Blood

I. Composition/function.

A. Introduction.

- 8% body volume; specialized connective tissue where cells are formed elements and plasma is extracellular matrix (ECM); the two ECM components are ground substance (serum) and fibers (soluble fibrinogen).

B. Composition.

1. Formed elements (42% in females, 45% in males).

    a. RBC - 99.9% of formed elements

    b. WBC.

    c. platelets.

2. Plasma (58% for women, 55% for men).

    a. water.

    b. plasma proteins.

    c. other solutes.

C. Functions of blood.

- Distribution of gases, nutrients , removal of waste products, hormone transport.
- Regulation of body temp, pH, fluid volume.
- Protection: clotting, prevention of infection.

II. Blood plasma.

A. Composition.

1. Water: 90-92%.

2. Solutes.

a. Proteins 7-8%

(i) albumins (60%): major contributors to osmotic pressure of blood; transport of fatty acids, thyroid and steroid hormones.

(ii) globulins (36%)

- transport globulins

- immunoglobulins

(iii) clotting proteins (4%).

(iv) other plasma proteins: hormones, enzymes.

b. "other solutes".
- nonprotein nitrogenous substances.
- nutrients.
- electrolytes.
- respiratory gases.

III. Formed elements: erythrocytes, leukocytes, platelets.

- all produced in bone marrow in adult from a pluripotent cell the hemocytoblast; hemocytoblast gives rise to myeloid stem cells (MSC) or lymphoid stem cells (LSC); MSC will give rise to RBC, WBC, platelets; LSC gives rise to lymphocytes.

A. Erythrocytes: have biconcave shape which gives them a huge surface area relative to volume; lack nucleus, organelles, contain predominantly hemoglobin.

1. Function of gas transport.

- a function of hemoglobin which binds easily and reversibly to oxygen.

a. Structure of hemoglobin.

(i) globin is protein unit: four polypeptide chains, each bound to heme group.

(ii) heme is a complex ring structure which has atom of iron in its center; iron binds reversibly to oxygen.

b. Oxygen transport.

- a hemoglobin molecule can transport 4 molecules of oxygen (oxyhemoglobin -- deoxyhemoglobin); most of oxygen in blood is bound to hemoglobin.

c. Carbon dioxide transport.
- 20% of CO_2 in blood is bound to amino acids of hemoglobin, not heme.

2. Production of erythrocytes (erythropoiesis).

- occurs in bone marrow.
- phase 1: ribosome production.
- phase 2: hemoglobin synthesis/accumulation.
- phase 3: ejection of nucleus.
- note that reticulocyte is released from bone marrow to circulation, mature RBC only appears about two days later.

3. Erythropoiesis.

a. Hormonal control.

- occurs by differential release of erythropoietin by kidneys in response to changing levels of O_2 in blood; involves negative feedback regulation.

- note that number of RBC in blood does not control erythropoiesis, control is based on ability to transport enough O_2 to meet tissue demands.

b. Dietary requirements.

- amino acids, iron. vitamins (B_{12}, folic acid).

4. Destruction of erythrocytes.

- usually occurs in large circulatory channels (spleen, liver).
- as cells age, they become abnormally shaped, fragment engulfed by macrophages; iron and amino acids are recycled, heme used for synthesis of bile by liver.

5. Erythrocyte disorders - anemias: conditions in which blood has abnormally low O2 carrying capacity; a symptom of a disorder, can have several causes.

a. Insufficient number of RBC.

- hemorrhagic anemias.
- hemolytic anemias.
- aplastic anemias.

b. Decreases in Hb content.

- iron-deficiency anemia.
- pernicious anemia.

c. Abnormal hemoglobin.

- thalassemias.
- sickle cell anemia.

6. Erythrocyte disorders - polycythemias: abnormal excess of erythrocytes, increased blood viscosity.

- polycythemia vera.
- secondary polycythemias.

B. Leukocytes: true cells, granulocytes and agranulocytes.

- function in body defense against pathogens.

- characteristics:

- amoeboid movement.
- diapedesis.
- positive chemotaxis.
- phagocytosis.

1. Granulocytes: contain specialized membrane-bound granules, lobed nuclei; all originate from MSC.

a. Neutrophils: most common WBC, have a mix of basophilic and acidophilic granules..

- first WBC to arrive at site of infection, very mobile; engulfs pathogen, respiratory rate increases dramatically (respiratory burst); phagocytic vesicle fuses with lyzosomes and granules containing defensins (degranulation); action of both destroy ingested pathogen.

- secrete prostaglandins and leukotrienes.

- die after phagocytosis of a dozen or so bacteria, death releases chemotactic compounds.

b. Eosinophils: have acidophilic granules.

- granules have a special variety of digestive enzymes lacking those that can digest bacteria.

- primary mode of attack involves exocytosis of toxic compounds onto target surface (multicellular organism too large to be phagocytosed, parasitic worms.

- attack objects coated in antibodies.

- also reduce severity of allergic reactions by phagocitizing Ag-Ab complexes.

c. Basophils: rarest WBC.

- cytoplasm contains histamine and heparin granules.

- migrate to site of injury, cross capillary endothelium, discharge granules
- histamine release.

2. Agranulocytes: lack obvious granules, have kidney-shaped or round nuclei.

a. Lymphocytes: have very large spherical nuclei with small rim of cytoplasm.

- most found in lymph nodes, spleen, marrow.

- participate in immune response, T-lymphocytes in cell-mediated immunity, B-lymphocytes in humoral immunity.

b. Monocytes: the largest WBC, large nucleus, kidney-shaped.

- only remain in circulation for 24 hours, enter peripheral tissues where they mature into macrophages. the body's greatest scavengers; very aggressive phagocytic cells.

- when encounter invader release many chemotaxic and growth factors that attract other WBCs and stimulate tissue repair.

- important participants of immune response.

3. Production of leukocytes (leukopoiesis).

- hormonally stimulated.

- hematopoietic hormones, colony stimulating factors (CSFs) prompt WBC precursors to divide and mature, enhance protective potency of WBCs.

- stem cell growth factor.
- macrophage-monocyte CSF (M-CSF).
- granulocyte CSF (G-CSF).
- granulocyte-macrophage CSF (GM-CSF).
- multi-CSF.

- CSFs are released in response to specific chemical signals in the environment and are closely tied to the immune response.
- leukocyte production: myeloid stem cells give rise to granulocytes and monocytes; lymphoid stem cells give rise to lymphocytes.

4. Leukocyte disorders.

a. Leukemia: excessive production of abnormal leukocytes

- renegade leukocytes member of one clone, remain unspecialized, mitotic, suppress and impair marrow function.

- named according to abnormal cell type primarily involved; myelocytic leukemia, lymphocytic leukemia.

- acute leukemia: (quick advancing), derived from blast-type cells like lymphoblast; usually affects children.

- chronic leukemia: (slow advancing), involves proliferation of later cell stages, more common in elderly people.

b. Leukopenia: low WBC due to glucocorticoids and/or anticancer agents.

c. Infectious mononucleosis: a virus that involves an excessive number of abnormal agranulocytes.

5. Platelets.

- not cells in the strict sense, cytoplasmic fragments of extremely large cells called megakaryocytes.

- contains many substances that aid in clotting processes such as calcium ions, serotonin, a variety of enzymes, ADP, PDGF, and other growth factors; many receptors to growth factors, insulin, signaling molecules (kinases, phosphatases), glycogen, and are capable of metabolism.

- are essential for clotting when blood vessels are ruptured or the lining is injured.

- platelet formation is stimulated by a hormone (thrombopoietin), which stimulates the production of megakaryocytes.

- platelet formation: hemocytoblast --> megakaryoblast --> repeated mitosis, not cytokinesis --> promegakaryocyte --> megakaryocyte --> cell fragmentation --> platelets.

A. Hemostasis:

- prevents blood loss through walls of damages vessels, establishes a framework for tissue repair.

1. Vascular spasms: damage to the blood vessel walls causes contraction of SMC fibers in the walls, constriction.

- endothelial changes during vascular phase: damaged endothelium releases ADP and hormones such as endothelin which stimulate the SMC cell to contract and also endothelial, SMC, and fibroblast proliferation; endothelial cells contract exposing underlying basal membrane; surface of endothelial cells becomes sticky

2. Platelet plug formation:

- platelets begin to attach to sticky endothelial cell membrane, and exposed collagen fibers, platelet adhesion.

- as platelets adhere they become activated, more platelets attach, platelet aggregation.

- <u>how does platelet activation lead to platelet aggregation?</u>

- activated platelets begin synthesizing and releasing many substances, such as the following:

- ADP
- thromboxane A_2
- serotonin
- platelet factors
- growth factors

- platelet plug limited to immediate area where it is needed by secretion of prostacyclin (inhibitor to platelet aggregation) in adjacent, undamaged endothelial cells.

3. Coagulation: blood clotting.

- complex series of steps involving many factors that lead to the conversion of circulating fibrinogen into insoluble protein fibrin, covers the surface of platelet plug and forms a blood clot; it is a three phase pathway.

PHASE 1: (2 pathways)

- intrinsic pathway: no tissue involvement; begins with activation of proenzymes exposed to collagen fibers at injury site; PF3+ calcium+ enzymes --> platelet thromboplastin.

- extrinsic pathway: involvement of tissue; tissue factor(TF) + calcium+enzymes --> tissue thromboplastin.

PHASE 2: common; prothrombin --> thrombin catalyzed by prothrombin activator.

PHASE 3: fibrinogen --> fibrin

XIII --> activated XIII -- binds fibrin strands together.

B. Clot retraction & repair

- within 30-60 minutes, a clot is stabilized further by the platelet induced process of clot retraction.

- effects of clot retraction: pulls the edges of the vessel together, lowers the residual bleeding, and stabilizes the injury site; also reduces the size of the damaged area.

C. Fibrinolysis.

- a process that removes unneeded clots when permanent healing has occurred
- clot "buster" is a fibrin-digesting enzyme, plasmin; produced by activation of a proenzyme plasminogen that was incorporated in large amounts into a forming clot, remains inactive until the appropriate signals reach it.
- the presence of clots in/around blood vessels are detected by ECs that release tissue plasminogen activator (t-PA); thrombin can also act on activation of plasminogen
- plasmin digests fibrin strands
- fibrinolysis begins within two days and continues over several days until the clot is completely dissolved.

D. Factors limiting clot growth and function.

- blood flow.
-. prostacyclin produced by adjacent ECs.
- thrombomodulin released by EC, binds thrombin and converts it to an enzyme that activates protein C, and inactivates several clotting factors.
- heparin.
- alpha2 macroglobulin.