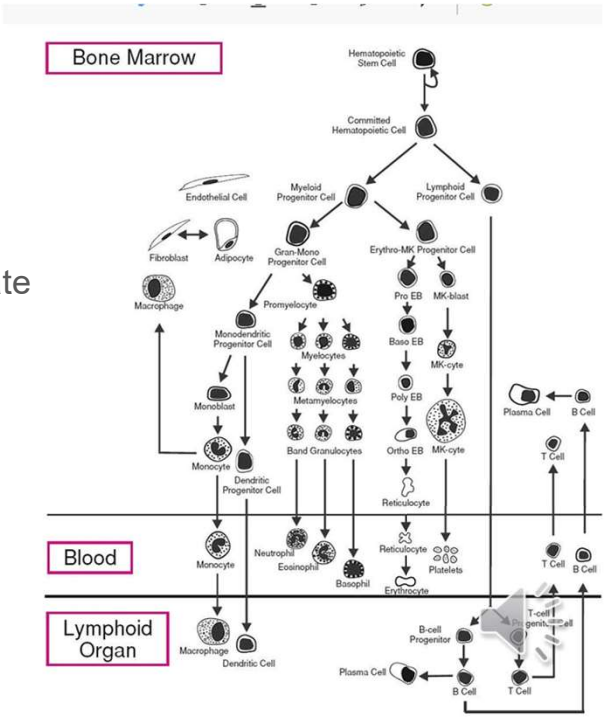
Hematopoeisis

- tightly controlled by growth factors and microenvironment

* ***Hematopoietic growth factors*** – regulate the differentiation and proliferation of particular progenitor cells

- interleukin 3
- granulocyte-monocyte CSF
- Thrombopoeitin – increases platelets
- Erythropoeitin – increases RBCs
- stem cell factor



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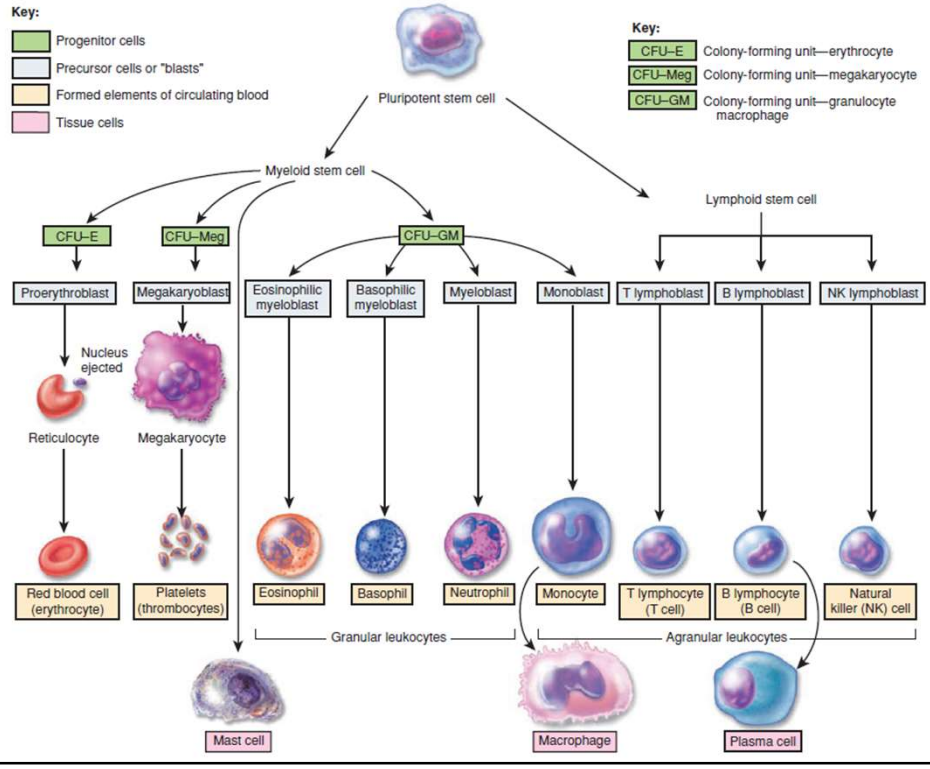

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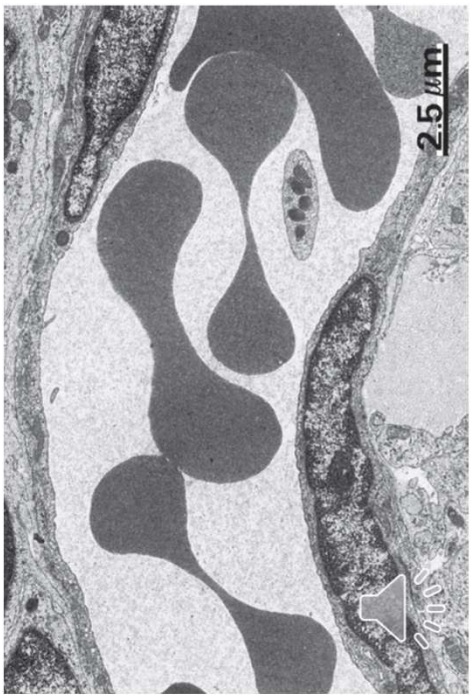
Blood (Cellular Components)

Erythrocytes (Red Blood Cells)

- biconcave disc: increased surface area for diffusion of gases
- 8 micrometers
- Thin, flexible membranes: ability to deform
  - Contain glycoipids in the membranes that act as antigens: basis for blood groups/types
- Lack a nucleus and other organelles



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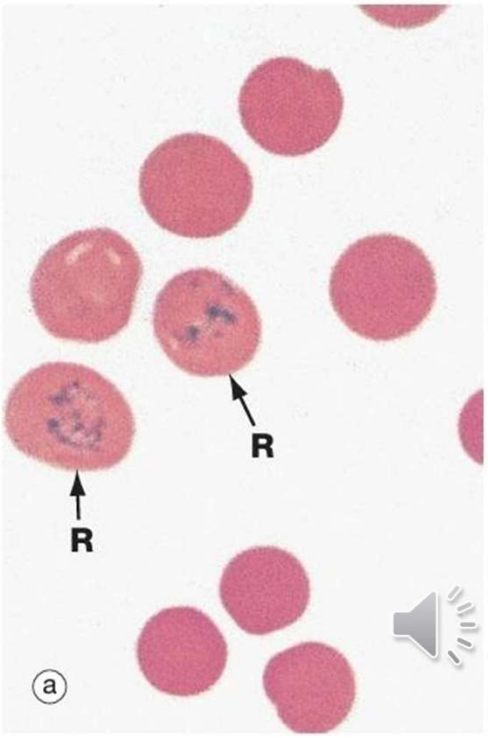
Blood (Cellular Components)

Erythrocytes (Red Blood Cells)

- Contain the oxygen-carrying iron-containing protein **hemoglobin**
  - Gives blood its red color
    - iron concentration in blood: 50-150 ug/dl



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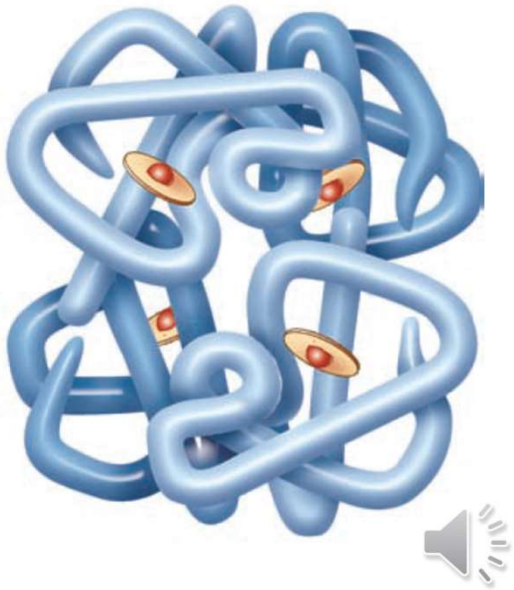
Blood (Cellular Components)

Erythrocytes (Red Blood Cells)

- **Hemoglobin -** composed of
  - **Heme –** ringlike nonprotein pigment attached to each globin chain that ***reversibly bind*** to oxygen molecules
  - **Globin –** protein composed of four polypeptide chains (2 alpha and 2 beta chains)
- Also binds 23% of carbon dioxide
- May release bound nitric oxide (causes vasodilation)



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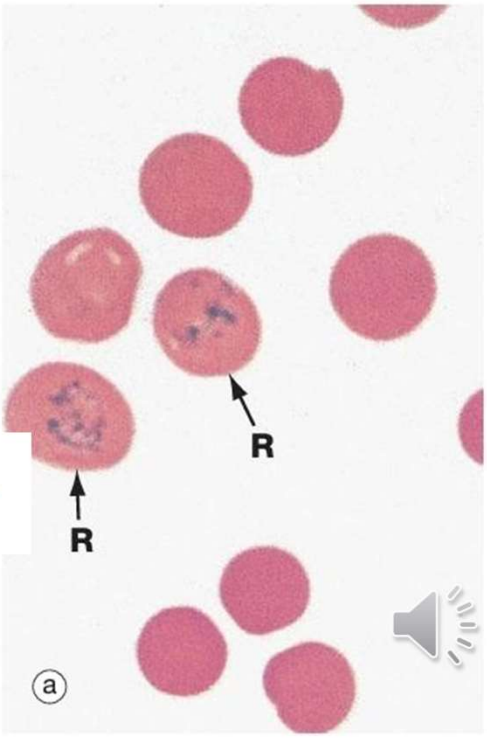
Blood (Cellular Components)

Erythrocytes (Red Blood Cells)

- Contains the enzyme ***carbonic anhydrase***, which converts carbon dioxide and water to carbonic acid, which in turn dissociates into H+ and HCO3-

$$\underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Water}}{H_2O} \overset{CA}{\rightleftharpoons} \underset{\text{Carbonic acid}}{H_2CO_3} \rightleftharpoons \underset{\text{Hydrogen ion}}{H^+} + \underset{\text{Bicarbonate ion}}{HCO_3^-}$$



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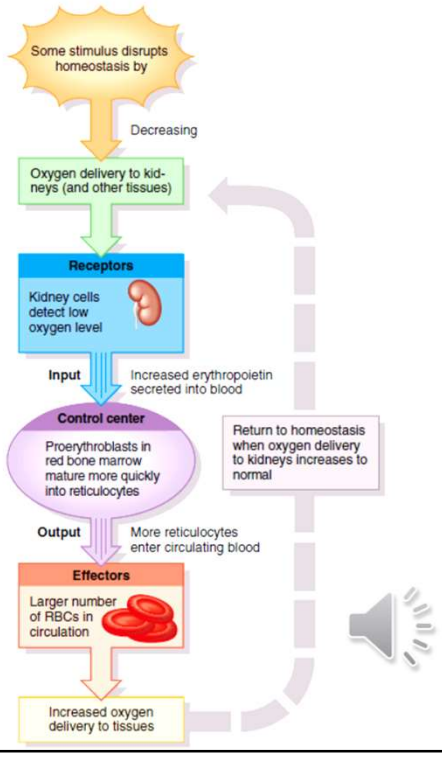
Blood (Cellular Components)

Erythrocytes (Red Blood Cells)

- 120 day life cycle
- Eythropoeisis - driven by **eythropoeitin** from the kidney
  - trigerred by low oxygen levels (***hypoxia***)
  - myeloid progenitor cell → eythroMK progenitor cell → erythroblast → reticulocyte → erythrocyte



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Blood (Cellular Components)

1. **Erythrocytes** (Red Blood Cells):lifespan: 120 days
   - Older, more fragile RBCs destroyed by macrophages in the spleen and liver
     - hemoglobin →
       - **Heme**
         - **Iron – recycled** by attaching to transferrin (complex taken in RBC precursor cells through receptor-mediated endocytosis)
         - **Non-iron portion** → biliverdin → **bilirubin** → released by liver cells as bile → converted by bacteria in the Large intestine into urobilinogen → most converted to stercobilin (pigment in stool)
       - **Globin** – broken down into amino acids

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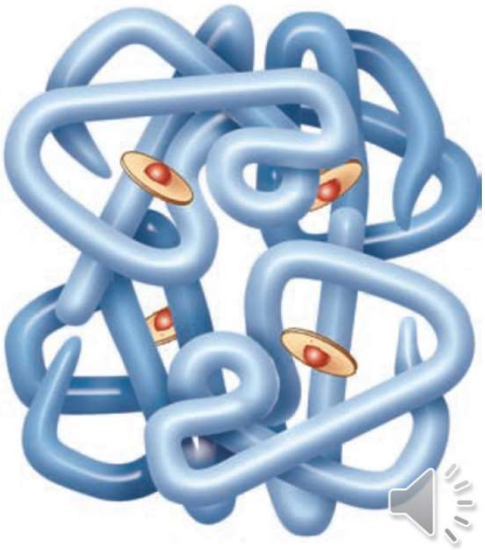
Oxygen Transport

- 98.5% of blood is bound to hemoglobin in red blood cells
- Occurs through the reversible reaction that produces ***oxyhemoglobin***

$$\underset{\text{Reduced hemoglobin (deoxyhemoglobin)}}{Hb} + \underset{\text{Oxygen}}{O_2} \underset{\text{Dissociation of } O_2}{\overset{\text{Binding of } O_2}{\rightleftharpoons}} \underset{\text{Oxyhemoglobin}}{Hb{-}O_2}$$

- Remaining 1.5% oxygen dissolved in plasma can diffuse out of capillaries into tissue cells
- ***Hemoglobin-bound oxygen must dissociate to be used***



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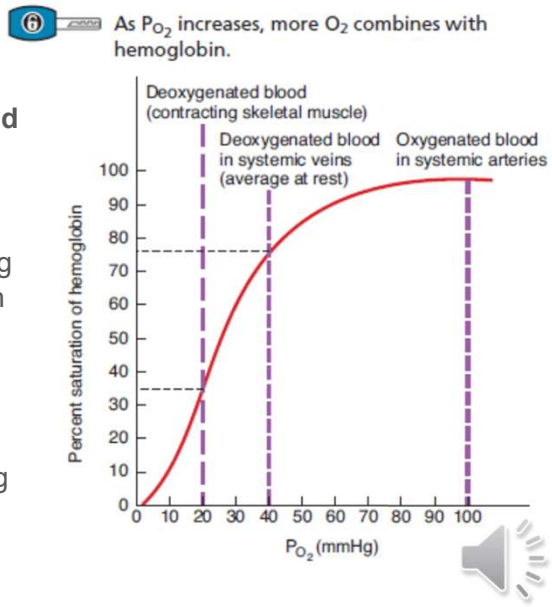
Oxygen Transport

Factors affecting hemoglobin-oxygen binding and dissociation:

1. **Partial Pressure of Oxygen**

- Most important factor that determines O2-binding
- The higher the PO2, the more O2 combines with hemoglobin;
  - When the PO2 is between 60-100 mmHg, hemoglobin is 90% or more saturated with O2
  - Pulmonary capillaries: High oxygen-binding
  - Tissue capillaries: decreased oxygen-binding



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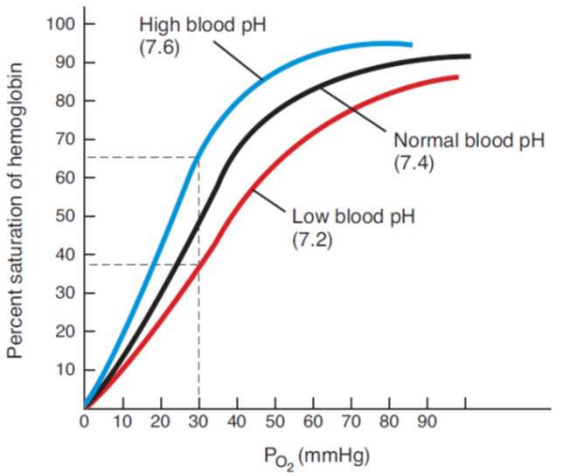
Oxygen Transport

Factors affecting hemoglobin-oxygen binding and dissociation:

2. **Acidity** (low pH, high H+ concentration in blood) **–** decreases hemoglobin affinity for oxygen; increased oxygen dissociation/unloading (shift of the oxygen-hemoglobin dissociation curve to the right **[Bohr Effect])**
   - Hemoglobin as buffer for hydrogen ions (H+ binding to amino acids in Hb → decreased oxygen binding)



(a) Effect of pH on affinity of hemoglobin for oxygen

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Oxygen Transport

Factors affecting hemoglobin-oxygen binding and dissociation:

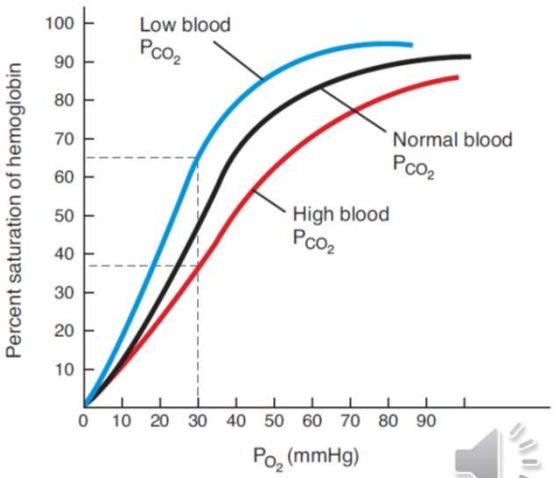
3. **Partial Pressure of carbon dioxide**

- Carbon dioxide can also bind to hemoglobin
  - Rise in PCO2 → increase in O2-hemogloibin dissociation
  - Related to low blood pH (acidity): high PCO2 → High H+, lower pH

$$CO_2 + H_2O \underset{}{\overset{CA}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Carbon dioxide + Water ⇌ (CA) Carbonic acid ⇌ Hydrogen ion + Bicarbonate ion

  - Increased oxygen dissociation (shifting the curve to the **right**)



(b) Effect of P_{CO_2} on affinity of hemoglobin for oxygen

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Oxygen Transport

Factors affecting hemoglobin-oxygen binding and dissociation:

4. **Temperature**

- As temperature increase (fever and exercise), oxygen dissociation increases

5. **2,3-bisphosphoglycerate (BPG)**

- Formed during breakdown of glucose to produce ATP in glycolysis
- Binds to amino groups in two beta globin chains → decreased 02 binding at the heme sites
- More O2, more O2 dissociation.
- Hormones and higher altitudes
- ***Fetal Hemoglobin (Hb-F)*** – binds BPG less strongly; higher O2 affinity (compared to adult hemoglobin)

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Carbon Dioxide Transport

- Transported as

1. **Dissolved carbon dioxide** – diffuses into alveolar air and is exhaled
2. **Carbamino compounds** – combining with amino acids and proteins, including hemoglobin, in blood

$$\underset{\text{Hemoglobin}}{Hb} + \underset{\text{Carbon dioxide}}{CO_2} \rightleftharpoons \underset{\text{Carbaminohemoglobin}}{Hb{-}CO_2}$$

3. **Bicarbonate ions** –

$$\underset{\substack{\text{Carbon}\\\text{dioxide}}}{CO_2} + \underset{\text{Water}}{H_2O} \overset{CA}{\rightleftharpoons} \underset{\substack{\text{Carbonic}\\\text{acid}}}{H_2CO_3} \rightleftharpoons \underset{\substack{\text{Hydrogen}\\\text{ion}}}{H^+} + \underset{\substack{\text{Bicarbonate}\\\text{ion}}}{HCO_3^-}$$

*Chloride shift – as HCO3 accumulates inside RBCs → diffuse out of RBC → chloride ions move inside to maintain electrical balance

- as blood passes through pulmonary capillaries, the reactions reverse.

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Carbon Dioxide Transport

- Affected by hemoglobin oxygen saturation
  - ***Haldane effect:*** Lower Hb-O2, the higher CO2-carrying capacity of the blood
    1. deoxyhemoglobin: binds and transports more CO2
    2. Deoxyhemoglobin binds more H+ → decreased H+ → conversion of CO2 to HCO3

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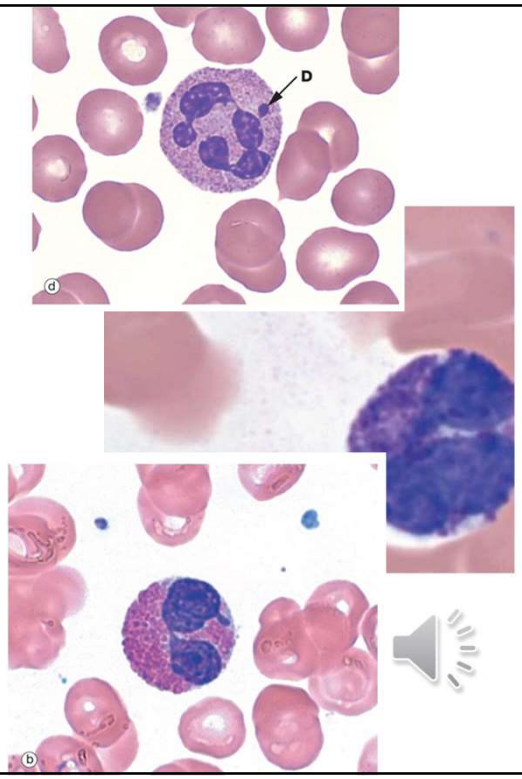
Blood (Cellular components)

White Blood Cells/Leukocytes

- Have nuclei and and other organelles
- General function: ***combat pathogens*** by phagocytosis or through the immune response
- Classified as granular or agranular



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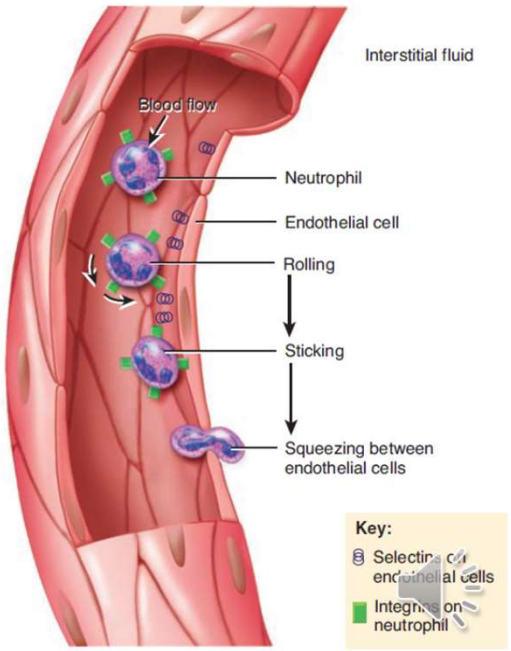
Blood (Cellular components)

White Blood Cells/Leukocytes

- General function: ***combat pathogens***

1. **Emigration or diapedesis** – white blood cells roll along then stick to the endothelium; then squeeze between endothelial cells
   - Adhesion molecules – molecules which which help WBCs stick to the endothelium
     - Selectins - adhesion molecules in damaged endothelium
     - Integrins – adhesion molecules in neutrophils



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Blood (Cellular components)

White Blood Cells/Leukocytes

- General function: ***combat pathogens*** through:
  - Phagocytosis – neutrophils and macrophages ingest pathogens and dispose dead matter (neutrophils first, then monocytes)
    - Chemotaxis – release of chemicals by microbes that attract phagocytes
    - Upon ingestion: release of chemicals to destroy the pathogen (lysozyme and oxidants), defensins
  - Support for inflamation through the release of granules
  - Immunity

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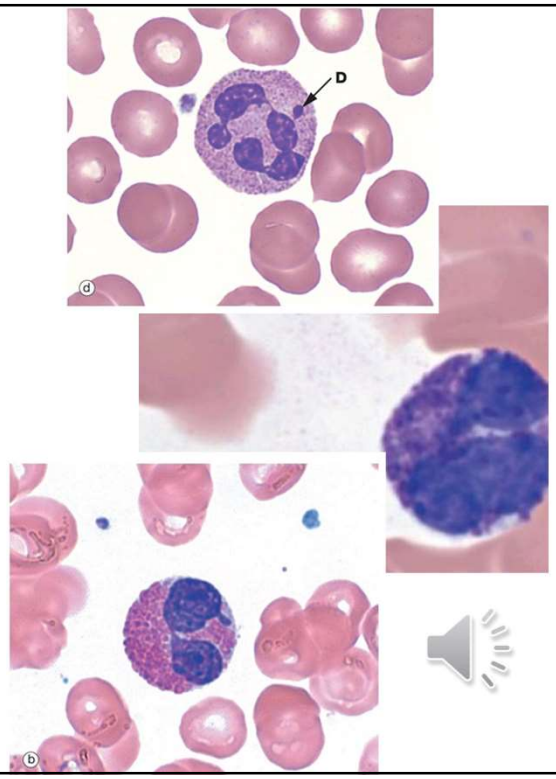
Blood (Cellular components)

Granulocytes:

i. **Neutrophils** – 2-5 lobes; motile and phagocytic
ii. **Eosinophils** – 2 lobes; granule and mediator release such as major basic protein toxic to parasites, histamine
iii. **Basophils** - bind to IgE (involved in immedate hypersensitivity reaction)



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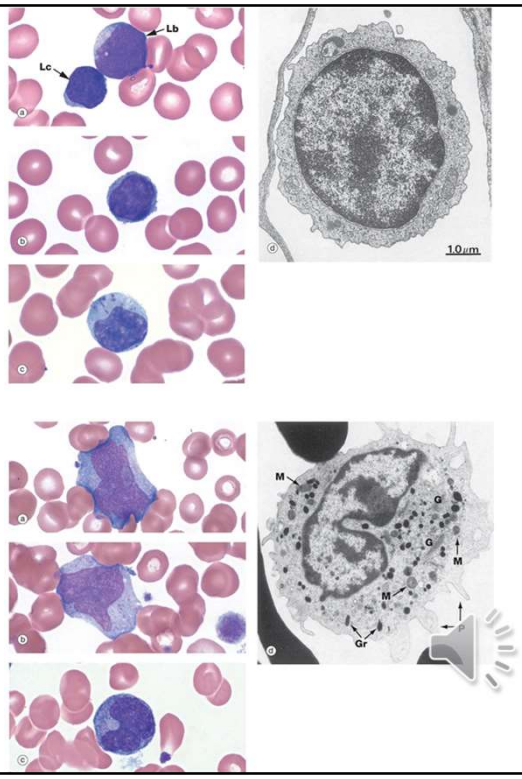
Blood (Cellular components)

Agranular/ Mononuclear Leucocytes:

i. **Lymphocytes** - directed towards specific antigens
    1. NK Cells
    2. Cytotoxic T Lymphocytes
    3. Helper T Lymphocytes
    4. B Lymphocytes → Plasma cells

ii. **Monocytes** – kidney-shaped nucleus; phagocytic and mature into **macrophages**



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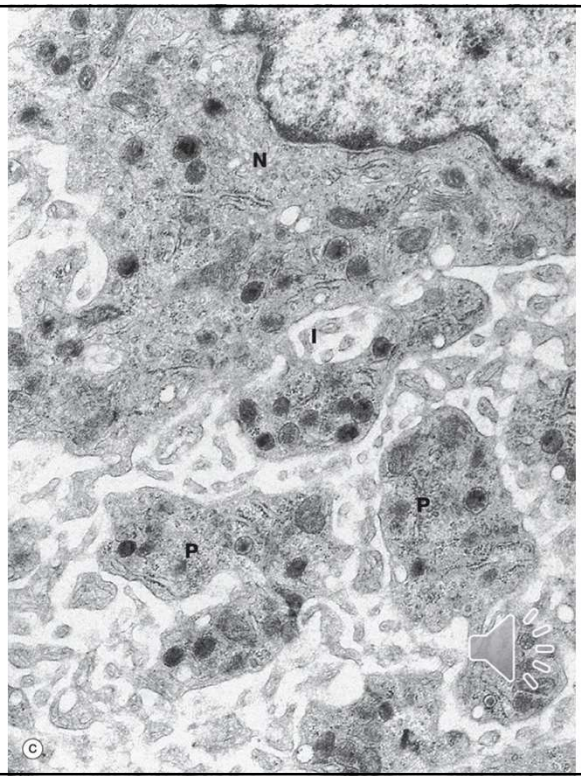
Blood (Cellular Components)

Platelets

- non-nucleated fragments of cytoplasm released from megakaryocytes
    - Influenced by **thrombopoietin** produced in the liver
- form a **platelet plug** when exposed to damaged tissue
    - Adhere to exposed collagen and basement membrane proteins
    - activated to contract and release granule contents → platelet recruitment and coagulation factors activation



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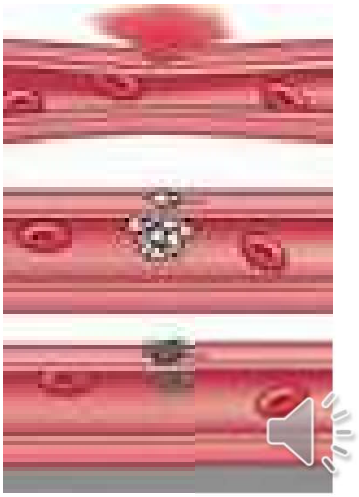
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

1. **Vascular spasm**: contraction of the circularly arranged smooth muscle in blood vessels
2. **Primary hemostasis: Platelet Plug Formation**



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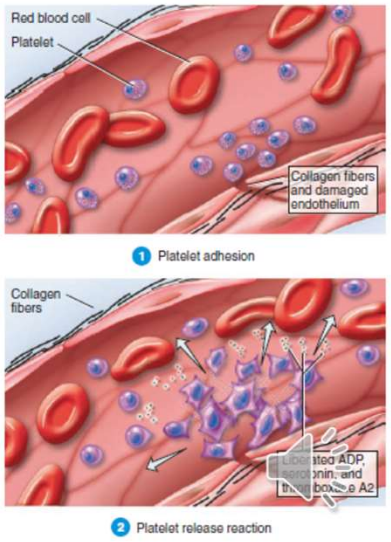
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

2. **Primary hemostasis: Platelet Plug Formation**
    1. **Platelet adhesion** to collagen and von Willebrand Factor exposure in the injured vessel
    2. **Platelet activation** – extend projections to interact with one another and release contents of vesicles
        - Activation of nearby platelets: ADP and Thromboxane A2
        - Vasoconstrictors: serotonin and thromboxane A2



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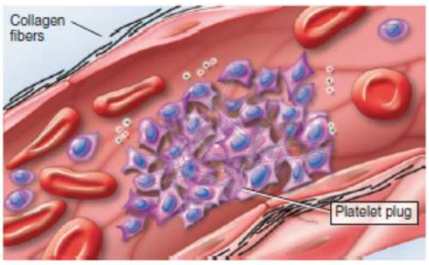
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

2. **Primary hemostasis: Platelet Plug Formation**
    3. **Platelet aggregation** – adherence of the newly recruited and activated platelets to the originally activated platelets forming the platelet plug



3 Platelet aggregation

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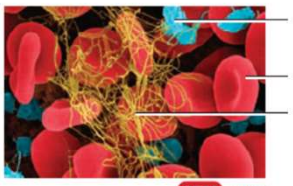
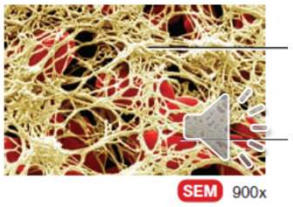
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

1. **Vascular spasm**: contraction of the circularly arranged smooth muscle in arteries and arterioles
2. **Primary hemostasis: Platelet Plug Formation**
3. **Secondary hemostasis: Blood Clotting**
    - Clot – network of fibrin, an insoluble protein fiber, in which formed elements of blood are trapped


SEM 900x
(a) Early stage


SEM 900x
(b) Intermediate stage


SEM 900x
(c) Late stage showing red blood cells trapped in fibrin threads

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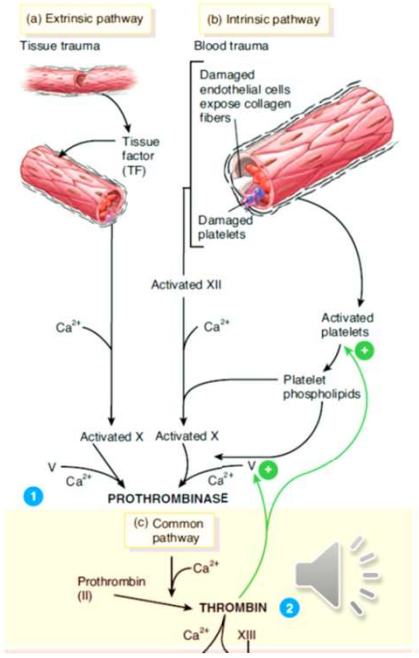
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

3. **Secondary hemostasis: Blood Clotting**
    - **Coagulation Cascade**
        - Extrinsic pathway: tissue factor or thromboplastin from damaged tissue leaks into blood and activates Clotting Factor X
        - Intrinsic pathways: activators are in contact with blood or in blood activating Clotting Factor XII



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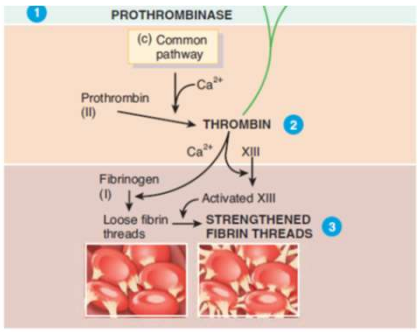
Hemostasis

Process of preventing blood loss from intact vessels and stopping bleeding from severed vessel

3. **Secondary hemostasis: Blood Clotting**
    - **Coagulation Cascade**
        - Common pathway: prothrombinase activates prothrombin to thrombin; thrombin converts fibrinogen to fibrin

      *Vitamin K – required for the synthesis of CF IX, X, VII, II
    - **Clot Retraction –** consolidation or tightening of the fibrin clot due to platelet contraction



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Antithrombotic Mechanisms

- Preserve blood fluidity and limits clotting to specific sites of injury
  - Endothelial cells: platelet adhesion and aggregation inhibitors (prostacyclin, nitric oxide, anticoagulant factors, and fibrinolysis mechanisms (tissue plasminogen activators)
  - Plasma: antithrombin (neutralizes thrombin and other activated coagulation factors), protein C, protein S, Tissue factor pathway inhibitor
  - ***Fibrinolytic system*** (activated to dispose intravascular fibrin)
    - Plasmin – degrades fibrin

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Blood Groups

- Determined by agglutinogens
- 24 blood groups, each with 2 or more blood types

Agglutinogens – genetically-determined glycoproteins and glycolipids in the surface of erythrocytes that act as antigens

- Determine whether the body will develop agglutinins

Agglutinins – antibodies in plasma that react with agglutinogens

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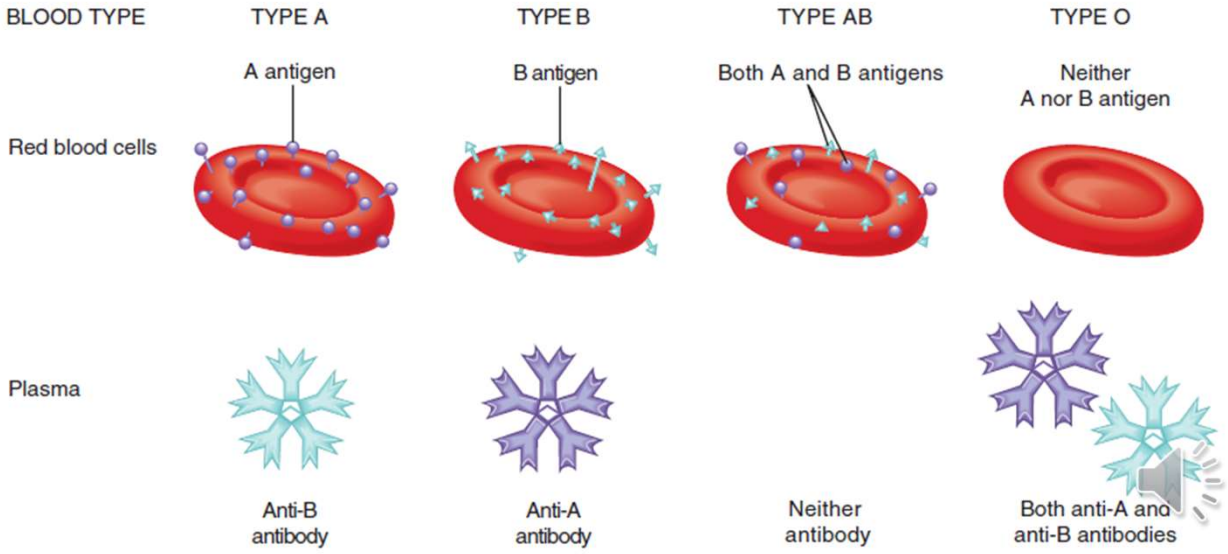
ABO Blood Group



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Agglutination Reactions

- An antigen-antibody reaction that causes clumping or red blood cells that happens when the recipient's plasma agglutinins react with the agglutinogens present in the donated blood.
- Causes hemolysis → kidney injury

	BLOOD TYPE			
CHARACTERISTIC	A	B	AB	O
Agglutinogen (antigen) on RBCs	A	B	Both A and B	Neither A nor B
Agglutinin (antibody) in plasma	Anti-B	Anti-A	Neither anti-A nor anti-B	Both anti-A and anti-B
Compatible donor blood types (no hemolysis)	A, O	B, O	A, B, AB, O	O
Incompatible donor blood types (hemolysis)	B, AB	A, AB	—	A, B, AB

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Rh Factor Blood Groups

- Rh blood types depend on the presence or absence of rhesus factors
- Most people are Rh-negative
- Significant in pregnancy:
  - A Rh-negative mother will develop antibodies to rhesus factor if blood from a Rh-positive fetus leaks into the maternal circulation, especially during delivery.
  - If the mother carries another Rh-positive fetus, the developed antigens will react with the erythrocytes of the succeeding Rh-positive fetuses, causing hemolysis

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Significance of Blood Groups and Typing

- Agglutination reactions can be fatal to the recipient of blood
  - In the case of Rh blood groups, they may be fatal to the baby.

- It is important to prevent agglutination reactions by:

1. Knowing the blood type of the patient and the donor
2. Ensuring compatibility of blood though crossmatching prior to transfusion
3. Verifying the blood-typing and crossmatching results prior to transfusion

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