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
  - 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
<table>
<thead>
<tr>
<th><strong>Erythrocytes continued</strong></th>
<th><strong>Leukocytes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hematocrit (Hct)</td>
<td>• 5,000 – 10000/mm³</td>
</tr>
<tr>
<td>– 45%</td>
<td>• Final destination:</td>
</tr>
<tr>
<td>– Packed red blood cell volume</td>
<td>– Granulocytes</td>
</tr>
<tr>
<td>– Percentage of total blood volume</td>
<td>– Neutrophils</td>
</tr>
<tr>
<td>• Unique RBC characteristics</td>
<td>– Eosinophils</td>
</tr>
<tr>
<td>– Biconcavity</td>
<td>– Basophils</td>
</tr>
<tr>
<td>– Reversible deformity</td>
<td>• Monocytes – Macrophages</td>
</tr>
<tr>
<td></td>
<td>• Lymphocytes</td>
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<table>
<thead>
<tr>
<th><strong>Neutrophils</strong></th>
<th><strong>Neutrophil</strong></th>
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<tbody>
<tr>
<td>• 57 – 67%</td>
<td>• Primary roles</td>
</tr>
<tr>
<td>• Polymorphonuclear (PMNs) “polys”</td>
<td>– Removal of debris</td>
</tr>
<tr>
<td>– Segmented: adults</td>
<td>– Phagocytosis of bacteria</td>
</tr>
<tr>
<td>– Bended: immature</td>
<td>– Prepare the injured site for</td>
</tr>
<tr>
<td>– Blasts: even less mature</td>
<td>– Healing</td>
</tr>
<tr>
<td>• Predominant phagocyte in early inflammation</td>
<td>• Lifespan 4 days</td>
</tr>
<tr>
<td></td>
<td>• Large reservoir in marrow</td>
</tr>
<tr>
<td></td>
<td>• Die 1-2 days after migrating to inflamed site</td>
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<table>
<thead>
<tr>
<th><strong>Eosinophil</strong></th>
<th><strong>Basophil</strong></th>
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<tbody>
<tr>
<td>• 1 – 4%</td>
<td>• &lt; 1%</td>
</tr>
<tr>
<td>• Primary roles</td>
<td>• Function unknown</td>
</tr>
<tr>
<td>– Allergy - Ingest antigenantibody complexes</td>
<td>– Defend against fungus?</td>
</tr>
<tr>
<td>– Mediate vascular effects of histamine and serotonin in allergic reactions</td>
<td>– Associated with allergic reactions and mechanical irritation</td>
</tr>
<tr>
<td>– Bind to and degranulate onto parasites (worms)</td>
<td>– Structurally similar to mast cells</td>
</tr>
<tr>
<td>• Lifespan – unknown: primarily distributed in tissue, not blood</td>
<td>• Lifespan unknown: primarily distributed in tissues</td>
</tr>
</tbody>
</table>
### 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 tissues: nodes, spleen, vessels, and ALTs
- T lymphocytes (cell mediated immunity)
- B lymphocytes (humoral immunity)

### Thrombocytes (Platelets)
- 140,000 – 340,000/mm³
- 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 erythropoietic 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