Blood Physiology

I. Introduction:
A. Cells within the human body are susceptible to changes in temperature, pH, and to toxic chemicals.
   1. Since most cells in the body are fixed within tissues they must have nutrients and oxygen brought to them and waste removed.
   2. Blood serves this transportation function.
B. The blood is classified as a fluid matrix connective tissue consisting of cells and cell fragments surrounded by a liquid matrix which circulates through the heart and blood vessels.
   1. The cells and cell fragments are the formed elements and the matrix of the blood is fluid.
   2. Therefore blood can be divided like other connective tissues into a cellular component and a matrix component.
C. Formed elements make up about 45% and plasma 55% of the total blood volume.
D. Blood volume: 4-5 L in females, 5-6 L in males

II. Functions of the Blood
A. Distribution and transport (estimate 60,000 miles of vessels in body)
   1. Respiration
      a. RBC transport Oxygen, CO₂
   2. Nutritive
      a. Carries absorbed nutrients, electrolytes and water from intestines:
   3. Excretory
      a. Metabolic Waste -urea, excess water, ions are carried to the kidney.
   4. Negative - also transports bacteria, viruses, toxins etc.
B. Regulation and maintenance
   1. Hormonal regulation
      a. From glands to target organs
      b. Transport of various enzymes
   2. Thermoregulation
      a. Diversion of blood from deeper to superficial cutaneous vessels to cool body or vice versa to retain heat.
   3. pH / acid-base balance
      a. Blood acts as a buffering system for the body.
      b. pH 7.35-7.45
4. Fluid volume

C. Protection
   1. Clotting
      a. Protects against blood loss when tissues / vessels are damaged
   2. Immunity
      a. Leukocytes protect against disease causing agents.
         (1) toxins, bacteria

III. Major Components of the Circulatory System
   A. Two divisions: Cardiovascular system and lymphatic system.
   B. Cardiovascular: Heart, blood vessels
      1. Heart:
         a. 4 chambers-
         b. at rest pumps 5 liters / min.
         c. Completely recirculates the blood every minute.
      2. Vessels
         a. Form a tubular network.
         b. Arteries carry blood away from heart to arterioles
         c. Blood enters capillaries -
            (1) thinnest and most numerous of vessels..
            (2) exchange of nutrients, fluids and waste occurs in capillaries.
         d. Blood flows into venules which enter into larger veins.
   C. Lymphatic: lymphatic vessels and lymphoid tissues in spleen, thymus, tonsils, and lymph nodes.
      1. The fluid portion of the blood (plasma) passes through the capillary walls under hydrostatic pressure (interstitial fluid).
         a. Some interstitial fluid returns to the blood and some enters the lymphatic system
         b. Lymphatic vessels carry interstitial fluid now called lymph back to the venous blood.
         c. Lymph nodes along the way filter and cleanse the blood before it is returned.

IV. Components of the blood.
   A. Fluid components
      1. Plasma - straw colored liquid composed of water and dissolved solutes.
         a. 90% water - solvent and suspending medium for blood components
         b. Over 100 different solutes - proteins, ions, nutrients, gases and waste products.
            (1) 7% Proteins
(a) Albumins (58%) - buffer / maintains osmotic pressure / viscosity
(b) Globulins (38%) - α & β -transport lipids and hormones. γ-Act as antibodies
(c) Fibrinogen (4%) - Blood clotting

(2) 2% Other solutes
(a) Ions - Na+, K+, Ca++, etc.
(b) Nutrients - Glucose, amino acids, cholesterol, triacglycerol
(c) Waste products - Urea, uric acid, creatinine, ammonia salts.
(d) Gases - Oxygen, CO₂, Nitrogen
(e) Regulatory substances- enzymes, hormones.

B. Formed Elements (Cells)
1. Erythrocytes (RBC)
   a. Hematocrit = % of blood composed of RBC
2. Leukocytes (WBC) - 5 types
   a. Granulocytes - neutrophils, eosinophils, basophils
   b. Agranulocytes - lymphocytes and monocytes
3. Thrombocytes (platelets)

V. Erythrocytes - red blood cells (RBC’s)
A. Characteristics
   1. Numbers: Female - 4.3 to 5.2 million / mm³ and Male 5.1 to 5.8 million / mm³.
   2. Shape “biconcave disks” - increases surface area
   3. 7 um in diameter and 2.2 um thick.
   4. Contains hemoglobin and iron.
   5. No nucleus, very few organelles.
B. Functions
   1. Carry oxygen to tissues and carbon dioxide away from tissues.
   2. Function dependent on hemoglobin
a. Hemoglobin
(1) Structure:
   (a) Composed of 4 protein chains, 2 alpha chains and 2 beta chains.
   (b) Each chain contains an iron containing heme group.
   (c) Iron in these heme groups is critical for oxygen to bind to the hemoglobin
   (d) Each hemoglobin is capable of binding 4 oxygens.
      i) Considerations: Each blood cell contains 280 million hemoglobin molecules. Each RBC therefore has the capability to bind over 1 billion oxygen molecules.
(2) The majority of CO$_2$ (70%) is carried in the blood as bicarbonate ions HCO$_3$-
   (a) CO$_2$ + H$_2$O ⇌ H$_2$CO$_3$ ⇌ HCO$_3$- + H+
   (b) Catalyzed by carbonic anhydrase in the RBC
(3) Carbon monoxide binds to Hemoglobin forming a stable carboxyhemoglobin - result O$_2$ can’t bind to hemoglobin and death occurs.

b. RBC Production:
(1) RBC’s are produced within the bone marrow. Through a process called erythropoiesis.
(2) Most blood cells derive from a common ancestor cell known as a hemocytoblast.
(3) Under appropriate conditions the hemocytoblast differentiates into a cell known as a proerythroblast (early erythrocyte forming cell) etc.
(4) History
   (a) Stem cell >
   (b) proerythroblast >
   (c) early (basophilic) erythroblast >
   (d) intermediate (polychromat) erythroblast > (hemoglobin production begins)
   (e) late erythroblast (loss of nucleus) >
   (f) reticulocyte >
   (g) erythrocyte
(5) Changes that occur during RBC development:
   (a) decrease in size, loose nucleus and many of its organelles including mitochondria
(6) Regulation of production
(a) production requires:
   i) folate and B12 for cell division and
   ii) iron for hemoglobin to be produced.

(b) Erythrocyte production is stimulated by low blood oxygen
   i) Causes: decreased or defective erythrocytes, diseases of the lungs, high altitude, cardiovascular delivery problems, increased demands for oxygen (endurance exercise).

(c) Decreased blood oxygen causes increased erythropoietin release from the kidneys.
   i) erythropoietin stimulates bone marrow to produce more erythrocytes and increase the rate of maturation.

c. Fate and destruction of RBC’s:
   (1) As RBC circulate they eventually become ragged and worn out as they squeeze through capillaries.
      (a) (RBC cannot produce new proteins - no nucleus)
      (b) Typical life span 100 - 120 days.

   (2) As RBC’s squeeze through the narrow capillaries of the spleen (or liver) the worn out cells become trapped and broken down by fixed macrophages.

   (3) Breakdown products are recycled as follows:
      (a) Macrophages engulf and destroy worn out RBCs in spleen and liver.
      (b) Hemoglobin is split into heme and globin
      (c) Globin is broken down into amino acids which can be used to synthesize other proteins.
      (d) Heme (iron + porphyrin) liberates its iron core which is recycled.
         i) Iron
            a) Fe$^{3+}$ is picked up and transported in blood by a plasma protein called transferrin
            b) Fe is carried to marrow for synthesis of Hb in new RBC or
            c) Is stored in muscle or liver where iron detaches from transferrin and binds to an iron storage protein called ferritin.
            d) Upon release from storage, iron can reattaches to transferrin
            e) Iron is then transported to bone marrow where RBC precursors take it up through receptor mediated endocytosis for use in producing new hemoglobin molecules.
f) Erythropoiesis in red bone marrow results in the production of RBC which enter the circulation.

(4) **Porphyrin** -
   
   (a) Non iron portion of heme (prophyrin) is converted to [biliverdin](#) (green pigment)
   
   (b) biliverdin is converted to [bilirubin](#) (orange pigment)
   
   (c) bilirubin enters the blood stream and is transported to the [liver](#).
   
   (d) Within the liver, bilirubin is secreted by the liver cells into bile which passes into the [small intestine](#).
   
   (e) In the [large intestine](#) bacteria convert bilirubin into [urobilinogen](#)
   
   (f) Some of the Urobilinogen is absorbed back into the blood and converted to [urobilin](#) (yellow pigment) and is excreted in the [urine](#).
   
   (g) Most urobiligen is eliminated in feces in the form of [stercobilin](#) which gives [feces](#) its characteristic color.

d. Jaundice - yellowish staining of skin and sclera causes by buildup of bilirubin.

C. **Disorders of Erythrocytes**

1. **Anemias** (deficiency of hemoglobin in blood)
   a. Result of either a decrease in hemoglobin / RBC or in the number of RBCs.
   b. [Symptoms](#): pale, lethargic, shortness of breath, tired.
   c. **Aplastic anemia**: inability of red bone marrow to produce RBCs
      (1) caused by:
      (a) damage to Red bone marrow by chemicals, drugs, radiation
      (b) Iron deficiency - RBCs are smaller than normal.
      (c) Folate deficiency - necessary for DNA replication - poor pregnant women and alcoholics
   
   d. **Pernicious anemia** - Vitman B12 deficiency - Vitamin B12 is necessary for production of folate.
   e. **Hemorhagic anemia** - results from loss of blood. Ie. Ulcers, menstration.
   f. **Hemolytic anemia** - erythrocytes rupture or are destroyed at an increased rate.
      (1) caused by:
      (a) genetic membrane problems,
      (b) snake venom,
      (c) immune diseases,
      (d) heart valve problems.
   
   g. **Thalasemia** - defective hemoglobin production
      (1) insufficient globin production - genetic disorder
(2) Sickle cell anemia - abnormal shaped hemoglobin
   (a) cells are rigid, fragile and sickle shaped
   (b) death by age 30.
   (c) protective against malaria
      i) caused by a protozoan (plasmodium)
      ii) carried by anopheles mosquito
      iii) protozoan develops in the RBCs releases toxins that cause RBCs to rupture.

VI. Leukocytes:
   A. Broad classification of white blood cells
   B. 4,000-11,000 / mm$^3$ (5-9,000 considered normal range)
   C. Characteristics
      1. Diapedesis - can cross capillary boundaries to fight infection
      2. Ameboid motion - cytoplasmic fluid movement
      3. Positive chemotaxis - ability to follow chemical trail through the body
   D. Characterized as granulocytes or agranulocytes
      1. Granulocytes - twice the size of RBC, cytoplasmic granules present, survive 12h to 3 days.
         a. Neutrophils
            (1) Appearance - see lab handout
               (a) 2-5 lobes, cytoplasmic granules that stain slightly pink
               (b) 10-12um
               (c) 54 to 62% of white cells
            (2) Characteristics
               (a) most common WBC
               (b) chemically attracted to sites of infection
               (c) good at fighting bacterial and fungal infections
               (d) contain peroxidases and other hydrolytic enzymes
               (e) contain defensins which act to digest foreign substances and puncture holes in bacteria
               (f) Numbers increase rapidly with meningitis and appendicitis
         b. Eosinophils
            (1) Appearance
               (a) bilobed nucleus
               (b) cytoplasmic granules that stain red or bright red
               (c) 11-14 um
(d) 1-3% of white blood cells

(2) Characteristics
(a) most effective in working against parasitic worms such as tape worms, flukes, pinworms, and hookworms
(b) release chemical that reduce inflammation
(c) secrete enzymes that break down clots.

c. Basophils
(1) Appearance
(a) two indistinct lobes
(b) cytoplasmic granules stain blue-purple
(c) 10-12 um
(d) less than 1% of white cells

(2) Characteristics
(a) contain and release histamine
(b) act as a chemoattractant to attract other WBC
(c) release heparin - prevents clots

2. Agranulocytes
a. Lymphocytes
(1) Appearance
(a) only slightly larger than RBC
(b) round nucleus nearly fills cell.
(c) 6-14um
(d) 25-33% of white blood cells

(2) Characteristics
(a) Generally found in lymphoid tissue
(b) provides specific immune response
   i) T-lymphocytes act directly against virus infected cells and tumor cells
   ii) B-Lymphocytes produce plasma cells which give rise to antibodies.

b. Monocytes
(1) Appearance
(a) Nucleus round, kidney of horseshoe shaped
(b) contains more cytoplasm than lymphocyte
(c) 12-20um
(d) 3-9% of white cells

(2) Characteristics
(a) Once activated transform into macrophages which attack and digest everything in their way (dead cells, bacteria, etc.)

VII. Platelets

A. Responsible for blood clot formation and are not cells at all but are fragments of cells.
   1. Characteristics
      a. Cytoplasmic fragment surrounded by a plasma membrane containing granules
      b. 2-4um
      c. 130,000 to 400,000 / mm³
      d. Enables clotting
      e. Releases serotonin which causes vasoconstriction

B. Hemostasis (prevention of blood loss) by clotting
   1. Can be divided into three stages (vascular spasm, platelet plug formation, coagulation).
      a. Vascular spasm
         (1) Once a blood vessel has been injured the first and most immediate response is for the blood vessel to start to spasm.
            (a) smooth muscle contraction
         (2) Vascular spasm is caused by nervous system reflexes and by chemicals (thromboxanes, endothelin)
      b. Platelet plug formation
         (1) Seals up small breaks in blood vessels
         (2) Process:
            (a) platelet adhesion
               i) Von willibrand’s factor from endothelial wall
               ii) binds platelets to collagen in vessel wall.
            (b) platelet activation
               i) release ADP and thromboxanes
               ii) cascade of chemical release by other platelets
            (c) Activated platelets also bind fibrinogen
               i) causes platelet aggregation.
               ii) Forms a plug.
            (d) Platelets also release platelet factor III and coagulation factor V.
               i) important in clot formation (discussed later).
         (3) Aspirin inhibits plug formation by blocking prostiglandin and thromboxane production.
      c. Coagulation
         (1) blood clot formation
(a) Fibrin protein fibers trap blood cells, platelets and fluid.
(b) Formation depends on a number of factors
(c) Coagulation factors are normally inactive
(d) Injury causes activation of clotting factors
(e) Activation depends on surface proteins on activated platelets.

(2) Process: (three main stages) Fig. 19.10
(a) **Formation of prothrombinase** by two pathways
(b) **Conversion of prothrombin to thrombin** (by prothrombinase)
(c) **Conversion of fibrinogen to fibrin** by thrombin
(d) 2 pathways for the formation of prothrombinase
   i) **Extrinsic pathway** - begins with factors released outside of plasma in damaged tissue
      a) Thromboplastin (tissue factors) released by damaged tissue
      b) Thromboplastin complexes with Factor VII to activate Factor X
      c) Factor X complexes with Factor V platelet phospholipids and Ca+ to activate prothrombinase.
   ii) **Intrinsic pathway** - begins with factors inside (intrinsic to) the blood.
      a) damage to blood vessels exposes collagen in C. T.
      b) factor XII is activated by collagen
      c) activated factor XII activates factor XI
      d) Factor XI activates factor IX
      e) IX joins with factor VIII, platelet phospholipids and Ca+ to activate factor X
      f) Factor X complexes with Factor V platelet phospholipids and Ca+ to activate prothrombinase.

2. Control of clot formation
   a. Anticoagulants prevent blood from clotting outside of the injury area.
      (1) Anticoagulants can counteract low levels of clotting factors.
      (2) Anticoagulants include: antithrombin and heparin

3. Clot retraction
   a. Fibrin meshwork adheres to the walls of the vessel
   b. Clot condenses
      (1) Platelets contain actin and myosin
      (2) bind to fibrin and pull it tight causing retraction
(3) Serum (=plasma - clotting factors) is extruded

c. Consolidation pulls the edges of the vessel together to stop blood flow, reduce infection and enhance healing.
d. Healing - fibroblasts multiply and produce new C.T., epithelial cells proliferate to fill in torn area

4. Clot and dissolution (Fibrinolysis)
a. Clot is dissolved by **plasmin** which hydrolyzes fibrin.
b. Plasmin is formed from inactive **plasminogen**
   (1) plasminogen is activated by tissue **plasminogen activator (t-PA)** or urokinase.
   (2) t-PA and urokinase can be injected as **clot busters** in case of blockage of major vessels due to inappropriate clotting.
   (3) **streptokinase** (produced by bacterial enzyme) can also be injected at the clot site as a clot dissolving drug.

5. Clinical notes
   a. Vitamin K
      (1) is a necessary cofactor for factor VII, IX and X to be activated.
      (2) Vitamin K is produced by bacteria in our gut and absorbed by the intestine.
         (a) absorption requires the presence of bile.
      (3) Low amounts of Vitamin K can lead to hemorrhage (Ie. Infants who don’t have bacteria.)
   b. Thrombus - formation of clot within major vessels.
   c. Embolus - clot floating in the circulation
      (1) can result in death - block of heart, brain, lung
      (2) counteracted by heparin, warfarin (vitamin K dependent factor suppressor; rat poison)

C. Blood Grouping (types)
   1. Covered in lab