Blood

The Circulatory System

- Circulatory System
  - Blood
  - Heart
  - Blood Vessels
- Cardiovascular system
  - Blood vessels
  - Heart
- Hematology: the study of blood, blood-forming tissues, and the disorders associated with them

Functions of Blood

- Transportation
  - Dissolved gases, nutrients, hormones, metabolic wastes, and stem cells
- Protection
  - Plays a role in inflammation
  - Cancer
  - Toxins and pathogens
  - Restriction of fluid losses at injury sites
- Regulation
  - Stabilizes fluid distribution in the body
  - pH and ion composition of interstitial elements
  - Stabilization of body temperature
General Properties of Blood

- Temperature 38°C (100.4°F)
- More viscous than water
  - 5 times more “sticky”
- pH 7.35-7.45
  - Average 7.4

Whole blood volume
- About 7-8% of total body weight in average-sized adults
  - Females 4-5 liters
  - Males 5-6 liters
- **Unit:** the amount collected from a blood donor for transfusion purposes
  - About 0.5 liter
  - Constitutes about 10% of total blood volume in many adults

Blood

**PLASMA**
Fluid portion of blood
Plasma
- 92% water
- Plasma proteins
  - Albumins
    - Maintain blood osmotic pressure
    - Transport proteins
    - Fatty acids, thyroid hormones, steroid hormones, etc
  - Globulins
    - Antibodies (immunoglobulins): bind to antigens
    - Transport globulins: bind small ions, hormones, etc
  - Fibrinogen --- for clotting
  - Others: plasminogen, prothrombin, insulin, prolactin, TSH, FSH, LH
- Origins of plasma proteins
  - 90% synthesized in liver
  - Antibodies synthesized in blood
  - Peptide hormones made in endocrine organs
- **Serum**: plasma with blood clots and solids removed

**Formed Elements**
- Red blood cells (erythrocytes)
- White blood cells (leukocytes)
  - Granular leukocytes
    - Neutrophils
    - Eosinophils
    - Basophils
  - agranular leukocytes
    - Lymphocytes: T cells, B cells, natural killer cells
    - Monocytes
- Platelets (thrombocytes)

**Most numerous of the formed elements**
- One drop has ~260 million cells
- Average adult has over 25 trillion cells
- Combined surface area larger than one football field
**Hematocrit**
- Percentage of blood occupied by cells
  - Female normal range
    - 38 - 46% (average of 42%)
  - Male normal range
    - 40 - 54% (average of 46%)
- Testosterone
- Anemia
  - Not enough RBCs or not enough hemoglobin
- Polycythemia
  - Too many RBCs (over 65%)
  - Dehydration, tissue hypoxia, blood doping

**Red Blood Cells (Erythrocytes)**

**Mature RBC**
- No nucleus
- Missing many organelles
- Biconcave shape
  - Surface area of volume?
  - Smooth laminar flow?
  - Most stable shape?
Function of RBC

- Transport – Hemoglobin (Hb)
  - 2 alpha chains and 2 beta chains bind
    - carbon dioxide
    - H+ ions
  - Heme
    - Iron ion binds oxygen

- Oxyhemoglobin – hemoglobin molecule bound to oxygen
- Deoxyhemoglobin – a hemoglobin molecule whose iron is not bound to oxygen
- Carbaminohemoglobin – alpha and beta chains bound to carbon dioxide

Recycling of Hemoglobin

- 90% Recycled by spleen
  - Heme
    - Iron – transported to bone marrow
    - Rest converted
      - Biliverdin (green)
      - Bilirubin (orange-yellow)
    - Transported to liver
    - Excreted in bile to small intestine
    - Urobilins (yellow)
    - Stercobilins (brown)
  - Amino acids
- 10% Hemolysis in blood
  - filtered and eliminated by kidneys
RBC Production

Erythropoiesis

- Red bone marrow (myeloid tissue)
  - Vertebrae, sternum, ribs, skull, pelvis, proximal limb bones
- Key stages
  - Hemopoietic stem cells (hemocytoblasts)
  - Myeloid stem cells
    - Erythropoietin (EPO)
  - Proerythroblasts --- start producing hemoglobin
  - Erythroblasts
  - Reticulocytes --- enter blood and eject nucleus
  - Erythrocytes

Regulation of Erythropoiesis

- Adequate nutrient levels
  - Vitamins B₁₂ and B₆, folic acid, iron, aa, copper, cobalt
- Erythropoietin (EPO)
  - Stimulates division of stem cells and erythroblasts
  - Speeds up RBC maturation
  - Released by hypoxia
    - Anemia
    - Decreased blood flow to kidneys
    - Decreased oxygen content of air at lungs
    - Damage to respiratory surfaces of lungs
- Testosterone
- Multi-CSF (Colony Stimulating Factor)
  - Hormone produced in the cells lining the blood vessels
White Blood Cells (Leukocytes)

- Combat infection and inflammation
- Principle types
  - Granular
    - Neutrophils
    - Eosinophils
    - Basophils
  - Agranular
    - Lymphocytes
    - Monocytes

![Neutrophil](image)

![Eosinophil](image)

![Basophil](image)
WBC Circulation & Movement
- All can migrate out of bloodstream
  - Only ~2% of population in circulating blood at any given time
  - Most are in lymphatic tissue, skin, lungs, lymph nodes, spleen
  - Use bloodstream as a "freeway system"
- All are capable of amoeboid movement
- All exhibit positive chemotaxis
  - Attracted to specific chemicals
- Some are capable of phagocytosis
  - Neutrophils, eosinophils, and monocytes
    - Macrophages: phagocytic monocytes in peripheral tissues
    - Microphages: phagocytic neutrophils and eosinophils in peripheral tissues

White Blood Cells
- White blood cells (leukocytes)
  - Granular leukocytes
    - Neutrophils
    - Eosinophils
    - Basophils
  - Agranular leukocytes
    - Lymphocytes: T cells, B cells, natural killer cells
    - Monocytes
**Neutrophil Function**

- Fastest response of all WBC to bacteria
- Direct actions against bacteria
  - Phagocytosis
  - Release lysozymes which destroy/digest bacteria
  - Release **defensin** proteins that poke holes in bacterial cell walls destroying them
  - Release strong oxidants (bleach-like, strong chemicals) that destroy bacteria
- Contribute to inflammation and pus

**Eosinophil Function**

- Phagocytize antibody-antigen complexes
- Anti-inflammatory responses
  - Release histaminase
  - Slows down inflammation caused by neutrophils and basophils
- Attack parasitic worms (hookworms, tapeworms, etc)
  - Exocytosis of toxic compounds

Most numerous in lining of respiratory tract and digestive tract. Why??

**Basophil Function**

- Involved in inflammatory and allergy reactions
- Leave capillaries & enter connective tissue as mast cells
- Release
  - **Heparin**: prevents blood clotting
  - **Histamine**: dilates blood vessels
- Heighten the inflammatory response and account for hypersensitivity (allergic) reaction

**Lymphocyte Functions**

- **B cells**
  - Destroy bacteria and their toxins
  - Turn into plasma cells that produces **antibodies**
- **T cells**
  - Attack viruses, fungi, transplanted organs, cancer cells & some bacteria
- **Natural killer cells**
  - Attack many different microbes & some tumor cells
  - Destroy foreign invaders by direct attack
**Monocyte Function**
- Take longer to get to site of infection, but arrive in larger numbers
- Destroy microbes and clean up dead tissue following an infection
- **Macrophages**

**Differential Counts**

A complete blood count (CBC) is used to determine blood cell counts, hemoglobin, hematocrit, white blood cell count, differential white blood cell count, and platelet count.

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<tr>
<th>Class</th>
<th>Normal Range (%)</th>
<th>Typical Value (%)</th>
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What would you expect to see with a bacterial infection?

The following patients show increased WBC counts:

1. Amy has a sore throat, runny nose, and a cough.
   - What is wrong with her?
   - What treatment do you suggest?

2. Joe is achy all over, fatigued, and has a fever and cough.
   - What is wrong with him?
   - What treatment do you suggest?

3. Chris has fatigue, diarrhea, nausea and vomiting
   - What is wrong with him?
   - What treatment do you suggest?

**Differential Counts**

- **Leukocytosis**: high white blood cell count
  - Microbes, strenuous exercise, anesthesia or surgery
- **Leukemia**: uncontrolled production of white blood cells
  - Myeloid leukemia – granulocytes
  - Lymphoid leukemia – lymphocytes or monocytes
- **Leukopenia**: low white blood cell count
  - Radiation, shock, chemotherapy, measles, mumps, chickenpox, polio, influenza, typhoid fever, AIDS, immunosuppressant drugs, or lead, arsenic, and mercury poisoning
Red bone marrow
- Hemocytoblasts
- Myeloid cells
- Progenitor cells
- All formed elements
  - Basophil
  - Eosinophil
  - Neutrophil
  - Monocyte
- EXCEPT lymphoblasts

Regulation of WBC Production
- Colony-stimulating factors (CSFs): stimulates production of formed elements
  - M-CSF: monocytes
  - G-CSF: granulocytes
  - GM-CSF: granulocytes and monocytes
  - Multi-CSF: granulocytes, platelets, RBCs

Platelet Function
- Release chemicals for clotting process
- Formation of temporary patch in walls of damaged blood vessels
- Active contraction after clot formation has occurred
Platelet Production

- **Thrombocytopoiesis**: platelet formation
- **Thrombopoietin (TPO)**
  - Thrombocyte-stimulating factor
  - Produced in kidneys and liver
  - Stimulates platelet formation
  - Stimulates production of megakaryocytes
- **Interleukin-6 (IL-6)**: stimulates platelet formation
- **Multi-CSF**: stimulates formation and growth of megakaryocytes

Hemostasis

- **Hemostasis**: stoppage of bleeding
  - Series of chemical reactions that takes place in a definite and rapid sequence resulting in a net of fibers that traps red blood cells
- Prevents
  - hemorrhage: loss of a large amount of blood
- Response must be
  - Quick
  - Localized
  - Controlled
- Phases
  - Vascular phase
  - Platelet phase
  - Coagulation phase
Blood

Vascular Phase

- Occurs in seconds, lasts ~30 minutes
- Damage to blood vessel produces stimulates pain receptors
- **Vascular spasm**: local contraction of the smooth muscle fibers in blood vessel wall
- Changes in endothelium of vessel
  - Endothelial cells contract and expose underlying basal lamina to bloodstream
  - Endothelial cells release chemical factors and local hormones
  - Endothelial cell membranes become “sticky”

Platelet Phase

- Begins ~15 sec after injury
- Attachment of platelets to sticky endothelial surfaces, basal lamina, and exposed collagen fibers
  - **Platelet adhesion**: attachment of platelets to exposed surfaces
  - **Platelet activation/aggregation**: platelets begin sticking to each other
    - **Platelet plug**: an aggregation of platelets that may close the break in the vessel wall

Platelet Adhesion

- **Platelet activation**
  - Form cytoplasmic processes (pseudopods)
  - Release chemicals
    - ADP: stimulates platelet aggregation and secretion
    - Thromboxane A2: vasoconstrictor (vascular spasm)
    - Serotonin: vasoconstrictor (vascular spasm)
    - Clotting factors
    - Platelet derived growth factor (PDGF): promotes vessel repair
    - Calcium ions: required for platelet aggregation and clotting
Platelet Phase

- Control of platelet aggregation
  - **Prostacyclin**
    - Released by endothelial cells
    - Inhibits platelet aggregation
  - Inhibitory compounds
    - Released by WBCs
  - Circulatory plasma enzymes break down ADP near plug
  - Blood clot isolates activated platelets from general circulation

Coagulation Phase

- Occurs at least 30 sec after injury
- **Coagulation**: blood clotting
  - Convert fibrinogen to fibrin
    - **Fibrinogen**: soluble plasma protein
    - **Fibrin**: insoluble fibrous protein
  - Two pathways to initiate
- **Blood clot**: fibrous tangle of fibrin and formed elements
Overview of the Clotting Cascade

Clotting factors (procoagulants)
- Calcium
- Prothrombin
- Prothrombinase
- Thrombin
- Fibrinogen
- Fibrin

Extrinsic Pathway
- Damaged tissues leak tissue factor (thromboplastin) into bloodstream
- Prothrombinase forms in seconds
  • ~15 sec for clot to occur
- Must have
  • Calcium
  • Clotting factors

Intrinsic Pathway
- Damaged blood vessels
- Activation occurs
  • Endothelium is damaged & platelets come in contact with collagen of blood vessel wall
  • Platelets damaged & release phospholipids
- Requires longer for reaction to occur
  • ~3 – 6 min for clot to occur
- Substances involved:
  • Calcium
  • Clotting factors

Clot Retraction & Blood Vessel Repair
- Begins 30-60 minutes after injury
- Platelets pull on fibrin threads causing clot retraction
  • Actin/Myosin
- Edges of damaged vessel are pulled together
- Fibroblasts & endothelial cells repair the blood vessel

Atherosclerosis, test tube
Fibrinolysis

- **Fibrinolysis**: dissolve the clot
- Inactive **plasminogen** is incorporated into the clot
  - Thrombin and clotting factors activate plasmin
  - **Plasmin** digests fibrin threads
- **Synthetic factors**
  - Streptokinase
  - Tissue plasminogen activator (t-pa)

Control

- **Control of extrinsic pathway**
  - Peripheral tissues not exposed to inside of blood vessels
- **Control of intrinsic pathway**
  - **Platelet repulsion**: platelets do not adhere to smooth healthy endothelium
  - Blood has **anticoagulants**
    - **Heparin** (from basophils and mast cells)
      - Interferes with formation of prothrombin activator
      - Blocks action of thrombin
      - Promotes anti-thrombin
    - **Anti-thrombin** from liver
- **Dilution**: blood disperses clotting factors

How would the following affect normal flow of blood and why?

1. Atherosclerosis
   - Plaque builds up inside the arteries
   - Plaque is made of cholesterol, fatty substances, cellular waste products, calcium and/or fibrin
2. Prolonged compression
3. Prolonged immobility

Role of Vitamin K in Clotting

- Normal clotting requires adequate vitamin K
  - Fat soluble vitamin absorbed if lipids are present
  - Absorption slowed if bile release is insufficient
- Required for synthesis of 4 clotting factors by hepatocytes
  - Factors II (prothrombin), VII, IX and X
- Produced by bacteria in large intestine
**Abnormal Clotting**

- **Hemophilia**: deficiency of coagulation
- **Thrombosis**: clotting in an unbroken blood vessel
- **Embolus**: a clot, air bubble, fat, or piece of debris transported by the bloodstream

**Anticoagulants**

*Suppress or Prevent Blood Clotting*

- **heparin**
  - administered during hemodialysis and surgery
- **warfarin (Coumadin)**
  - antagonist to vitamin K so blocks synthesis of clotting factors
  - slower than heparin
- stored blood in blood banks treated with citrate phosphate dextrose (CPD) that removes Ca^{2+}

**Hematologic Tests**

- Total white blood cell count
- Differential white blood cell count
- Total red blood cell count
- Hemoglobin concentration
- Bleeding time
- Hematocrit
- Microscopic examination
- Sickle cell anemia
- Blood typing
Blood Typing

- **Antigens**: substance able to produce an immune response
  - Ex: protein molecules on surface of RBCs
- **Antibodies**: protein molecules that bind to specific antigens
  - Inhibit or destroy it
- **Agglutination**: clumping of red blood cells due to antibodies binding antigens
  - also causes **hemolysis** due to activation of additional plasma proteins
Antibodies cause agglutination
Agglutination causes hemolysis

Transfusion Reaction

**ABO / Rh Blood Systems**

- Possible antigens (proteins)
  1. A
  2. B
  3. Rh

- Genetically inherited from mother and father
  - Potential to make 2 copies/proteins in ABO
    - Ex: AA, BB, AB, A/none, B/none, none/none
  - Potential to make Rh or not
    - Rh/Rh, Rh/none = positive
    - None/none = negative

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Blood

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Hemolytic Disease of the Newborn

Clinical Information

- **Antisera (antiserum):** man-made solution containing antibodies
- **Serum:** blood plasma with blood clotting proteins removed (unable to clot)
  - Still able to agglutinate
Blood