Blood

Introduction
1. Primitive circulatory systems depend upon diffusion for distribution of gases, wastes, and nutrients
2. Advanced circulations use a pump, the heart, and vessels to deliver blood and then diffusion takes place
3. General Functions of circulatory system
   a. Distribution of:
   b. Protection from:
4. Major Components
   a. Divided generally into:
      1) Cardiovascular
      2) Lymphatic
   b. Heart-4 chambered pump
   c. Blood vessels
      1) Carry blood
      2) Arteries carry blood away from heart
      3) Veins return blood to the heart
      4) Capillaries connect arteries to veins and allow exchanges
   d. Interstitial fluid
      1) Derived from plasma that leaks out of capillaries
      2) Interstitial fluid captured by lymphatic capillaries is called lymph
      3) Lymph vessels include capillaries and lymphatic veins
5. Blood functions
   a. Transports dissolved gases, nutrients, and wastes
   b. Delivers enzymes and hormones
   c. Regulates pH, temperature, and electrolyte composition
   d. Restricts fluid losses (hemostasis)
   e. Defends the body against pathogens and toxins
6. Blood characteristics
   a. Temperature 100.4 F & 38 C
   b. pH 7.35-7.45
   c. Salinity 0.9%
   d. Volume
      1) Males 5-6 L
      2) Females 4-5 L
   e. % Body weight 8%
   f. Viscosity 4-5
7. Blood Components
   a. Whole blood can be fractionated by centrifugation into plasma and formed elements
b. % of blood occupied by cellular components, called formed elements, is called the hematocrit
   1) Male hematocrit
   2) Female hematocrit
b. Straw-colored liquid (matrix) is called plasma
c. Useful diagnostic tool for problems with blood composition

Plasma
1. Defined:
   a. Is the liquid ground substance
   b. Therefore is a connective tissue
2. Composition
   a. 92% water
   b. Many electrolytes such as:
   c. Dissolved nutrients and wastes
   d. Hormones, transport proteins, and enzymes
   e. Higher oxygen, lower carbon dioxide than interstitial fluid
3. Plasma proteins
   a. Albumins
      1) 60% of plasma proteins
      2) Maintain osmotic pressure keeping water from leaving blood vessels
      3) Some transport fatty acids and hormones
   b. Globulins
      1) 33% of plasma proteins
      2) Kinds:
         a) Immunoglobulins
            i. Also called antibodies
            ii. Formed from B lymphocytes and transform into plasma cells
            iii. Bind to specific chemical targets on foreign substances called antigens
         b) Transport proteins
            i. Deliver ions, hormones, and other that prevent loss (filtration) in the kidney
            ii. Metallobulins such as transferrin for Fe++
      3) Both albumins and globulins can attach to lipids forming lipoproteins
   c. Fibrinogen
      1) 7% plasma proteins
      2) Important in hemostasis
      3) Fibrinogen is inactive form that is converted to fibrin a long stringy protein
4) Removal of clotting proteins from plasma forms serum
d. Liver synthesizes 90% of these proteins
   1) Hormones made by specific glands
   2) Immunoglobulins made by plasma cells
e. Plasma expanders-used to increase blood volume quickly
   1) Isotonic electrolyte solutions-Ringer’s solution
   2) Easy to store and keep sterile

Formed Element: Erythrocytes
1. Also know as: Red Blood Cells
2. 25 trillion present
3. Density counts:
   a. males 4.5-6.3 million/mm3
   b. females 4.2-5.5 million/mm3
4. Structure
   a. Biconcave disc (7-8 um)
      1) Increases surface area for diffusion
      2) Allows Rouleau stacks to form for easier passage through capillaries
      3) Gives great flexibility for passing through small capillaries
   b. No nucleus, mitochondria, ER, or ribosomes
   c. Packed with Hemoglobin (Hb)
5. Hb structure
   a. Porphyrin ring with Fe++ at center is called:
   b. 4 globular proteins called: globins
   c. One Hb can bind 4 O2’s forming oxyhemoglobin (O2Hb)
   d. Can also bind CO2’s; referred to as carbaminohemoglobin
      1) Does not bind to Fe++, but to amino acids
   e. 280 million Hb’s/RBC = ~ 1 billion oxygens
   f. Counts:
      1) Males: 14-18 g/dl
      2) Females: 12-16 g/dl
6. Erythropoeisis
   a. Defined: process of RBC formation in the myeloid tissue of red marrow
   b. Location in sternum, vertebrae, scapulae, ribs, skull, and pelvis
   c. Requires aa, Fe++, folic acid, and Vitamin B12
   d. Regulated by the hormone erythropoietin (EPO) released from kidneys
      1) Kidney cells monitor oxygen levels
      2) Decline of O2 is due to High Altitude, Exercise, Hemorrhage
      3) EPO released and stimulates stem cells in red marrow
e. Rate of formation
   1) Normal: 3 mil/sec
   2) Maximum: 30 mil/sec

f. Testosterone and estrogen influence rates

g. Stages of process
   1) Hemocytoblast (Hemopoietic stem cell/pluripotent stem cell)- gives rise to all other blood cells
   2) Proerythroblast (Erythrocyte colony forming unit)-genetic lineage committed to only RBCs
      a) Develops receptors for EPO
      b) EPO stimulates divisions (mitosis) forming erythroblasts
   3) Early erythroblast
      a) Ribosome synthesis increases
      b) Still can divide some
      c) Begins Hb synthesis
   4) Middle stage erythroblast
      a) Hb production continues
   5) Late stage erythroblast
      a) Hb synthesis peaks
      b) Nuclear function ceases
      c) Also called a normoblast
   6) Reticulocyte forms when normoblast ejects nucleus
      a) rER gives speckled appearance-hence name
      b) 0.5-1.0 % enter circulation
      c) Higher levels indicate hemorrhage
      d) With ejection of nucleus, cell collapses inward forming biconcave shape
   7) Erythrocyte forms when rER disappears
   8) Timing:
      a) Hemocytoblast-Reticulocyte: 3-5 days
      b) reticulocyte-Erythrocyte: 2-3 days

7. Erythrocyte Destruction and Recycling
   a. Longevity
      1) Males: 120 days
      2) Females: 109 days
      3) What causes cells to wear out? (see b-1 below)
   b. Stages of:
      1) Begin leaking as squeezed through small vessels
      2) In liver, spleen, or marrow are macrophages that detect leakage (by chemotaxis) and phagocytize
      3) Within macrophage:
         a) Heme and globin separated
b) Globins are hydrolyzed into aa which can be used by macrophage to make own proteins or released into blood for use by other cells
c) Heme is stripped of Fe++ and converted to biliverdin
d) Biliverdin is converted to bilirubin and released into blood
e) Bilirubin carried by an albumin to liver where it is modified, and released in bile
f) Fe++ is released and picked up by the metalloglobulin transferrin
g) Transferrin delivers to liver, spleen, or marrow where Fe++ is stored as Ferritin or Hemosiderin
h) Fe++ also used in myoglobin and cytochromes (ETS)

8. Anemias
   a. Defined:
   b. Kinds:
      1) Nutritional
         a) Lack of dietary proteins or Fe++
         b) Males: 3.5 g with 2.5 g used in Hb
         c) Females have 2.4 g with 1.9 g used in Hb
         d) Females lose Fe++ via menstruation
         e) Diet of red meats, liver, egg yolks, spinach, carrots, and kidney beans high in Fe++
         f) Vegetarians have problems because:
      2) Hemorrhagic
         a) Caused by:
         b) Very low hematocrit
      3) Pernicious
         a) Lack of vitamin B12
         b) Form of nutritional anemia
         c) W/o B12 RBCs abnormally large and irregular in shape
         d) Intrinsic factor from stomach important in absorption of B12
      4) Aplastic
         a) Cause:
      5) Sickle-cell
         a) Genetic disorder of mostly Negroid populations in tropical Africa (0.14% US)
         b) Caused by single aa substitution in one of the globin chains
         c) RBCs deprived of O2 cause Hb to alter conformation and distort (sickle) RBC
         d) Severe pain and damage to all vital organs
e) Provides genetic resistance to malaria in heterozygous state

9. Polycythemia
   a. Defined:
   b. Kinds:
      1) Polycythemia vera
         a) Bone marrow cancer
         b) Hematocrit 80%!
         c) High blood viscosity
         d) Also caused by emphysema
      2) Secondary polycythemia
         a) Hypoxic conditions or increased EPO
         b) Normal response to high altitudes
         c) Exercise also causes raising hematocrits to 45-55%
   c. Blood doping
      1) Reinfusing stored RBCs
      2) Injections of EPO

10. Blood Groups: ABO System
    a. Best known and most important to transfusions
    b. Presence or absence of surface glycoproteins on plasma membranes of RBCs
       1) Glycoproteins called agglutinogens or antigens
          a) Antigens trigger immune response when antibodies, or agglutinins, are present
          b) Antibodies bind antigens to inactivate
    c. Blood Type | Antigen | Antibody | Blood that can be received
      A
      B
      O
      AB

    d. One of several blood systems such as: MN, Duffy, Kell, etc
    e. Type O is universal donor
       1) Most common blood type, but numbers vary by race
    f. Type AB is universal recipient
       1) Concept of universal is misleading because donor’s plasma contains antibodies
       2) Donations often okay because antibodies get diluted and cannot initiate coagulation
3) Best solution is to transfuse packed RBC’s with reduced plasma as antibodies are found in plasma

g. Antibody origins
  1) Appear in plasma 2-8 months after birth with max concentration by 10 years
  2) Do not develop antibody that would react with own blood type
  3) Bacteria also have antigens A and B
  4) Solid food intake initiates immune response causing body to synthesize antibody to antigen you lack

h. Introducing correct antigen to antibody causes agglutination reaction
  1) Antibodies cross-link antigens in such a way as to clump RBCs
  2) Clumping causes transfusion reaction
    a) Hemolysis
    b) Clogs vessels cutting off O2 to vital organs
    c) Hemolysis releases Hb that clogs kidneys-renal failure
    d) Immune response raises temperature-pyrogenic effect

  3) Treatment
    a) Infuse alkaline fluids to dissolve and dilute Hb
    b) Diuretics to increase urine flow and get kidneys functioning

11. Rh Group
  a. Rh or D agglutinogens discovered in rhesus monkey
  b. Blood type is Rh+ if agglutinogens (antigens) present on RBCs
  c. Anti-D agglutinins (antibodies) are not normally present in blood nor are they introduced by bacteria
  d. Anti-D antibodies are formed by:
    1) Rh- woman carrying an Rh+ fetus
      a) During birth some Rh antigens leak into mother’s blood and she eventually forms antibodies
      b) During second pregnancy with Rh+ fetus, antibodies leak across placental and attack fetus-erythroblastosis fetalis or hemolytic disease of newborn
      c) Mother’s antibodies attack fetal blood causing anemia and toxic brain syndrome
      d) Can treat with phototherapy to breakdown built-up bilirubin or transfusion
      e) Also treated with RHOGAM shot that prevents antibody formation-these bind fetal antigens in her blood so she cannot form antibodies
    2) Blood transfusions of an Rh+ (e.g. A+) to and Rh- (e.g.A-) person
a) No issue on first transfusion, but second Rh+ transfusion would cause reaction

e. AB agglutinogens not a problem during pregnancy because they are too large to cross placental

**Formed Element: Leukocyte**

1. Density:
2. 1% blood volume
3. Functions (general):
4. Characteristics:
   a. Pavementing (Margination)
      1) Defined:
      2) Chemicals released during damage cause endothelial cells to produce adhesion molecules
      3) WBCs (Neutrophils) can adhere to vessel near damaged area
   b. Diapedesis
      1) Defined:
      2) Aided by chemical mediators such as histamines that help spread endothelial cells further apart
   c. Chemotaxis
      1) Defined:
      2) Damaged cells release chemical mediators that leave trail to damaged area
   d. Amoeboid motion
      1) Describe:
         a) Cytoplasm brought up from rear of cell to form extensions
         b) Same process used in phagocytosis
   e. Phagocytosis
      1) Defined:
      2) Cellular debris, bacteria engulfed
   f. Opsonization
      1) Foreign cells are coated with antibodies by other immune cells
      2) These provide binding sites and tagging for neutrophils
      3) Tagging identifies for disposal
      4) Binding sites make phagocytosis easier

5. Leucocyte diversity
   a. Granulocytes-lobed nuclei and relatively large; cytoplasmic granules present and stained; mostly short-lived; classified by stains/pH they absorb
      1) Neutrophils
         a) 60-70%
b) 12 um diameter  
c) Granules smallest and least visible of granulocytes  
d) Granules in all are lysosomes containing peroxidases and hydrolytic enzymes  
e) Absorbs both acidic and basic stains—hence neutral  
f) Multilobed (3-6) nucleus and sometimes nicknamed POLYs (polymorphonuclear)  
g) Phagocytic of bacteria at sites of inflammation; first line of defense at injury  
h) Produce H2O2 and defensins, molecules that form large channels in bacterial membranes  
i) Release leukotrienes to other other neutrophils  
j) Live 30 min to a few days  
k) Increase during bacterial infections, meningitis, and appendicitis

2) Eosinophils  
a) 1-4%  
b) ~12 um diameter  
c) Blue-red nucleus in shape of telephone receiver  
d) Granules are large and absorb eosin (acidic) stains that is red  
e) Often protects against parasitic worms releasing enzymes on worm’s surface  
f) Also phagocytize proteins that might cause allergies

3) Basophils  
a) 0.5-1%  
b) 8-10 um diameter  
c) Nucleus is U or S shaped, but very hard to see  
d) Coarse granules large, stain blue-black, and obscure nucleus  
e) Absorb basic stains  
f) Granules contain histamines and heparin  
   i. Histamine causes vasodilation and attracts other WBCs to injury  
   ii. Heparin helps prevent clotting and helps other WBCs find area

b. Agranulocytes—Granules present, but very small under light microscope

1) Lymphocytes  
a) 25%  
b) 5-17 um diameter in 3 size classes  
c) Nucleus is rounded and notched with sparse amts of cytoplasm
d) Most lymphocytes not in blood, but in various lymphatic organs

e) Functions:
   i. Important in immunity
   ii. Destroy virus-infected cells and tumors
   iii. secrete antibodies
   iv. Activate other immune cells

f) Kinds:
   i. B cell lymphocytes-for humoral (plasma) immunity; secrete antibodies; differentiate into plasma cells that produce the antibodies (neutralize foreign antigens
   ii. T cell lymphocytes for cell-mediated immunity; most circulating lymphocytes; defend against foreign cells and tissues; can be called Cytotoxic, Regulatory, or Helper
   iii. Natural Killer-immune surveillance of abnormal (precancerous or cancerous) tissues

2) Monocytes
   a) 3-8%
   b) 18 um diameter
   c) Blue-purple U-shaped or ovoid nucleus with clear cytoplasm
   d) Also known as macrophages when taking up residence in other organs

   e) Functions:
      i. Phagocytic against bacteria, viruses, cell debri, and parasites
      ii. Release attractants to other immune cells
      iii. Follow neutrophils to site of inflammation

6. Leucocyte Counts/Diseases
   a. Normal count:
   b. Leukopenia defined:
      1) Count:
      2) caused by anticancer drugs and glucocorticoids
   c. Leukocytosis defined:
      1) Count:
      2) Often follows bacterial infection
   d. Leukemia defined:
      1) Count:
      2) Kinds:
         a) Lymphogenous-affects lymphocytes
i. Acute-short and severe; caused by radiation exposure and viral infections
   ii. Chronic-long term; chromosome abnormalities and immune system failure

b) Myelogenous-affects descendents of myeloblasts
   i. Bone marrow packed with WBCs
   ii. WBCs nonfunctional; as counts increase cells replace healthy cells in organs
   iii. Treatment is gamma interferon and bone marrow transplants

7. Inflammation
   a. Defined:
   b. Triggered by an injury to body tissues
   c. Symptoms:
   d. Events:
      1) Tissue damage
      2) Release of chemical mediators
         a) Histamine
         b) PG’s
         c) Kinins
         d) Serotonin
         e) Others:
      3) Hemostasis happens within first 30-60 minutes; priority is to stop blood loss and access by more bacteria
         a) Initial response will be vasoconstriction to stop blood loss.
         b) Once stopped, histamine slowly increases and leads to vasodilation
      4) Vasodilation
         a) Allows increased blood flow to area that creates swelling, redness, and heat
         b) Brings in more neutrophils
         c) Chemical mediators increase capillary permeability allowing WBCs to marginate and undergo diapedesis
      5) Neutrophils find damaged area by chemotaxis
         a) Release leukotrienes to attract more neutrophils
         b) Phagocytize bacteria and cell debri
      6) As blood flow increases, slows down entry of additional blood
         a) Capillaries leak fluids leading to more swelling
         b) Tissue repair has begin
      7) Macrophages reach area and continue clean up
         a) Build up of dead cells, debri, and bacteria forms pus
         b) If repair seals off pus, then an abcess is formed
c) Rarely, bacteria become resistant in abscess and form baseball-sized granuloma

e. Chemical mediators
1) Histamine
   a) From basophils
   b) Promotes vasodilation and increased capillary permeability
2) Kinins
   a) Formed from plasma protein kininogen
   b) Similar to histamine, but also induces chemotaxis and pain
3) Prostaglandins (PGs)
   a) Source is damaged membranes
   b) Sensitizes vessels to mediators; causes pain
   c) Leukotrienes are PG from WBCs that attract more WBCs
4) Complement system
   a) 20 normally inactive circulating proteins
   b) Enhance mediators
   c) Penetrate bacterial membranes causing them to leak and eventually lyse (cytolysis)
5) Serotonin
   a) Source is platelets
   b) Promotes vasoconstriction during vascular spasm phase of hemostasis

Formed Element: Thrombocyte
1. Pinched cytoplasmic fragments of a megakaryocyte
2. Size:
3. Density:
4. Life span:
5. Function:
6. Hemostasis
   a. Defined:
   b. 3 main phases: vascular spasm, platelet plug, coagulation
   c. Vascular spasm
      1) Injury to vessel wall activates pain receptors and stimulates smooth muscle contraction
      2) Platelets release serotonin also causing vasoconstriction
      3) Events lead to reduced blood loss
      4) Blunt blow produces best results
   d. Platelet Plug
      1) Ruptured endothelium exposes collagen fibers
2) Endothelium normally has + charge
3) Platelets normally have + charge on outer surface and are therefore repelled by endothelium
4) Exposed endothelium has – charge; platelets now attracted to damaged area
5) Platelets change shape having long cytoplasmic extensions allowing them to adhere to vessel wall and other platelets
6) Platelets release serotonin for vasoconstriction
   a) ADP-aggregating agent for more platelets binds to receptor called aggregin
   b) Thromboxane is an eicosanoid for platelet aggregation
   c) Ca++ important for next stage-coagulation
7) More platelets release more chemicals which brings in more platelets-a positive feedback loop
8) PGI2 or prostacyclin, released from undamaged endothelium inhibits platelet aggregation away from injury; clot cannot grow indefinitely

e. Coagulation
1) Critical for vessel leakage to be stopped quickly, but not to clot if undamaged
2) Balance between procoagulants, those chemicals that cause clotting, and anticoagulants, those chemicals that prevent clotting
   a) Procoagulants numbered I-XIII in order of discovery
   b) Procoagulants made by liver and kept inactive until vessel damage
3) Coagulation involves over 30 reactions
   a) A series of reactions where next reaction depends on product of previous reaction is a cascade
   b) Final reaction and ultimate goal is to convert fibrinogen into fibrin
4) 2 reaction pathways lead to coagulation
   a) Both triggered by vessel damage
   b) Both identical after factor X
   c) Intrinsic Pathway
      i. Identified when blood clotted in test tube
      ii. Internal vessel damage causes, but both activated by external injury
      iii. Arteriosclerosis activates intrinsic pathway leading to stationary clots called thrombi; smaller clots (emboli) break off from a thrombus and move through vessels until becoming lodged
iv. An embolus in brain is a stroke; embolus in heart vessel is a myocardial infarct
v. Characteristics: Large amt of thrombin produced slowly because there are many steps (reactions)
d) Extrinsic pathway
   i. Characteristics: small amts of thrombin produced rapidly because of fewer steps
e) After factor X plus 3 other the procoagulant, prothrombin activator (Prothrombinase), is formed
f) Prothrombinase converts prothrombin to thrombin
g) Thrombin converts fibrinogen to fibrin
h) Fibrin is a long stringy polymer; also requires Ca++ and another factor to form

5) Conclusions
   a) Fibrin captures escaped blood cells like a net
   b) Platelets have actomyosin that pulls platelets, fibrin, and collagen more tightly together closing vessel wall
c) Platelets use cytoplasmic extensions to wrap around fibrin and collagen
d) Clot formation occurs within 30-60 minutes, but bleeding has been dramatically reduced by vascular spasm and platelet plug
e) As clot dries, a scab is formed
f) Platelets also release platelet-derived growth factor that stimulates division of smooth muscle and fibroblasts for repair

7. Fibrinolysis
   a. Defined:
   b. Coagulation complete, tissue repair begins
c. Speed depends on wound size, but new endothelium, connective tissue, and skin for under scab
      1) Fibroblasts invade and stabilize scab
d. Plasma enzyme called kallikrein (plasminogen activator or tPA converts plasminogen to plasmin
      1) Plasmin is a fibrin-dissolving enzyme
      2) t-PA is important clinically for dissolving unwanted clots

8. Prevention of Clot Formation
   a. Do not become too large because coagulation factors are removed
   b. Clotting factors dilute the further from injury
c. Clotting factors normally inhibited by anticoagulants in healthy vessels
d. Anticoagulants
   1) Antithrombin III-alphas globulin in plasma that binds thrombin
2) Protein C-from liver inactivates 2 factors and stimulates plasmin formation
3) Heparin-activates antithrombin; prevents platelet sticking (test tubes are heparinized)
4) Prostacyclin-repels platelets from healthy endothelium

9. Coagulation Disorders
   a. Vitamin K deficiency-important cofactor in synthesis of 4 procoagulants
      1) Absorption in GI tract depends on bile; therefore gall bladder or liver malfunctions can lead to clotting problems
   b. Hemophilies
      1) Sex-linked genetic disorder
      2) Hemophilia A-Factor VIII missing; 83% of cases; 1/5000 males
      3) Hemophilia B-Factor IX missing; 15% cases; 1/30000 males
      4) Treated with genetically engineered factors
   c. Thrombocytopenia-abnormally low platelet count
      1) Value:
      2) Cause: marrow destruction by radiation, drugs, poisons, or leukemia
      3) Symptoms: Hemorrhagic spots under skin; slight blows cause large hematomas

10. Drugs
   a. Coumadin (warfarin) or dicumarol-blocks vitamin K; used in rat poisons and for treating blood clots after surgeries
   b. tPA, streptokinase, urokinase-clot dissolvers
   c. Aspirin-prevents formation of thromboxane and other PG’s
   d. EDTA (Ethylene diamine tetroacetic acid)-removes Ca++ for blood storage in crime scenes
   e. Hirudin-polypeptide of 65 a secreted by leeches
      1) Medicinal leeches for amputations