Lecture: Physiology of Blood

I. Components, Characteristics, Functions of Blood

A. Major Components of Blood

1. formed elements - the actual cellular components of blood (special connective tissue)
   
   a. erythrocytes - red blood cells
   b. leukocytes - white blood cells
   c. platelets - cell fragments for clotting

2. blood plasma - complex non-cellular fluid surrounding formed elements; protein & electrolytes

B. Separation of Components in a Centrifuge

<table>
<thead>
<tr>
<th>VOLUME</th>
<th>LAYER</th>
</tr>
</thead>
<tbody>
<tr>
<td>clear/yellowish PLASMA</td>
<td>55%</td>
</tr>
<tr>
<td>thin/whitish buffy coat with LEUKOCYTES &amp; PLATELETS</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>reddish mass - ERYTHROCYTES</td>
<td>45%</td>
</tr>
</tbody>
</table>
C. Characteristics of Blood

1. bright red (oxygenated)
2. dark red/purplish (unoxgenated)
3. much more dense than pure water
4. pH range from 7.35 to 7.45 (slightly alkaline)
5. slightly warmer than body temperature 100.4 F
6. typical volume in adult male 5-6 liters
7. typical volume in adult female 4-5 liters
8. typically 8% of body weight

D. Major Functions of Blood

1. Distribution & Transport
   a. oxygen from lungs to body cells
   b. carbon dioxide from body cells to lungs
c. nutrients from GI tract to body cells

d. nitrogenous wastes from body cells to kidneys

e. hormones from glands to body cells

2. Regulation (maintenance of homeostasis)

a. maintenance of normal body pH
   i. blood proteins (albumin) & bicarbonate

b. maintenance of circulatory/interstitial fluid
   i. electrolytes aid blood proteins (albumin)

c. maintenance of temperature (blushed skin)

3. Protection

a. platelets and proteins "seal" vessel damage

b. protection from foreign material & infections
   i. leukocytes, antibodies, complement proteins

<table>
<thead>
<tr>
<th>Element</th>
<th>Diameter (in μm)</th>
<th>Number (per mm²)</th>
<th>Scientific notation (per mm²)</th>
<th>Main function</th>
</tr>
</thead>
<tbody>
<tr>
<td>red blood cells</td>
<td>7 - 8</td>
<td>4,500,000 - 52500,000</td>
<td>4.5 x 10⁶ - 5.25 x 10⁷</td>
<td>oxygen transport</td>
</tr>
<tr>
<td>white blood cells</td>
<td>9 - 12</td>
<td>7,000 - 10,000</td>
<td>7 x 10³ - 1 x 10⁴</td>
<td>defense against microorganisms</td>
</tr>
<tr>
<td>platelets</td>
<td>2 - 4</td>
<td>300,000</td>
<td>3 x 10⁵</td>
<td>blood-clotting</td>
</tr>
</tbody>
</table>
II. Erythrocytes (red blood cells; RBCs)

A. Structure

1. 7.5 micron diameter; 2.0 micron thick
2. biconcave disk shape; ideal for gas exchange
   i. spectrin - elastic protein; allows shape change
3. mature cells are anucleate (no nucleus)
4. very few organelles; mainly a hemoglobin carrier
   i. hemoglobin – 33% of cell mass; carries oxygen
5. no mitochondria; only anaerobic respiration
6. ratio erythrocytes:leukocytes = 800:1
7. red blood cell count: # cells per cubic millimeter
   i. normal male count - 5.1 to 5.8 million
   ii. normal female count - 4.3 to 5.2 million

B. Functions (oxygen & carbon dioxide transport)

1. hemoglobin - large molecules with globin and hemes
   a. globin - complex protein with 4 polypeptides (2 alpha and 2 beta polypeptides)
   b. heme group - IRON containing pigment part of hemoglobin to which oxygen binds
      i. each polypeptide has one heme group; each heme carries one O₂
   c. normal hemoglobin levels (grams/100 ml blood)
      i. infants 14-20 grams/100 ml
      ii adult female 12-16 grams/100 ml
iii adult male 13-18 grams/l00 ml

2. states of hemoglobin
   a. oxyhemoglobin - when oxygen is bound to IRON
   b. deoxyhemoglobin - no oxygen bound to IRON
   c. carbaminohemoglobin - when carbon dioxide bound (to polypeptide chain)

C. Hematopoiesis and Erythropoiesis

1. hematopoiesis (hemopoiesis) - the maturation, development and formation of blood cells
   a. red bone marrow (myeloid tissue) - location of hematopoiesis; in blood sinusoids which connect with capillaries; mainly in axial skeleton and heads of femur & humerus
   
   b. hemocytoblast (stem cell) - the mitotic precursor to blood cells before differentiation
      i. differentiation - maturing cell becomes "committed" to being certain type blood cell

2. erythropoiesis - the maturation, development, and formation of Red Blood Cells (erythrocytes)

   hemocytoblast ->
   proerythroblast ->
   early (basophilic) erythroblast ->
   late (polychromatophilic) erythroblast ->
   (hemoglobin) normoblast -> (nucleus ejected when enough hemoglobin)
   reticulocyte -> (retaining some endoplasmic reticulum)

ERYTHROCYTE
hemocytoblast -> reticulocyte 3-5 DAYS
reticulocyte -> ERYTHROCYTE 2 DAYS (in blood)
ERYTHROCYTE lifespan 100-120 DAYS
(primarily destroyed by macrophages in the spleen)

3. Regulation of Erythropoiesis

a. hormonal controls - erythropoietin is the hormone that stimulates RBC production
   DECREASED oxygen level in blood causes KIDNEYS to increase release of erythropoietin

   1. Less RBCs from bleeding
   2. Less RBCs from excess RBC destruction
   3. Low oxygen levels (high altitude, illness)
   4. Increased oxygen demand (exercise)

Eythropoietin now genetically engineered and synthesized by AMGEN of Thousand Oaks.

Testosterone can also mildly stimulate production of RBCs in humans
b. Iron - essential for hemoglobin to carry oxygen
   i. 65% of Fe in body is in hemoglobin
   ii. liver and spleen store most excess Fe bound to ferritin and hemosiderin
   iii. Fe in blood bound to transferrin
   iv. daily Fe loss: 0.9 mg men/l.7 mg women
   v. women also lose Fe during menstrual flow

c. B-complex Vitamins - Vitamin B12 and Folic Acid essential for DNA synthesis in early mitotic divisions leading to erythrocytes

D. Erythrocyte Disorders (Anemias & Polycythemias)

1. Anemias - a symptom that results when blood has lower than normal ability to carry oxygen
   a. Insufficient erythrocyte count
      i. hemorrhagic anemia - loss of blood from bleeding (wound, ulcer, etc.)
      ii. hemolytic anemia - erythrocytes rupture (hemoglobin/transfusion problems, infection)
      iii. aplastic anemia - red marrow problems (cancer treatment, marrow disease, etc.)

   b. Decrease in Hemoglobin
      i. iron-deficiency anemia - low Iron levels (diet; absorption, bleeding, etc.)
      ii. pernicious anemia - low Vitamin B12 (diet, intrinsic factor for Vit B absorption)

   c. Abnormal Hemoglobin (usually genetic)
      i. thalassemia - easily ruptured RBCs (Greek & Italian genetic link)
      ii. sickle-cell anemia - sickle-shaped RBCs (genetic Africa, Asia, southern Europe link)

2. Polycythemia - excess RBC count, causes thick blood
a. polycythemia vera - bone marrow problem; hematocrit may jump to 80%

b. secondary polycythemia - high altitude (normal); or too much erythropoietin release

c. blood doping in athletes - RBCs previously withdrawn are transfused before an event; more RBCs, more oxygen delivery to the body

III. Leukocytes (white blood cells; WBCs)

A. General Structure and Function
   1. protection from microbes, parasites, toxins, cancer
   2. 1% of blood volume; 4-11,000 per cubic mm blood
   3. diapedesis - can "slip between" capillary wall
   4. amoeboid motion - movement through the body
   5. chemotaxis - moving in direction of a chemical
   6. leukocytosis - increased "white blood cell count" in response to bacterial/viral infection
   7. granulocytes - contain membrane-bound granules (neutrophils, eosinophils, basophils)
   8. agranulocytes - NO membrane-bound granules (lymphocytes, monocytes)
B. Granulocytes - granules in cytoplasm can be stained with Wright's Stain; bilobar nuclei; 10-14 micron diameter; all are phagocytic cells (engulf material)

1. neutrophils - destroy and ingest bacteria & fungi (polymorphonuclear leuks.; "polys")
   a. most numerous WBC
   b. basophilic (blue) & acidophilic (red)
   c. defensins - antibiotic-like proteins (granules)
   d. polymorphonuclear - many-lobed nuclei
   e. causes lysis of infecting bacteria/fungi
   f. HIGH poly count --> likely infection
2. **Eosinophils** - lead attack against parasitic worms
   a. only 1-4% of all leukocytes
   b. two-lobed, purplish nucleus
   c. acidophilic (red) granules with digest enzymes
   d. phagocytose antigens & antigen/antibody complex
   e. inactivate chemicals released during allergies

3. **Basophils** - releases Histamine which causes inflammation, vasodilation, attraction of WBCs
   a. RAREST of all leukocytes (0.5%)
   b. deep purple U or S shaped nucleus
   c. basophilic (blue) granules with HISTAMINE
   d. related to "mast cells" of connective tissue
   e. BOTH release Histamine with "IgE" signal
   f. antihistamine - blocks the action of Histamine in response to infection or allergic antigen

C. **Agranulocytes** - WBCs without granules in cytoplasm
   1. **Lymphocytes** - two types of lymphocytes
      a. **T lymphocytes** - (thymus) respond against virus infected cells and tumor cells
      b. **B lymphocytes** - (bone) differentiate into different "plasma
cells" which each produce antibodies against different antigens
   c. lymphocytes primarily in lymphoid tissues
d. very large basophilic (purple) nucleus
e. small lymphocytes in blood (5-8 microns)
f. larger lymphocytes in lymph organs (10-17 mic)

2. monocytes - differentiate to become macrophages; serious appetites for infectious microbes
   a. largest of all leukocytes (18 microns)
   b. dark purple, kidney shaped nucleus

D. Leukopoiesis and Colony Stimulating Factors (CSFs)
   1. leukopoiesis - the production, differentiation, and development of white blood cells
   2. colony stimulating factors (CSF) - hematopoietic hormones that promote leukopoiesis
      a. produced by Macrophages and T lymphocytes
         i. macrophage-monocyte CSF (M-CSF)
         ii. granulocyte CSF (G-CSF)
         iii. granulocyte-macrophage CSF (GM-CSF)
         iv. multi CSF (multiple lymphocyte action)
         v. interleukin 3 (IL-3) (general lymphocytes)
   3. leukopoiesis - all cells derived from hemocytoblast

![Diagram of blood cell formation](image-url)
E. Disorders of Leukocytes

1. leukopenia - abnormally low WBC count
   a. HIV infection, glucocorticoids, chemotherapy

2. leukemia - cancerous condition of "line" of WBCs
   a. myelocytic leukemia (myelocytes)
   b. lymphocytic leukemia (lymphocytes)
   c. acute leukemia - cancer spreads rapidly
   d. chronic leukemia - cancer progresses slowly
   e. anemia, fever, weight loss, bone pain
   f. death from internal hemorrhage or infection
   g. chemotherapy & radiation therapy used to treat

3. infectious mononucleosis - caused by Epstein-Barr virus, excessive monocytes and lymphocytes; fatigue, sore throat, fever; 3 week course

IV. Platelets (thrombocytes - "clotting")

A. General Characteristics
   1. very small, 2-4 microns in diameter
   2. approximately 250-500,000 per cubic millimeter
   3. essential for clotting of damaged vasculature
   4. thrombopoietin - regulates platelet production

B. Formation of Platelets
   hemocytoblast-> myeloid stem cell-> megakaryoblast-> promegakaryocyte->
   megakaryocyte-> (large multilobed nucleus) >platelets (anucleated parts of megakaryocyte cytoplasm)
V. Plasma (the liquid part of blood)

A. General Characteristics

1. plasma makes up 55% of normal blood by volume
2. water is 90% of the plasma by volume
3. many different SOLUTES in the plasma
   a. albumin - pH buffer & osmotic pressure
   b. globulins - binding proteins & antibodies
   c. clotting proteins - prothrombin & fibrinogen
   d. other proteins - enzymes, hormones, others
   e. nutrients - glucose, fatty acids, amino acids, cholesterol, vitamins
   f. electrolytes - $\text{Na}^+$, $\text{K}^+$, $\text{Ca}^{++}$, $\text{Mg}^{++}$, $\text{Cl}^-$, phosphate, sulfate, bicarbonate, others
VI. Hemostasis (stoppage of blood flow after damage)

A. General Characteristics
   1. vascular spasms (vasoconstriction at injured site)
   2. platelet plug formation (plugging the hole)
   3. coagulation (blood clotting - complex mechanism)

B. Vascular Spasms
   1. first response to vascular injury - VASOCONSTRICTION is stimulated by:
      a. compression of vessel by escaping blood
      b. injury "chemicals" released by injured cells
      c. reflexes from adjacent pain receptors

C. Formation of a Platelet Plug
   1. damage to endothelium of vessel
   2. platelets become spiky and sticky in response
   3. platelets attach to damaged vessel wall to plug it
   4. platelets produce thromboxane A2 - granule release
   5. serotonin release enhances vascular spasm
   6. ADP - attracts and stimulates platelets at site
   7. prostacyclin - inhibits aggregation at other sites
VII. Coagulation (blood clotting)

A. General Events in Clotting

platelet cells activated by damage ->
PF3 and/or Tissue Factor produced by platelet cells ->
Factor X activated ->
prothrombin activator (enzyme) produced ->
prothrombin conversion -> thrombin (another enzyme)
thrombin stimulates: fibrinogen -> fibrin mesh

1. anticoagulant - chemical that inhibits clotting
2. procoagulant - chemical that promotes clotting
3. intrinsic pathway - within the damaged vessel
   a. more procoagulants needed (I-XIII) toward PF3 and Factor X
   b. allows more "scrutiny" before clotting occurs

4. extrinsic pathway - in outer tissues around vessel
   a. tissue thromboplastin (Tissue Factor) - skips intrinsic steps
      straight to PF3 and Fac X
   b. allows rapid response to bleeding out of vessel (clot can form in 10 to 15 seconds)

5. After activation of Factor X, common pathway:
   Factor X, PF3 (thromboplastin), Factor V, Ca^{++} ->
   prothrombin activator ->
   prothrombin converted -> thrombin (active enzyme)
thrombin stimulates: fibrinogen -> fibrin (meshwork)
Ca^{++} & thrombin -> Factor XIII (fibrin stabilizer)

B. Clot Retraction (shrinking of clot)

1. actomyosin - causes contraction of platelets
2. blood serum - plasma WITHOUT clotting Factors
3. platelet-derived growth factor (PDGF) - stimulates fibroblast migration and endothelial growth
C. Clot Eradication (Fibrinolysis)

1. healing occurs over 2 - 10 days
2. tissue plasminogen activator (TPA) - causes the activation of plasminogen
3. plasminogen --> plasmin
4. plasmin degrades proteins within the clot

D. Factors Limiting Growth and Formation of Clots

1. Limiting Normal Clot Growth
   a. blood moves too fast to allow procoagulants
   b. factors interfere with normal clotting
      i. prothrombin III - deactivates thrombin
      ii. protein C - inhibits clotting Factors
      iii. heparin - inhibits thrombin; prevents adherence of platelets to injured site

VII. Disorders of Hemostasis

A. Thromboembololytic Disorders (undesirable clotting)
   1. thrombus - blood clot in normal blood vessel
   2. embolus - blood clot/gas bubble floating in blood
      a. TPA, streptokinase - can dissolve a clot
      b. aspirin - inhibits Thromboxane formation
      c. heparin - inhibits thrombin & platelet deposit
      d. dicumarol - anticoagulant, blocks Vitamin K

B. Bleeding Disorders

1. thrombocytopenia - reduced platelet count; generally below 50,000 per cubic millimeter; can cause excessive bleeding from vascular injury
2. impaired liver function - lack of procoagulants (Clotting Factors) that are made in liver a. vitamin K - essential for liver to make Clotting Factors for coagulation
3. hemophilias - hereditary bleeding disorders that occur almost exclusively in males
   a. hemophilia A - defective Factor VIII (83%)
   b. hemophilia B - defective Factor IX (10%)
   c. Genentech, Inc. - now produces genetically engineered TPA and Factor VIII; patients do not need transfusions as often

http://www.mhhe.com/biosci/esp/2002_general/Esp/folder_structure/tr/m1/s7/trm1s7_3.htm

VIII. Blood Transfusions and Blood Typing

A. Transfusion of Blood
   1. whole blood transfusion - all cells and plasma; anticoagulants (citrate and oxalate salts) used
   2. packed red blood cells - most of the plasma has been removed prior to transfusion

B. Human Blood Groups
   1. agglutinogens - glycoproteins on the surface of blood cells; causes "agglutination" (clumping)
   2. ABO Blood Groups - determined by presence or absence of Type A and Type B agglutinogen proteins on cell membrane

<table>
<thead>
<tr>
<th>TYPE</th>
<th>GENES</th>
<th>PEOPLE</th>
<th>Antibodies</th>
<th>Receive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood from:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>type A</td>
<td>A/A, A/O, O/A (30-40%)</td>
<td>Anti-B</td>
<td>A, O</td>
<td></td>
</tr>
<tr>
<td>type B</td>
<td>B/B, B/O, O/B (10-30%)</td>
<td>Anti-A</td>
<td>B, O</td>
<td></td>
</tr>
<tr>
<td>type AB</td>
<td>A/B or B/A (3-5%)</td>
<td>none</td>
<td>A, B, AB, O</td>
<td></td>
</tr>
<tr>
<td>type O</td>
<td>no A or B (40-50%)</td>
<td>Anti-A, Anti-B</td>
<td>O only</td>
<td></td>
</tr>
</tbody>
</table>

3. agglutinins - antibodies against either A or B agglutinogen (whichever is not present) a. transfusion reaction - patient's antibodies attack the donor blood
   i. A (anti-B) receives A, O (not B)
   ii. B (anti-A) receives B, O (not A)
iii. AB (none) receives A, B, AB, O universal recipient
iv. O (anti-A, anti-B) receives O universal donor

c. agglutination - when incorrect blood transfused, antibodies will "clump" new blood

d. hemolysis - after clumping, RBCs may rupture, releasing hemoglobin, harming kidney
  i. dilute hemoglobin, administer diuretics
4. Rh factor - a different group of agglutinogens
   a. Rh positive (Rh+) - an Rh factor is present
   b. Rh negative (Rh-) - NO Rh factor
   c. transfusion reaction - delayed and less severe than in ABO confrontation
   d. erythroblastosis fetalis - Rh- mother antibodies attack Rh+ of older newborn; results in anemia and low oxygen levels (hypoxia)
      i. RhoGAM - serum with anti-Rh agglutinins which will clump the Rh factor, blocking the reaction of mothers antibodies
         ii. exchange transfusion - directly from the mother (Rh-) to the newborn (Rh+)

5. Blood Typing - mixing Donors Blood with Recipient Antibodies (Anti-A, Anti-B, anti-Rh) in order to identify agglutination

6. Expanding Blood Volume to Avoid Shock
   a. pure plasma without antibodies
   b. plasma expanders - purified human serum albumin, plasminate, dextran
   c. isotonic saline - normal electrolyte solution isotonic to blood plasma (Ringer's Solution)

7. Diagnostic Blood Tests
   a. anemia - low hematocrit (below 35%)
   b. lipidemia - high in fat; yellowish plasma
   c. diabetes - blood glucose level
d. Infection - generally higher WBC count

e. Leukemia - significantly higher WBC count

f. Differential WBC count - counts % of each of the different leukocytes (helps diagnose)

g. Prothrombin time - time for clotting to occur

h. Platelet count - diagnose thrombocytopenia

i. Complete blood count - overall blood review