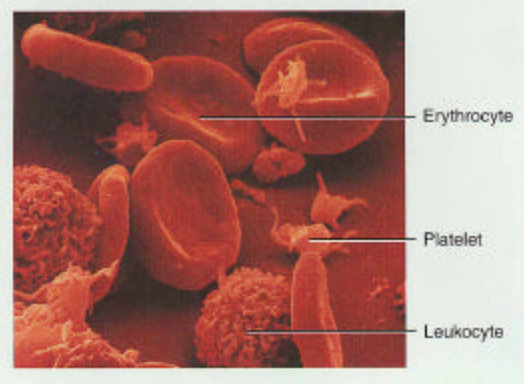
The Cardiovascular System: The Blood

Fluids of the Body



- Cells of the body are serviced by 2 fluids
  - blood
    - composed of plasma and a variety of cells
    - transports nutrients and wastes
  - interstitial fluid
    - bathes the cells of the body
- Nutrients and oxygen diffuse from the blood into the interstitial fluid & then into the cells
- Wastes move in the reverse direction
- Hematology is study of blood and blood disorders

Functions of Blood

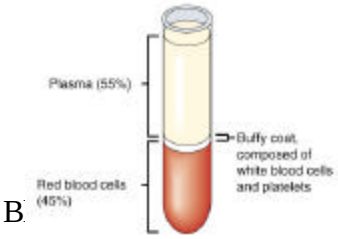
- Transportation
  - O2, CO2, metabolic wastes, nutrients, heat & hormones
- Regulation
  - helps regulate pH through buffers
  - helps regulate body temperature
    - coolant properties of water
    - vasodilatation of surface vessels dump heat
  - helps regulate water content of cells by interactions with dissolved ions and proteins
- Protection from disease & loss of blood

Physical Characteristics of Blood

- Thicker (more viscous) than water and flows more slowly than water
- Temperature of 100.4 degrees F
- pH 7.4 (7.35-7.45)

Components of Blood

- Hematocrit
  - 55% plasma
  - 45% cells
    - 99% RBCs
    - < 1% WBCs and platelets



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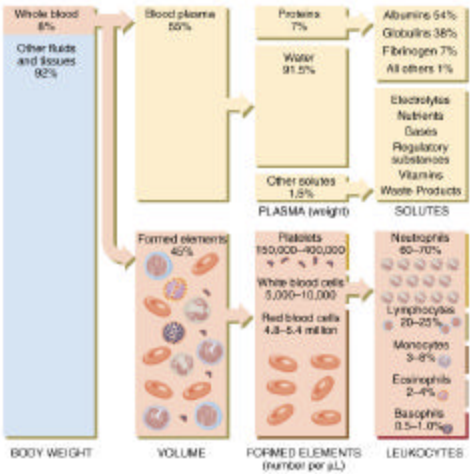
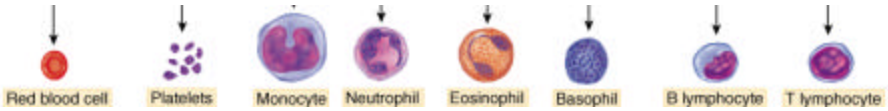


- 0ver 90% water
- 7% plasma proteins
  - created in liver
  - confined to bloodstream
  - albumin

        - maintain blood osmotic pressure
    - globulins (immunoglobulins)
        - antibodies bind to foreign substances called antigens
        - form antigen-antibody complexes
    - fibrinogen
        - for clotting
- 2% other substances
    - electrolytes, nutrients, hormones, gases, waste products

Formed Elements of Blood

- Red blood cells (erythrocytes)
- White blood cells (leukocytes)
    - granular leukocytes
        - neutrophils
        - eosinophils
        - basophils
    - agranular leukocytes
        - lymphocytes = T cells, B cells, and natural killer cells
        - monocytes



- Platelets (special cell fragments)

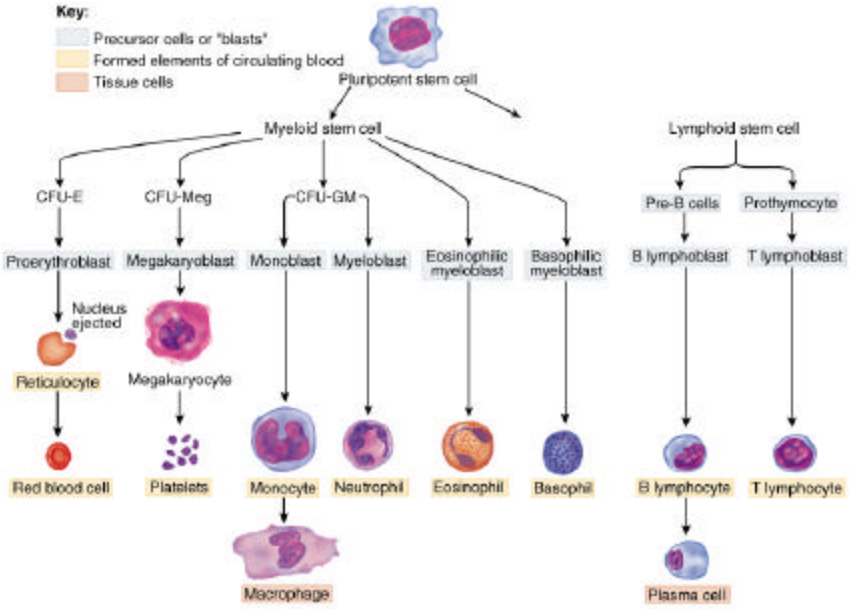
Hematocrit

- Percentage of blood occupied by cells
    - female normal range
        - 38 - 46% (average of 42%)
    - male normal range
        - 40 - 54% (average of 46%)
        - testosterone
- Anemia
    - not enough RBCs or not enough hemoglobin
- Polycythemia
    - too many RBCs (over 65%)
    - dehydration, tissue hypoxia, blood doping in athletes

Formation of Blood Cells

- Most blood cells types need to be continually replaced
    - die within hours, days or weeks
    - process of blood cells formation is hematopoiesis or hemopoiesis
- In the embryo
    - occurs in yolk sac, liver, spleen, thymus, lymph nodes & red bone marrow
- In adult
    - occurs only in red marrow of flat bones like sternum, ribs, skull & pelvis and ends of long bones

Hematopoiesis



Hemopoietic Growth Factors

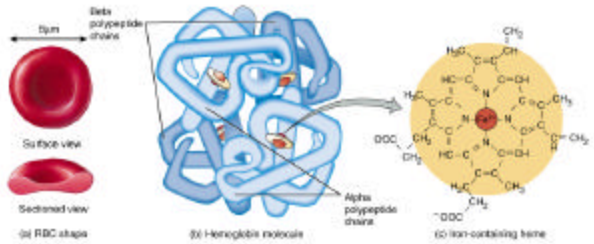
- Regulate differentiation & proliferation
- Erythropoietin (EPO)
  - produced by the kidneys increase RBC precursors
- Thrombopoietin (TPO)
  - hormone from liver stimulates platelet formation
- Cytokines are local hormones of bone marrow
  - produced by some marrow cells to stimulate proliferation in other marrow cells
  - colony-stimulating factor (CSF) & interleukin stimulate WBC production

Red Blood Cells or Erythrocytes

- Contain oxygen-carrying protein hemoglobin that gives blood its red color
  - 1/3 of cell's weight is hemoglobin
- Biconcave disk 8 microns in diameter
  - increased surface area/volume ratio
  - flexible shape for narrow passages
  - no nucleus or other organelles
    - no cell division or mitochondrial ATP formation
- Normal RBC count
  - male 5.4 million/drop ---- female 4.8 million/drop
  - new RBCs enter circulation at 2 million/second

Hemoglobin

- Globin protein consisting of 4 polypeptide chains
- One heme pigment attached to each polypeptide chain
  - each heme contains an iron ion (Fe+2) that can combine reversibly with one oxygen molecule

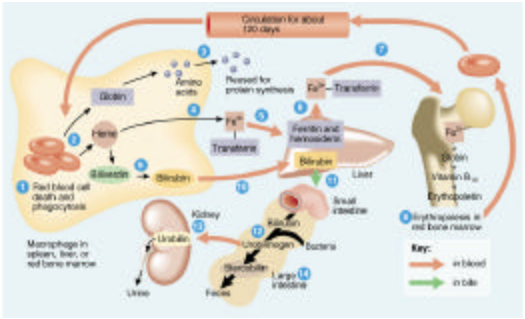


Transport of O2, CO2 and Nitric Oxide

- Each hemoglobin molecule can carry 4 oxygen molecules from lungs to tissue cells
- Hemoglobin transports 23% of total CO2 waste from tissue cells to lungs for release
  - combines with amino acids in globin portion of Hb

Recycling of Hemoglobin Components

- In macrophages of liver or spleen
  - globin portion broken down into amino acids & recycled
  - heme portion split into iron (Fe+3) and biliverdin (green pigment)

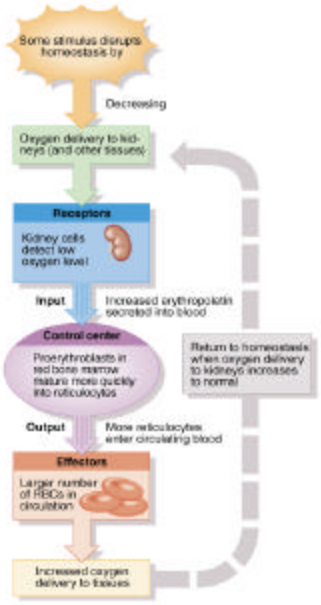


Fate of Components of Heme

- Iron(Fe+3)
  - transported in blood attached to transferrin protein
  - stored in liver, muscle or spleen
    - attached to ferritin or hemosiderin protein
  - in bone marrow being used for hemoglobin synthesis
- Biliverdin (green) converted to bilirubin (yellow)
  - bilirubin secreted by liver into bile
    - converted to urobilinogen then stercobilin (brown pigment in feces) by bacteria of large intestine
    - if reabsorbed from intestines into blood is converted to a yellow pigment, urobilin and excreted in urine

Erythropoiesis: Production of RBCs

- Proerythroblast starts to produce hemoglobin
- Many steps later, nucleus is ejected & a reticulocyte is formed
  - orange in color with traces of visible rough ER
- Reticulocytes escape from bone marrow into the blood
- In 1-2 days, they eject the remaining organelles to become a mature RBC



Feedback Control of RBC Production

- Tissue hypoxia (cells not getting enough O2)
  - high altitude since air has less O2
  - anemia
    - RBC production falls below RBC destruction
  - circulatory problems
- Kidney response to hypoxia
  - release erythropoietin
  - speeds up development of proerythroblasts into reticulocytes

Normal Reticulocyte Count

- Should be .5 to 1.5% of the circulating RBC's
- Low count in an anemic person might indicate bone marrow problem
  - leukemia, nutritional deficiency or failure of red bone marrow to respond to erythropoietin stimulation
- High count might indicate recent blood loss or successful iron therapy

WBC Anatomy and Types

- All WBCs (leukocytes) have a nucleus and no hemoglobin
- Granular or agranular classification based on presence of cytoplasmic granules made visible by staining
  - granulocytes are neutrophils, eosinophils or basophils
  - agranulocytes are monocyes or lymphocytes

Neutrophils (Granulocyte)

- Polymorphonuclear Leukocytes or Polys
- Nuclei = 2 to 5 lobes connected by thin strands
  - older cells have more lobes
  - young cells called band cells because of horseshoe shaped nucleus (band)
- Fine, pale lilac practically invisible granules
- Diameter is 10-12 microns
- 60 to 70% of circulating WBCs

Eosinophils (Granulocyte)

- Nucleus with 2 or 3 lobes connected by a thin strand
- Large, uniform-sized granules stain orange-red with acidic dyes
  - do not obscure the nucleus

- Diameter is 10 to 12 microns
- 2 to 4% of circulating WBCs

Basophils (Granulocyte)

- Large, dark purple, variable-sized granules stain with basic dyes
  - obscure the nucleus
- Irregular, s-shaped, bilobed nuclei
- Diameter is 8 to 10 microns
- Less than 1% of circulating WBCs

Lymphocyte (Agranulocyte)

- Dark, oval to round nucleus
- Cytoplasm sky blue in color
  - amount varies from rim of blue to normal amount
- Small cells 6 - 9 microns in diameter
- Large cells 10 - 14 microns in diameter
  - increase in number during viral infections
- 20 to 25% of circulating WBCs

Monocyte (Agranulocyte)

- Nucleus is kidney or horse-shoe shaped
- Largest WBC in circulating blood
  - does not remain in blood long before migrating to the tissues
  - differentiate into macrophages
    - fixed group found in specific tissues
      - alveolar macrophages in lungs
      - kupffer cells in liver
    - wandering group gathers at sites of infection
- Diameter is 12 - 20 microns
- Cytoplasm is a foamy blue-gray
- 3 to 8% o circulating WBCs

WBC Physiology

- Less numerous than RBCs
  - 5000 to 10,000 cells per drop of blood
  - 1 WBC for every 700 RBC
- Leukocytosis is a high white blood cell count
  - microbes, strenuous exercise, anesthesia or surgery
- Leukopenia is low white blood cell count
  - radiation, shock or chemotherapy
- Only 2% of total WBC population is in circulating blood at any given time
  - rest is in lymphatic fluid, skin, lungs, lymph nodes & spleen

Emigration & Phagocytosis in WBCs

- WBCs roll along endothelium, stick to it & squeeze between cells.
  - adhesion molecules (selectins) help WBCs stick to endothelium
    - displayed near site of injury
  - molecules (integrins) found on neutrophils assist in movement through wall
- Neutrophils & macrophages phagocytize bacteria & debris
  - chemotaxis of both
    - kinins from injury site & toxins

Neutrophil Function

- Fastest response of all WBC to bacteria
- Direct actions against bacteria
  - release lysozymes which destroy/digest bacteria
  - release defensin proteins that act like antibiotics & poke holes in bacterial cell walls destroying them
  - release strong oxidants (bleach-like, strong chemicals) that destroy bacteria

Monocyte Function

- Take longer to get to site of infection, but arrive in larger numbers
- Become wandering macrophages, once they leave the capillaries
- Destroy microbes and clean up dead tissue following an infection

Basophil Function

- Involved in inflammatory and allergy reactions
- Leave capillaries & enter connective tissue as mast cells
- Release heparin, histamine & serotonin
  - heighten the inflammatory response and account for hypersensitivity (allergic) reaction

Eosinophil Function

- Leave capillaries to enter tissue fluid
- Release histaminase
  - slows down inflammation caused by basophils
- Attack parasitic worms
- Phagocytize antibody-antigen complexes

Lymphocyte Functions

- B cells
  - destroy bacteria and their toxins
  - turn into plasma cells that produces antibodies
- T cells
  - attack viruses, fungi, transplanted organs, cancer cells & some bacteria
- Natural killer cells
  - attack many different microbes & some tumor cells
  - destroy foreign invaders by direct attack

Differential WBC Count

- Detection of changes in numbers of circulating WBCs (percentages of each type)
  - indicates infection, poisoning, leukemia, chemotherapy, parasites or allergy reaction
- Normal WBC counts
  - neutrophils 60-70% (up if bacterial infection)
  - lymphocyte 20-25% (up if viral infection)
  - monocytes 3 -- 8 % (up if fungal/viral infection)
  - eosinophil 2 -- 4 % (up if parasite or allergy reaction)
  - basophil <1% (up if allergy reaction or hypothyroid)

Platelet (Thrombocyte) Anatomy

- Disc-shaped, 2 - 4 micron cell fragment with no nucleus
- Normal platelet count is 150,000-400,000/drop of blood
- Other blood cell counts
  - 5 million red & 5-10,000 white blood cells

Platelets--Life History

- Platelets form in bone marrow by following steps:
  - myeloid stem cells to megakaryocyte-colony forming cells to megakaryoblast to megakaryocytes whose cell fragments form platelets
- Short life span (5 to 9 days in bloodstream)
  - formed in bone marrow
  - few days in circulating blood
  - aged ones removed by fixed macrophages in liver and spleen

Complete Blood Count

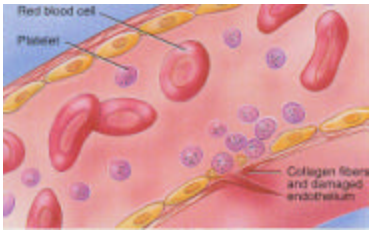
- Screens for anemia and infection
- Total RBC, WBC & platelet counts; differential WBC; hematocrit and hemoglobin measurements
- Normal hemoglobin range
  - infants have 14 to 20 g/100mL of blood
  - adult females have 12 to 16 g/100mL of blood
  - adult males have 13.5 to 18g/100mL of blood

Hemostasis

- Stoppage of bleeding in a quick & localized fashion when blood vessels are damaged
- Prevents hemorrhage (loss of a large amount of blood)
- Methods utilized
  - vascular spasm
  - platelet plug formation
  - blood clotting (coagulation = formation of fibrin threads)

Vascular Spasm

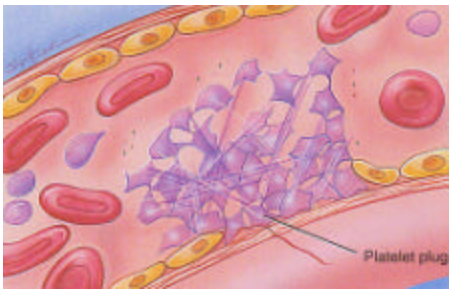
- Damage to blood vessel produces stimulates pain receptors
- Reflex contraction of smooth muscle of small blood vessels
- Can reduce blood loss for several hours until other mechanisms can take over



- Only for small blood vessel or arteriole

Platelet Plug Formation

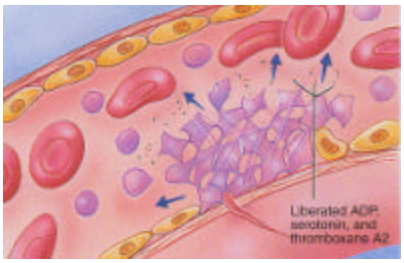
- Platelets store a lot of chemicals in granules needed for platelet plug formation
  - alpha granules
    - clotting factors
    - platelet-derived growth factor
      - cause proliferation of vascular endothelial cells, smooth muscle & fibroblasts to repair damaged vessels
  - dense granules
    - ADP, ATP, Ca+2, serotonin, fibrin-stabilizing factor, & enzymes that produce thromboxane A2
- Steps in the process
  - (1) platelet adhesion (2) platelet release reaction (3) platelet aggregation



Platelet Adhesion

- Platelets stick to exposed collagen underlying damaged endothelial cells in vessel wall

Platelet Release Reaction



- Platelets activated by adhesion
- Extend projections to make contact with each other
- Release thromboxane A2 & ADP activating other platelets
- Serotonin & thromboxane A2 are vasoconstrictors decreasing blood flow through the injured vessel

Platelet Aggregation

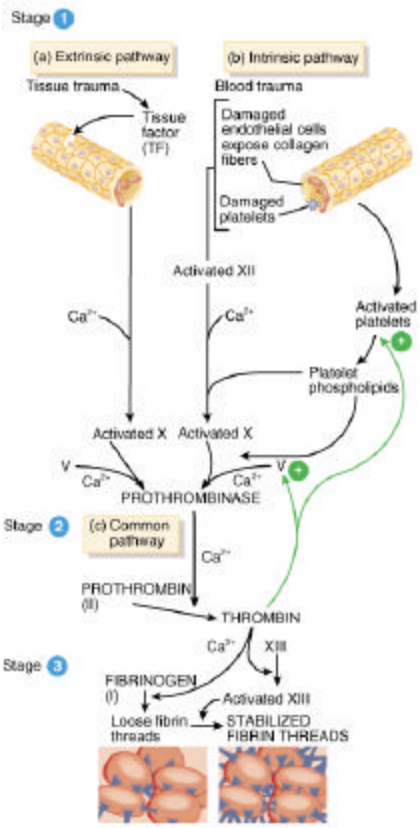
- Activated platelets stick together and activate new platelets to form a mass called a platelet plug
- Plug reinforced by fibrin threads formed during clotting process

Blood Clotting

- Blood drawn from the body thickens into a gel
  - gel separates into liquid (serum) and a clot of insoluble fibers (fibrin) in which the cells are trapped
- If clotting occurs in an unbroken vessel is called a thrombosis
- Substances required for clotting are Ca+2, enzymes synthesized by liver cells and substances released by platelets or damaged tissues
- Clotting is a cascade of reactions in which each clotting factor activates the next in a fixed sequence resulting in the formation of fibrin threads
  - prothrombinase & Ca+2 convert prothrombin into thrombin
  - thrombin converts fibrinogen into fibrin threads

Overview of the Clotting Cascade

- Prothrombinase is formed by either the intrinsic or extrinsic pathway
- Final common pathway produces fibrin threads



Extrinsic Pathway

- Damaged tissues leak tissue factor (thromboplastin) into bloodstream
- Prothrombinase forms in seconds
- In the presence of Ca+2, clotting factor X combines with V to form prothrombinase

Intrinsic Pathway

- Activation occurs
  - endothelium is damaged & platelets come in contact with collagen of blood vessel wall
  - platelets damaged & release phospholipids
- Requires several minutes for reaction to occur
- Substances involved: Ca+2 and clotting factors XII, X and V

Final Common Pathway

- Prothrombinase and Ca+2
  - catalyze the conversion of prothrombin to thrombin
- Thrombin
  - in the presence of Ca+2 converts soluble fibrinogen to insoluble fibrin threads
  - activates fibrin stabilizing factor XIII
  - positive feedback effects of thrombin
    - accelerates formation of prothrombinase
    - activates platelets to release phospholipids

Clot Retraction & Blood Vessel Repair

- Clot plugs ruptured area of blood vessel
- Platelets pull on fibrin threads causing clot retraction
  - trapped platelets release factor XIII stabilizing the fibrin threads
- Edges of damaged vessel are pulled together
- Fibroblasts & endothelial cells repair the blood vessel

Role of Vitamin K in Clotting

- Normal clotting requires adequate vitamin K
  - fat soluble vitamin absorbed if lipids are present
  - absorption slowed if bile release is insufficient
- Required for synthesis of 4 clotting factors by hepatocytes
  - factors II (prothrombin), VII, IX and X
- Produced by bacteria in large intestine

Intravascular Clotting

- Thrombosis
  - clot (thrombus) forming in an unbroken blood vessel
    - forms on rough inner lining of BV
    - if blood flows too slowly (stasis) allowing clotting factors to build up locally & cause coagulation
  - may dissolve spontaneously or dislodge & travel
- Embolus
  - clot, air bubble or fat from broken bone in the blood
    - pulmonary embolus is found in lungs
- Low dose aspirin blocks synthesis of thromboxane A2 & reduces inappropriate clot formation
  - strokes, TIAs and myocardial infarctions

Anticoagulants and Thrombolytic Agents

- Anticoagulants suppress or prevent blood clotting
  - heparin
    - administered during hemodialysis and surgery
  - warfarin (Coumadin)
    - antagonist to vitamin K so blocks synthesis of clotting factors
    - slower than heparin
  - stored blood in blood banks treated with citrate phosphate dextrose (CPD) that removes Ca+2
- Thrombolytic agents are injected to dissolve clots
  - directly or indirectly activate plasminogen
  - streptokinase or tissue plasminogen activator (t-PA)

Anemia = Not Enough RBCs

- Symptoms
  - oxygen-carrying capacity of blood is reduced
  - fatigue, cold intolerance & paleness
    - lack of O2 for ATP & heat production
- Types of anemia
  - iron-deficiency =lack of absorption or loss of iron
  - pernicious = lack of intrinsic factor for B12 absorption
  - hemorrhagic = loss of RBCs due to bleeding (ulcer)
  - hemolytic = defects in cell membranes cause rupture
  - thalassemia = hereditary deficiency of hemoglobin
  - aplastic = destruction of bone marrow (radiation/toxins)