Hematologic Disorders and Medications

Functions of blood

- Delivery of substances needed for cellular metabolism, esp:
  - Glucose
  - Oxygen
- Transport of waste substances
- Defense against invading organisms & injury
- Acid-Base Balance

Composition of Blood

- Suspension in a colloid solution
  - Plasma: Water portion of blood (50 – 55%)
    - 91-92% water
    - 8% solids
      - Proteins: Albumin, globulins, clotting factors, complement, enzymes, etc,
      - Other organic: Fats, phospholipids, cholesterol, glucose, nitrogenous substances (urea, uric acid, creatinine, etc.)
      - Inorganic minerals and electrolytes Cells
  - Formed Elements (45 – 50%)
    - Cells and Platelets

Plasma Proteins

- Albumin ~53% formed in liver
- Globulins ~ 43% formed in liver and lymphoid tissue (immunoglobulins)
- Fibrinogen ~4%

Formed Elements

- Erythrocytes: red blood cells
- Leukocytes: White blood cells
- Platelets

- All have a finite life span; must constantly be replaced
- Hematopoiesis: process of growing new formed elements

Erythrocytes (RBCs)

- ~5 million
- Primarily responsible for tissue oxygenation
- Lifespan = 120 days
- Hemoglobin (Hgb) ~15 grams
  - Hb A: adult
  - Hb F: fetal
  - Hb: S: sickle cell
  - Hb A1C: glycosolated

Erythrocytes continued

- Hematocrit (Hct)
  - 45%
  - Packed red blood cell volume
  - Percentage of total blood volume
- Unique RBC characteristics
  - Biconcavity
  - Reversible deformity

Leukocytes

- 5,000 – 10000/mm^3
- Final destination:
- Granulocytes
  - Neutrophils
  - Eosinophils
  - Basophils
- Monocytes – Macrophages
- Lymphocytes

Neutrophils

- 57 – 67%
- Polymorphonuclear (PMNs) "polys"
  - Segmented: adults
  - Bended: immature
  - Blasts: even less mature
- Predominant phagocyte in early inflammation

Neutrophil

- Primary roles
  - Removal of debris
  - Phagocytosis of bacteria
  - Prepare the injured site for
  - Healing
- Lifespan 4 days
- Large reservoir in marrow
- Die 1-2 days after migrating to inflamed site

Eosinophil

- 1 – 4 %
- Primary roles
  - Allergy - Ingest antigenantibody complexes
  - Mediate vascular effects of histamine and serotonin in allergic reactions
- Bind to and degranulate onto parasites (worms)
- Lifespan – unknown; primarily distributed in tissue, not blood

Basophil

- < 1%
- Function unknown
  - Defend against fungus?
  - Associated with allergic reactions and mechanical irritation
  - Structurally similar to mast cells
- Lifespan unknown: primarily distributed in tissues

Monocyte - Macrophages

- Monocytes (monos) 3 -7%
  - Become macrophages upon entering tissues
  - Arrive 3 – 7 days after injury
  - Long term defense against infection
  - Promote wound healing, clotting
  - Are directed by TH1 lymphocytes
  - Secrete colony stimulating factors (CSF)
- Lifespan months or years

Lymphocytes

- 25 – 33%
- Primary function
  - React against specific antigens or cells bearing those antigens
  - Circulate in blood, but primarily live in lymph tisues: node, spleen, vessels, and –ALTs
- T lymphocytes (cell mediated immunity)
- B lymphocytes (humoral immunity)

Thrombocytes (Platelets)

- 140,000 – 340,000/mm^3
- Irregularly shaped cytoplasmic fragments
  - Break off of megakaryocytes
  - Cell fragments
- Primary function
  - Form blood clots
  - Contain cytoplasmic granules that release in response to endothelial injury
- Lifespan 7 – 10 days; 1/3 stored in spleen

Hematopoiesis

- Occurs in marrow of skull, vertebrae, pelvis, sternum, ribs, proximal epiphyses
- Production is regulated by colony stimulating factors (CSF)
  - Erythropoietin
  - G-CSF
- Two stage process
  - Proliferation
  - Differentiation

Pluripotent Stem Cell

- Gives rise to colony forming units
  - Myeloid progenitor
    - CFU GM: neutrophils and monocytes
    - CFU E: Erythrocytes
    - CFU Meg: Platelets
    - CFU Bas: Basophils
    - CFU Eo: Eosinophils
  - Lymphoid progenitor
    - B lymphocyte
    - T lymphocyte

Colony Stimulating factors

- M-CSF stimulates Macrophages
- GM-CSF stimulates Neutrophils, Macrophages, and Eosinophils
- G-CSF stimulates Neutrophils, Eosinophils, and Basophils
- IL-3 stimulates Neutrophils and Macrophages
- IL – 2 stimulates Platelets
- Erythropoietin stimulates Erythrocytes

Development of Erythrocytes

- Uncommitted pluripotent Stem Cell
- Erythropoietin stimulation
- Myeloid Stem Cell (CFU-GEMM) differentiates
- Erythroblast
  - Huge nucleus
  - Hemoglobin synthesis
- Normoblast
  - Nucleus shrinks
  - Hemoglobin quantity increases
- Reticulocyte (~1%)
  - Once the nucleus is lost
  - matures into an erythrocyte within 24-48 hours
  - remain in the bone marrow ~ 1 day and then are released into the circulation
  - is a good indication of erythropietic activity

Hemoglobin A

- 90% of RBC weight
- O2 carrying protein
  - Oxyhemoglobin (Hgb that is carrying O2)
  - Deoxyhemoglobin (reduced Hgb that has released its O2)
  - Methemoglobin (unstable type of Hgb incapable of carrying O2)
- Heme - 4 complexes of Fe + protoporphyrin
- Globin - 2 pairs of polypeptide chains (amino acids)

Nutritional Requirements for Erythropoiesis

- Proteins
- Vitamin B12
- Folic acid (folate)
- Iron

Protein

- Important structural component for the plasma membrane
  - Strength
  - Flexibility
  - Elasticity
- Amino Acid (polypeptide) chains form the Hgb

Vitamin B12

- From animal products – meat, shellfish, milk, eggs
- DNA synthesis, erythrocyte maturation, & facilitator of folate metabolism
- Intrinsic Factor (IF) needed for B12 absorption
  - IF is secreted by the parietal cells of the gastric mucosa
  - IF facilitates Vit B12 absorption in the ileum
- B12 is stored in the liver until needed for erythropoiesis
  - B12 stores may last for several years

Folic Acid

- From liver, yeast, fruits, leafy vegetables, eggs, milk
  - Fragile, significantly reduced by cooking
- Synthesis of DNA & RNA, erythrocyte maturation
- Not IF dependent
- Absorbed in upper small intestine
- Minimally stored (few months at most)
- Pregnancy increases folate demand

Iron

- From Liver, red meat, dried fruits, Dk green leafy vegetables, Enriched bread and cereal
  - Vitamin C is required for absorption
- Critical element for hemoglobin synthesis
- 67% is bound to Heme (Hemoglobin)
- 30% is stored as Ferritin or Hemosiderin
- 3% is lost daily in the urine, sweat, bile, and epithelial cells of the gut

Iron Cycle

- Dietary Iron absorbed from the small bowel (duodenum, and proximal jejunum)
- Transferrin - carrier protein
- Bone Marrow - Hemoglobin Synthesis
- Removed by MPS after ~120 days in Spleen
- Iron Recycling
- Ferritin and Hemosiderin are storage forms of iron
  - liver
  - spleen
  - macrophages in the bone marrow

Regulation of Hematopoiesis

- Erythropoietin – secreted by kidney
- Tissue hypoxia is trigger

Destruction of Senescent Erythrocytes

- Destroyed by Macrophages in spleen and liver
- Globin broken down into amino acids
- Heme
  - Catabolized to porphyrin
  - Reduced to Unconjugated Free Bilirubin
  - Transported to Liver by Albumin
  - Bilirubin is Conjugated in Liver
    - Excreted in Bile
    - Transformed in intestine by Bacteria into Urobilinogen
      - Urobilinogen is excreted in Feces
        - » small amount excreted by kidneys
        - » and small amount is reabsorbed

Aging of Hematologic System

- Blood composition does not change
- Decreased iron
  - Decreased intrinsic factor
  - Decreased total iron binding capacity (TIBC)
- Erythrocyte membrane becomes fragile
- Lymphocyte function decreases
- Platelet numbers do not change, but clotting increases
  - Increased fibrinogen, and Factors V, VII, IX