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\textsubscript{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\textsubscript{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\textsubscript{2} to meet tissue demands.
   
   b. Dietary requirements.
      - amino acids, iron. vitamins (B\textsubscript{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 O\textsubscript{2} 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.

   • 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 lysosomes 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 damaged 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.

- how does platelet activation lead to platelet aggregation?

- activated platelets begin synthesizing and releasing many substances, such as the following:
  - ADP
  - thromboxane A₂
  - 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.


- 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.